LORCASERIN HYDROCHLORIDE

Briefing Document for FDA Advisory Committee Meeting

Product Name:	Lorcaserin hydrochloride
Dose:	10 mg twice daily (BID)
Formulation:	Tablets
Indication:	Weight Management
Sponsor:	Arena Pharmaceuticals, Inc. 6166 Nancy Ridge Drive San Diego, CA 92121
Date:	06 April 2012

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF END-OF-TEXT TABLES

LIST OF END-OF-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADME	absorption, distribution, metabolism and excretion
AE	adverse event
AgRP	agouti-related protein
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
AP	alkaline phosphatase
APD	action potential duration
API	active pharmaceutical ingredient
AR	aortic regurgitation
BCS	Biopharmaceutics Classification System
BDI-II	Beck Depression Inventory II
bid (BID)	twice daily
BMI	body mass index
BOCF	baseline observation carried forward
CHO	Chinese hamster ovary
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CoxPH	Cox proportional hazards model
CRP	C-reactive protein
CSF	cerebrospinal fluid
CV	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DIO	diet-induced obese
DOM	2,5-dimethoxy-4-methylamphetamine
ECG	electrocardiogram
FDA	Food and Drug Administration
FMO1	flavin-containing monooxygenase
FOB	functional observation battery
FPG	fasting plasma glucose
FSG	fasting serum glucose
GEE	generalized estimating equation
GERD	Gastroesophageal reflux disease

GLP	Good Laboratory Practice
H&E	hematoxylin and eosin
Hct	hematocrit
HDL	high density lipoprotein
Hgb	hemoglobin
HOMA-IR	homeostatic model assessment—insulin resistance
HR	hazard ration
HsCRP	highly sensitive C-reactive protein
ITT	intent-to-treat (population)
IVRS	interactive voice recognition system
IW52 or Wk 52/RDP	Intended Week 52 (population)
LDL	low density lipoprotein
LOCF	last observation carried forward
MAO	monoamine oxidase
MC-4R	melanocortin-4 receptor
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat (population)
MR	mitral regurgitation
MRD	maximum recommended dose
MTD	maximum tolerated dose
NDA	New Drug Application
NHANES	National Health and Nutrition Examination Survey
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NPY	neuropeptide Y
p.o.	per os
PASP	pulmonary artery systolic pressure
PCNA	proliferating cell nuclear antigen
PD	pharmacodynamic
PEM	piecewise exponential model
PK	pharmacokinetic
PP/2	Per Protocol (population)/year 2
PT	preferred term
PWG	pathology working group
QD	once daily
RBC	red blood cell (count)
RDP	Returning Dropout population

RR	relative risk
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
S-D	Sprague-Dawley
SDV	subjective drug value
SFU	sulfonylurea
SMD	standardized mean difference
SMQ	Standardised MedDRA Query
SNRI	selective norepinephrine reuptake inhibitors
SOC	system organ class
SSQ	subjective sensation questionnaire
SSRI	selective serotonin reuptake inhibitors
SULT	sulfotransferase
T3	triiodo-thyronine
T4	thyroxine
TBG	thyroxine-binding globulin
TR	tricuspid regurgitation
TSH	thyroid stimulating hormone
U.S.	United States
UGT	UDP-glucuronosyltransferases
V/F	volume of distribution
VAS	visual analogue scale
WBC	white blood cell (count)
α-MSH	α-melanocyte stimulating hormone

1 EXECUTIVE SUMMARY

INTRODUCTION

Arena Pharmaceuticals, Inc. is seeking approval of lorcaserin hydrochloride 10 mg twice daily for weight management. The proposed indication is as follows:

> Lorcaserin 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 ≥ 30 kg/m^2, or overweight patients with a body mass index ≥ 27 kg/m^2 in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea, type 2 diabetes).

The recommended clinical dose of lorcaserin will be 10 mg twice daily (BID) and the intended patient population is adults, ages 18 and older.

The efficacy and safety of lorcaserin for weight loss are supported primarily by the year 1 data from three phase 3 trials that included 7190 non-diabetic patients (APD356-009, a 2-year trial, and APD356-011, a 1-year trial) and 604 patients with type 2 diabetes (APD356-010, a 1 year study). Efficacy and safety for maintenance of weight loss are supported by the year 2 data from phase 3 trial APD356-009.

OVERVIEW OF RELEVANT REGULATORY HISTORY

Arena Pharmaceuticals, Inc. submitted a New Drug Application (NDA 22-529) on 22 December 2009, seeking approval of lorcaserin hydrochloride 10 mg tablets for weight management. The application was supported by 2 completed pivotal clinical trials in the non-diabetic population; a third phase 3 trial in patients with type 2 diabetes was ongoing at the time of the initial submission. The Agency issued a Complete Response Letter on October 22, 2010, requesting certain additional preclinical and clinical information which focused on 4 main issues: (1) mammary tumor findings in female rats in a carcinogenicity study, (2) astrocytoma in male rats, (3) a request to include data from the phase 3 clinical trial APD356-010 in the application; and (4) the conduct of 2 rodent experiments related to the assessment of abuse potential. Arena submitted a Complete Response to address the FDA's requests on 27 December 2011.

ORGANIZATION OF THIS BRIEFING DOCUMENT

In addition to information previously submitted with the original NDA for lorcaserin, this briefing document focuses on new data and analyses generated to address the issues raised by the FDA in their Complete Response Letter. Clinical efficacy and safety data are first presented for the three pivotal trials, in a format that allows side-by-side comparison of the previously submitted data in the non-diabetic population and the newly submitted data from study APD356-010 in patients with type 2 diabetes. New statistical analyses of pooled echocardiographic data from all three of these clinical studies and human serum prolactin data from studies APD356-010 and APD356-011 are included in the clinical safety section. This is followed by preclinical information as it addresses each Completed Response item. Information that was submitted with the original NDA, including a summary of nonclinical pharmacology and toxicology, and an overview of clinical pharmacology trials is provided as background information in the appendices to the briefing document.

OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

The safety database for the 19 trials included in the NDA includes 5425 subjects/patients who received lorcaserin (Figure 1). Of these, 333 were healthy adult subjects; 99 were subjects in special populations exposed to lorcaserin at doses ranging from 0.1 mg to 60 mg; and 4993 were obese or overweight adult patients exposed to lorcaserin at doses ranging from 1 mg to 15 mg QD and 10 mg BID in Phase 2 and Phase 3 trials. Actual exposures of 1 year or greater were evaluated in 467 patients at 10 mg QD and 1567 patients at 10 mg BID; 426 patients were exposed to lorcaserin 10 mg BID for 2 years.

The 7784 patients in the safety population (all patients exposed to study drug or placebo) of the Phase 3 program included 6173 (79.3%) women and 1611 (20.7%) men. The majority (66.5%) were Caucasian. African American and Hispanic patients were well-represented (19.4% and 11.8%, respectively). Lorcaserin was administered to approximately 135 people age 65 or older during clinical development. The development program did not include children or adolescents. Lorcaserin has not been studied in pregnant or lactating women.

Phase 1 trials of lorcaserin were conducted in healthy volunteers to assess the safety and pharmacokinetic (PK) properties of lorcaserin (Section 7), as well as psychomotor and cognitive effects, food intake, and self-rated hunger and appetite. The trials guided dose selection for Phase 2 proof of concept studies; absorption, distribution, metabolism, and excretion (ADME) evaluation; drug interaction studies; and special safety studies that included a thorough ECG trial and an abuse liability trial. Reduced tolerability was seen at doses ≥ 20 mg. Preclinical evaluations showed that lorcaserin was not an inducer of CYP enzymes, and a potential inhibitor of CYP2D6. Lorcaserin was neither a substrate nor an inhibitor of P-glycoprotein. Accordingly, formal clinical drug-drug interaction studies were limited to testing the potential impact of lorcaserin on the metabolism of the model CYP2D6 substrate dextromethorphan.

Lorcaserin is extensively metabolized through multiple enzymatic pathways predominantly in the liver, and its metabolites are then cleared mainly by renal excretion. Hence, the PK properties of lorcaserin were evaluated in patients with mild or moderate hepatic impairment, and separately in patients with renal impairment ranging from mild to end stage (with or without dialysis). A PK study in the elderly was also conducted.

Lorcaserin exposure was determined at steady state in the cerebrospinal fluid. The brain to cerebrospinal fluid (CSF) ratio measured in mice, rats, and monkeys was essentially a constant, and was assumed to be equivalent for humans. Using this assumption, measured CSF lorcaserin concentrations predict that lorcaserin brain exposure is 1.7 times plasma exposure at steady state.

Phase 2 trials APD356-003 and APD356-004 provided proof of concept for weight loss efficacy in the absence of lifestyle modification and generated initial echocardiographic heart valve safety data. These trials also guided dose selection for the Phase 3 trials. Study APD356-014 evaluated the effects of lorcaserin on energy intake and energy expenditure.

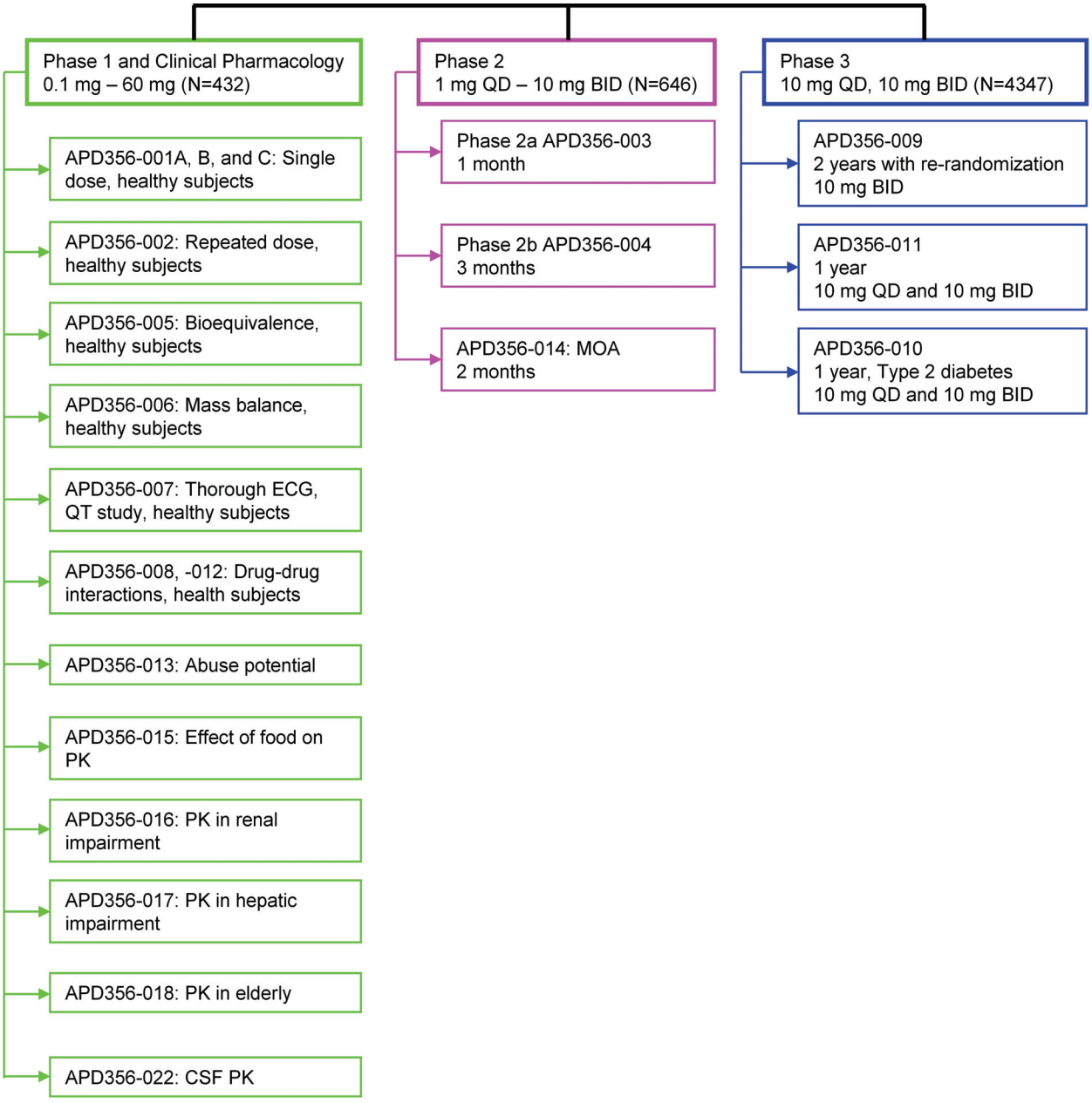
The well controlled Phase 3 trials, APD356-009, APD356-010, and APD356-011, evaluated the safety and efficacy of lorcaserin for weight management during 1 or 2 years of administration against a background of standardized lifestyle modification. Efficacy assessments included a

panel of cardiometabolic parameters, quality of life, and concurrent use of medications to treat weight-related co-morbid conditions. Further, these trials generated an extensive echocardiographic database used to evaluate whether lorcaserin use was associated with cardiac valve liability. The design and size of the Phase 3 trials, including the parameters of echocardiographic safety monitoring, were based on discussions with the FDA.

Thorough ECG/QT safety study. This study evaluated the highest anticipated clinical dose (15 mg at the time the trial was planned), and a supratherapeutic dose of lorcaserin (40 mg) given QD for 7 days. Lorcaserin did not increase QT or QTc interval; the positive control moxifloxacin induced the expected increase in QT and QTc.

Abuse liability study. Lorcaserin acts in the central nervous system (CNS), and was therefore evaluated for abuse potential. Because the adverse event (AE) profile for lorcaserin shared some similarities to that of zolpidem (schedule IV), zolpidem was selected as a primary comparator. Ketamine (schedule III) was selected for use as a secondary comparator to address the theoretical risk of $5HT_{2A}$-mediated hallucinogenic activity. Lorcaserin single doses of 20, 40, and 60 mg were used. Lorcaserin's abuse potential was low, with ratings related to overall drug liking and likelihood to use again lower than those of zolpidem or ketamine. Subjects disliked doses of 40 mg and 60 mg for recreational purposes.

Figure 1. Lorcaserin Exposure: Clinical Development Overview



SUMMARY OF EFFICACY

Lorcaserin produced significant dose-related weight loss relative to placebo in controlled clinical studies. In addition, continued use of lorcaserin following weight reduction in Year 1 was efficacious for maintaining weight loss as compared to placebo. The weight reduction was associated with significant improvements in cardiovascular risk factors that included glycemic control, lipids, blood pressure, insulin resistance, waist circumference, total body fat, c-reactive protein (CRP), and quality of life.

Weight Loss in Non-Diabetic Patients

Two Phase 3 studies (APD356-009, a 2-year study, and APD356-011, a 1-year study) evaluated lorcaserin used concurrently with a supervised behavioral modification program that included a reduced-calorie diet and an exercise program (Section 3.9.1).

In the pooled dataset, 47.1% of patients taking lorcaserin 10 mg BID lost ≥ 5% of baseline bodyweight at 1 year, compared to 22.6% of patients taking placebo ($p < 0.001$ using a modified intent-to-treat [MITT] analysis with last observation carried forward imputation for missing values [LOCF]). Lorcaserin 10 mg BID caused significantly greater mean weight loss ($5.8 \pm 0.1\%$) than placebo ($2.5 \pm 0.1\%$; $p < 0.001$). A greater proportion of patients taking lorcaserin 10 mg BID achieved ≥ 10% weight loss from baseline at Year 1 (22.4%) compared to the placebo group (8.7%; $p < 0.001$). The 10 mg QD dose was included only in Study APD356-011, and a dose response effect on body weight was evident.

Lorcaserin demonstrated greater efficacy among patients who completed 1 year of study participation (Completers) as compared to the MITT/LOCF analyses. The ≥ 5% weight loss level was met by 63.9% and 33.5% of the lorcaserin BID and placebo groups, respectively ($p < 0.001$), with mean weight losses of 7.9% and 3.7%, respectively ($p < 0.001$).

Lorcaserin was also superior to placebo for weight loss according to a panel of sensitivity analyses that evaluated the intent-to-treat population (ITT), a per-protocol population (PP), and a population of all patients with a Week 52 body weight, even if they had withdrawn from the study and returned only for the weight measurement ([RDP/Wk52], Section 3.9.1). Similarly, various imputation methods, including baseline observation carried forward (BOCF), multiple imputation and repeated measures analysis, confirmed the results of the pre-specified primary efficacy analysis.

Weight Loss in Patients with Type 2 Diabetes Mellitus

Obese and overweight patients enrolled in study APD356-010 had type 2 diabetes that was inadequately controlled by metformin, sulfonylurea (SFU), or both. Lorcaserin was associated with significantly greater weight loss than was placebo, with 44.7% on lorcaserin 10 mg QD, 37.5% on lorcaserin 10 mg BID and 16.1% on placebo achieving ≥ 5% weight loss at 1 year ($p < 0.001$ for each vs. placebo, MITT/LOCF). Mean weight loss was 5.0% with lorcaserin QD, 4.5% with lorcaserin BID and 1.5% with placebo ($p < 0.001$ for each vs. placebo).

Lorcaserin 10 mg BID met the efficacy benchmark defined by the *2007 draft Guidance for Industry relevant to the development of weight management drugs* in each of the three individual studies and in the pooled analyses.[1]

Weight Loss Maintenance

Patients who remained in the study at the end of Year 1 of the 2-year APD356-009 trial were re-randomized to participate for a second year. In blinded fashion, patients on placebo in Year 1 were continued on placebo in Year 2, and patients on lorcaserin BID in Year 1 were re-randomized in a 2:1 ratio to either remain on lorcaserin BID for Year 2 or switch to placebo. The primary efficacy endpoint for Year 2 was the proportion of patients who had lost ≥ 5% of baseline body weight at Year 1 maintaining at least 5% weight reduction from baseline at Year 2. Patients who had switched from lorcaserin to placebo at Week 52 were compared to patients who remained on lorcaserin during both years. A significantly larger proportion of patients who remained on lorcaserin (67.9%) maintained at least 5% weight loss as compared to patients who switched to placebo (50.3%; $p < 0.0001$). Mean weight loss from baseline to the end of Year 2 was significantly greater in the group assigned to lorcaserin for 2 years (5.8%) as compared to the group assigned to placebo (2.1%) (MITT/LOCF for Year 2).

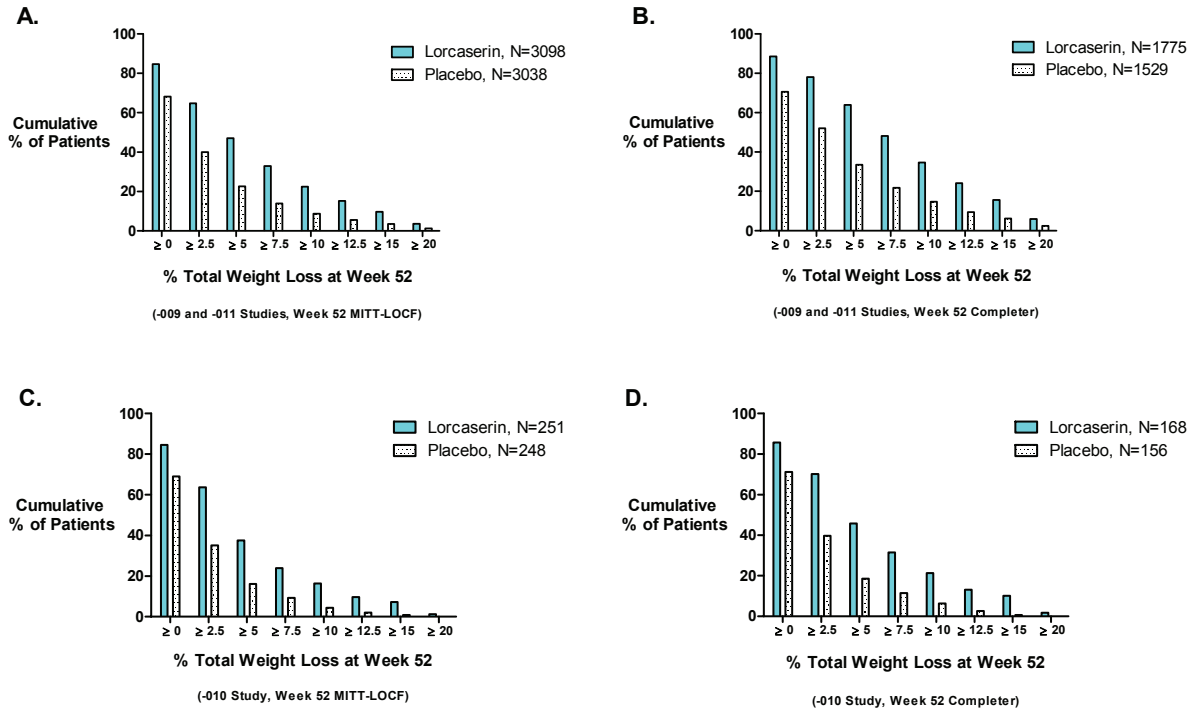
Weight Loss in Non-Diabetic and Diabetic Patients: Additional Analyses of Efficacy

As is true of any weight loss drug, individual responses vary. To determine how the patients most responsive to lorcaserin fared, Week 52 weight loss was determined for the upper quartile of lorcaserin BID-treated patients using both MITT/LOCF and Completer analyses in pooled phase 3 studies of non-diabetic patients (APD356-009 and -011) and in patients with type 2 diabetes (APD356-010). In the non-diabetic population, the quartile with the greatest Week 52 percent weight loss lost on average ~13 kg, or ~29 lbs, by MITT/LOCF analysis and ~16 kg, or ~35 lbs, by Completer analysis. In study APD356-010, the top quartile of lorcaserin BID patients lost on average ~11 kg, or ~24 lbs by MITT/LOCF analysis and ~13 kg, or ~29 lbs, by Completer analysis.

Recognizing the large number of discontinuing patients typical of one year weight loss trials, a conservative analysis was undertaken which utilized all patients randomized regardless of whether they took study drug or returned for a baseline visit (the ITT population) and which did not require imputation assumes all dropouts are nonresponders): the proportion of the ITT population who remained in the study for 52 weeks and achieved responder status at this timepoint. This analysis conservatively assumes that all patients not completing 52 weeks are treatment failures. In the pooled studies of the non-diabetic patients, 35.7% (1143 of 3198) of patients randomized to lorcaserin 10 mg BID completed the study and were categorized as responders; these patients achieved a mean percent weight loss of 11.2%. In the APD356-010 study, 30.5% of patients randomized to lorcaserin 10 mg BID (78 of 256) completed the study and were categorized as responders; mean percent weight loss in this group was 10.4%. The amount of weight loss achieved by placebo responders was similar, but the proportion of responders was approximately half of that in the lorcaserin BID groups, 16.2% in the pooled non-diabetic patient population (APD356-009 and -011) and 11.5% in the type 2 diabetic population (APD356-010). These results demonstrate that lorcaserin is highly effective in a large subgroup of patients taking the medication.

Lastly, the Figure 2 below display the proportions of patients achieving various categorical weight loss levels at Week 52 by both MITT/LOCF and Completer analyses for the combined non-diabetic (APD356-009 and -011) and the diabetic population (APD356-010). More than 80% of lorcaserin BID patients had 0 to 2.4% weight loss from baseline, and at each greater categorical level thereafter, approximately 2-3 times as many lorcaserin BID patients as placebo patients achieved each threshold of weight loss.

Figure 2. Categorical Weight Loss Achieved by Lorcaserin BID and Placebo Patients at Week 52 by MITT/LOCF and Completer Analyses of the Phase 3 Non-diabetic and Diabetic Populations



Secondary Endpoints Including Cardiovascular Risk Factors and Metabolic Parameters

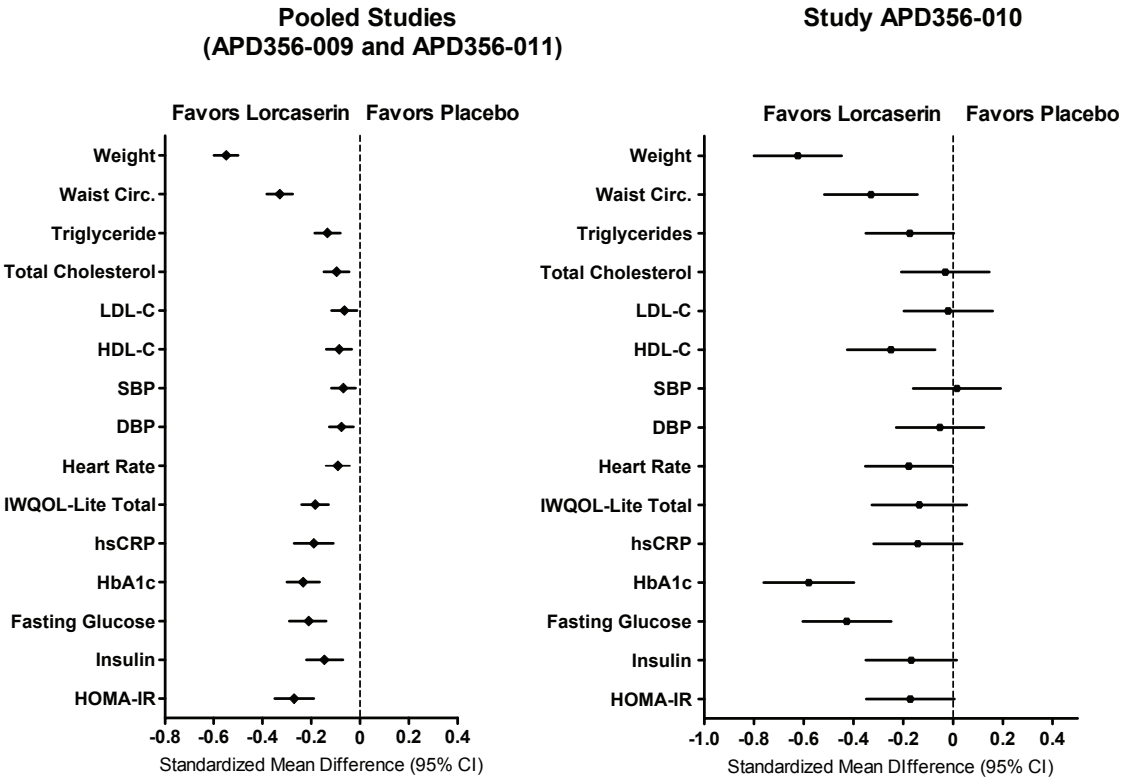
Lorcaserin was associated with favorable effects relative to placebo on BMI, waist circumference, body fat, lipids, blood pressure, heart rate, quality of life scores on IWQOL-Lite, and insulin sensitivity among non-diabetic patients (Figure 3). Similarly, patients with type 2 diabetes experienced favorable changes relative to placebo in glycemic control, waist circumference, body fat, lipids, diastolic blood pressure, quality of life, and hsCRP after 52 weeks of lorcaserin 10 mg BID (Figure 3). Note that the single point estimate that fell within the "favors placebo" range, systolic blood pressure in the APD356-010 study, did not represent an increase in blood pressure for the lorcaserin BID group; systolic blood pressure decreased from baseline in both groups, but the decrease in the lorcaserin BID group was slightly smaller (by 0.1 mmHg) than in the placebo group.

Among the largest lorcaserin effects were the significant decreases in HbA1c and fasting glucose in patients with type 2 diabetes. These changes were accompanied by decreases in total daily doses of anti-hyperglycemic agents.

Changes in some individual parameters were small; however, multiple concurrent changes resulted in net benefit with respect to total use of medications for hypertension, use of medications for dyslipidemia, and Framingham risk scores.

The effect sizes for primary and secondary endpoint results are summarized in Figure 3 as standardized mean differences for the Phase 3 data, and are presented in detail in Section 3.9.2.

Figure 3. Effect Sizes for Primary and Secondary Endpoints in Phase 3 Studies (Lorcaserin 10 mg BID vs. Placebo)



Abbreviations: SBP=systolic blood pressure; DBP=diastolic blood pressure.

Lipids and body weight are percentage change from baseline.

SMD and confidence interval were computed from the least square means of LOCF value at Week 52 and pooled standard deviations produced by ANCOVA model with treatment as factor and baseline parameter value as covariate.

SUMMARY OF SAFETY

At the proposed clinical dose of 10 mg BID, the most common adverse events reported by more patients on lorcaserin than placebo were headache, dizziness, nausea, fatigue, and dry mouth. All tended to be mild or moderate in intensity and self-limited. None tended to recur during continued dosing once the initial event had resolved.

Overview of Adverse Events

Events that were observed in preclinical toxicology studies in rats were not observed during clinical trials. In particular, lorcaserin was not associated with neoplasia or with evidence of hepatic toxicity. Lorcaserin also did not cause clinically significant increases in serum prolactin.

No patient subgroup with increased or differing susceptibility to lorcaserin-associated adverse events was identified.

No patient died while taking lorcaserin during clinical development. The incidence of serious adverse events (SAEs) was relatively low, and only gallbladder related events (which are known to be increased by weight loss) consistently exceeded the placebo incidence.

Evaluation of Depression and Suicidal Ideation

The incidence of adverse events related to depression, as identified using the "narrow" Standard MedDRA Query for depression (terms specifically related to depression), was similar in the placebo and lorcaserin groups in all Phase 3 trials. However, although the incidences were similar, study discontinuation due to an adverse event of depression occurred slightly more often in the lorcaserin groups than in the placebo groups. There was no apparent reason for this difference. The events were of similar severity in the two groups, and similar numbers of subjects discontinued taking an SSRI or SNRI. Total scores on the Beck Depression Inventory-II (BDI-II) instrument and changes in the BDI-II scores did not differ among treatment groups.

Suicidal ideation was evaluated by routine adverse event reporting and by analysis of Item #9 of the BDI-II, which asks about suicidal thoughts. Responses indicating suicidal thoughts occurred with similar incidences in the placebo and lorcaserin groups. Two adverse events of suicide attempt were reported; one occurred in a patient taking lorcaserin; the second occurred in a patient taking placebo.

Evaluation of Echocardiographic Valvular Insufficiency

Cardiac valves and pulmonary artery pressure were monitored using serial echocardiograms in the Phase 3 trials. The primary endpoint was incidence of new FDA-defined valvulopathy (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation) from baseline to Week 52, and the primary pre-specified statistical analysis was a non-inferiority analysis of the risk difference between placebo and lorcaserin 10 mg BID, ruling out a 50% or greater increase in the projected rate of valvulopathy in the control group (2.5%). At 1 year, 2.04% of patients in the placebo group developed new echocardiographic criteria for valvulopathy, compared to 2.37% of patients in the lorcaserin 10 mg BID group. Lorcaserin was non-inferior to placebo

using a risk-difference approach. The phase 3 program was not powered for Week 52 relative risk assement and did not contain enough events of valvulopathy for these assessements. Nevertheless, Week 52 risk ratios were calculated for the MITT/LOCF and Completer populations. Relative risk for the MITT/LOCF population was 1.16, with an upper bound on the 95% confidence interval of 1.67, and for the Completer population, 1.03, with an upper 95% confidence interval bound of 1.47. If all echo data from the 2 year phase 3 program are included, there are a sufficient number of valvulopathy events to provide at least 80% power for risk ratio assessments. Time to event analysis were conducted using the Piecewise Exponential and Cox Proportional Hazards models, and average prevalence of valvulopathy over the four 6-month time intervals of the 2 year program was assessed (Generalized Estimating Equation). Using these adequately powered approaches provided relative risks or hazard ratio point estimates of 1.08 to 1.16, with upper 95% confidence intervals <1.5 (Figure 4). Pergolide and cabergoline, two agents known to be associated with cardiac valvular disease in humans, are provided for comparison.[2]

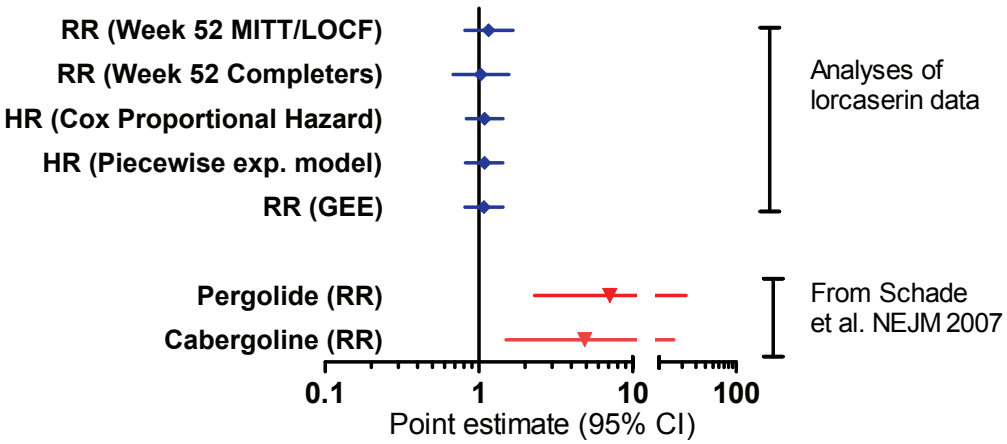
Due to the previous observation of a negative correlation between BMI and cardiac valvulopathy in the Framingham Heart Study (Singh, 1999), logistic regression analysis of the phase 3 echocardiograpy data was undertaken to determine if there were a relationship between weight loss and the incidence of cardiac valvulopathy. The analysis revealed significant negative associations between percent change in body weight or change in BMI and incidence of FDA-defined valvulopathy at Week 52. In other words, the analysis of the pooled Phase 3 data predicted that the apparent incidence of echocardiographic valvulopathy would increase with greater weight loss. The predicted risk of valvulopathy associated with a 5% weight loss increases 1.15 times; the predicted risk associated with a decrease in BMI of 2 kg/m^2 increases 1.16 times. Differential weight loss may therefore contribute to point estimates of risk that slightly exceed unity.

Multiple other observations suggest that there is no difference between rates of valvulopathy between the lorcaserin and placebo groups, including the finding of an imbalance in only one of the two large phase 3 studies, a lack of dose response, and a lack of relative time response. APD356-010 did not have enough patients per group to be considered independently, with each patient constituting ~0.4% of the BID and placebo groups. The incidences of valvulopathy at Week 52 for the placebo and lorcaserin BID groups were 2.3% and 2.7%, respectively, in APD356-009 (3182 patients enrolled) and 2.0% vs. 2.0% in APD356-011 (4008 patients enrolled).

In APD356-011, which included the QD dosing, the Week 52 incidence of valvupathy was 1.4% in this dose group, lower than the 2.0% observed in the placebo and BID groups. And finally, rates of valvulopathy were slightly lower in the lorcaserin BID group than the placebo group during Year 2 of APD356-009 (Week 76: 3.1% placebo, 2.9% lorcaserin BID; Week 104: 2.7% placebo, 2.6% lorcaserin BID).

Mean pulmonary artery systolic pressure was not affected by lorcaserin.

Figure 4. Risk Analyses for FDA-Defined Valvulopathy; Phase 3 Studies



RR, relative risk; HR, hazard ratio; GEE, generalized estimating equation

Vital Sign, Laboratory and ECG Evaluations

Lorcaserin 10 mg BID did not increase mean heart rate or mean blood pressure in any clinical study.

No lorcaserin-related laboratory trends were identified in clinical trials. No cases meeting Hy's Law criteria were observed in any treatment group. Indeed, lorcaserin was associated with small mean decreases relative to placebo in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase.

A thorough ECG/QT study showed no effect of lorcaserin to increase the QTc interval. No significant effects on other ECG intervals were identified in a formal ECG study.

Dose Adjustment

No circumstances that require dose adjustment were identified.

Exposures of lorcaserin metabolites M1 (lorcaserin sulfamate) and M5 (*N*-carbamoyl glucuronide of lorcaserin), but not lorcaserin itself, were increased in patients with calculated (Cockcroft-Gault) creatinine clearance ≤ 30 mL/min as compared to those in subjects with normal renal function. In the absence of long-term studies in patients with severe or end stage renal disease, lorcaserin should not be used in patients with a creatinine clearance ≤ 30 mL/min.

Dose Selection

Lorcaserin's efficacy was dose-related among non-diabetic patients in Phase 2 study APD356-004 and in Phase 3 study APD356-011. In patients with type 2 diabetes, the once daily (QD) and twice daily (BID) doses had essentially equivalent efficacy for weight loss. Recruitment to the QD dose was terminated early, and only 95 patients were randomized to this arm. Other individual endpoints varied in dose relatedness in the APD356-010 study, but

composite analyses such as changes in Framingham risk scores or changes in use of concomitant medications for hypertension suggested that the BID dose may have greater net benefit than the QD dose.

The safety and tolerability of the 10 mg QD and 10 mg BID doses were comparable. No demographic subgroup was identified in which the lower dose was preferable or generally better tolerated.

Hence, given the greater efficacy of the 10 mg BID dose in the overall Phase 3 population, the recommended clinical dose is 10 mg BID.

CONTENT OF COMPLETE RESPONSE LETTER

The FDA's Complete Response Letter focused on 4 main issues: (1) mammary tumor findings in female rats in a 2-year carcinogenicity study, (2) astrocytoma in male rats in the 2-year carcinogenicity study, (3) a request to include data from the phase 3 clinical trial APD356-010 in the application; and (4) the conduct of 2 preclinical experiments related to the assessment of abuse potential. Arena provided responses to all items.

The specific requests, as enumerated in the Complete Response Letter are paraphrased as follows:

1. Diagnostic uncertainty in the classification of mammary masses in female rats in the 2 year rat carcinogenicity study
    - Provide details of all slides from female rats that contributed to mammary tumor incidence data in interim and final reads
    - Convene a pathology working group (PWG) to re-adjudicate all mammary and lung tissues from female rats
2. Unresolved exposure-response relationship for lorcaserin-emergent mammary adenocarcinoma

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

3. Unidentified mode of action and unclear safety margin for lorcaserin-emergent brain astrocytoma
    - Provide information about the distribution of lorcaserin to the CNS in animals and humans to provide a better estimate of exposure margins
    - Demonstrating a substantial margin to clinical exposure is unnecessary if mode of action shown to be reasonably irrelevant to human risk is shown
4. In reference to an assessment of marginal weight loss efficacy of lorcaserin 10 mg twice a day relative to placebo in overweight and obese individuals without type 2 diabetes
    - Submit the study report for study APD356-010

- If concerns regarding clinical relevance of mammary tumor and astrocytoma in rats cannot be alleviated, additional clinical studies may be required

5. (In reference to two studies of abuse-related behaviors in rats, and the previous recommendation that lorcaserin be placed into Schedule IV of the Controlled Substances Act) Repeating these studies and submitting data in your complete response to this letter may lead to a different recommendation
6. Include a safety update

Complete Response Item 1: Diagnostic uncertainty in the classification of mammary masses in female rats

A panel of 5 veterinary pathologists not affiliated with the applicant reviewed and adjudicated all relevant tissue slides derived from female animals in the previously-conducted 2-year rat carcinogenicity study in a blinded fashion. The adjudication focused on malignant mammary adenocarcinoma and benign mammary fibroadenoma. Importantly, these tumors are genotypically distinct, and benign fibroadenoma rarely if ever progresses to adenocarcinoma in the rat or human. Initial diagnoses of mammary adenocarcinoma were unanimous in 92.5% of cases, and mammary fibroadenoma diagnoses were unanimous in 97.1% of cases. The high level of consensus supports analyzing the data for malignant mammary adenocarcinoma and benign mammary fibroadenoma separately.

The proportion of rats with mammary adenocarcinoma was lower in each lorcaserin dose group following the PWG re-adjudication as compared with the original report (Table 1). In both analyses, the incidence of mammary adenocarcinoma was significantly increased over vehicle control only at the lorcaserin high dose (100 mg/kg/day) providing a safety margin of 24 times human exposure for incidence. Benign mammary fibroadenoma was significantly increased over vehicle control at all lorcaserin doses tested in both the original report and in the PWG re-adjudicated analysis. Some mammary tumors were re-classified as either fibroadenomas or adenomas in the re-adjudicated dataset; no diagnoses of adenoma were made in the original report. The PWG was also tasked with identifying whether pulmonary metastases were derived from a primary mammary malignancy or another source, a distinction not made in the original report. The panel reported an "equivocal increase" in mammary adenocarcinoma metastatic to lung in the lorcaserin mid and high dose treatment groups relative to vehicle control (Table 1). The PWG, considering incidence, multiplicity, onset rate, and lung metastases, concluded that mammary adenocarcinoma was treatment related at the high dose, establishing a safety margin of 24 fold for this tumor. Mammary fibroadenoma was found to be treatment related at all lorcaserin doses, with no safety margin established.

Table 1. Mammary Gland and Lung Tumor Incidence – Summary of Original Report and the PWG Re-adjudicated Findings

	Original Report				PWG Re-adjudication			
Dose (mg/kg/day)	**0**	**10**	**30**	**100**	**0**	**10**	**30**	**100**
Number of Female Rats	**65**	**65**	**65**	**75**	**65**	**65**	**65**	**75**
Mammary Gland:								
Mammary Adenocarcinoma	28	34	35	60	26	21	24	51
Percent incidence	43.08%	52.31%	53.85%	80%	40%	32.31%	36.92%	68%
Fisher Exact Test P value	--	0.3800	0.2923	<0.0001	--	0.4655	0.8570	0.0012
Multiplicity, n	nd	nd	nd	nd	7	6	6	17
Multiplicity, %	nd	nd	nd	nd	10.77%	9.23%	9.23%	22.67%
Onset rate (p value)	<0.0001				<0.0001			
Peto Test (p value)	0.9025				0.5135			
Mammary Fibroadenoma	20	47	53	45	24	54	55	51
Percent incidence	30.77%	72.31%	81.54%	60%	36.92%	83.08%	84.62%	68.00%
Fisher Exact Test P value	--	<0.0001	<0.0001	0.0007	--	<0.0001	<0.0001	0.0003
Multiplicity, n	nd	nd	nd	nd	7	39	51	41
Multiplicity, %	nd	nd	nd	nd	10.77%	60.0%	78.46%	54.67%
Onset rate (p value)	<0.0001				<0.0001			
Peto Test (p value)	0.9952				0.6479			
Mammary Adenoma					1	2	5	4
Percent incidence	0	0	0	0	1.54%	3.08%	7.69%	5.33%
Fisher Exact Test (p value)					--	1.0000	0.2078	0.3725
Onset rate (p value)	nd	nd	nd	nd	0.3260			
Peto Test (p value)	nd	nd	nd	nd	0.1905			
Mammary Carcinosarcoma	0	0	0	1	0	0	0	1
Percent incidence	0%	0%	0%	1.33%	0%	0%	0%	1.33%
Fisher Exact Test (p value)	--	--	--	--	--	1.0000	1.0000	1.0000
Lung:								
Carcinoma, secondary[a]	0	4	9	6	0	3	4	2
Adenocarcinoma, secondary[b]	nd	nd	nd	nd	0	1	5	5

nd, not determined

[a] Carcinoma, secondary in the original report refers to tumors of both mammary and non-mammary origin

[b] Adenocarcinoma, secondary refers only to tumors of mammary gland origin. Carcinoma, secondary in the PWG re-adjudication refers only to tumors not of mammary gland origin

Complete Response Item 2. Unresolved exposure-response relationship for lorcaserin-emergent mammary adenocarcinoma. Demonstrate that the apparent increase in aggressiveness of adenocarcinoma in rats administered lorcaserin is reasonably irrelevant to human risk assessment.

Aggressiveness

This request was based on possible increased incidence of lung metastases, earlier onset, increased number of animals with more than one primary tumor, and shortened survival among low- and/or mid-dose rats with mammary adenocarcinoma, despite overall incidences that did not differ statistically from control in the original study. Arena addressed the request in two ways: (1) analyzed indicators of tumor aggressiveness using the PWG re-adjudicated data; (2)

further tested the hypothesis that mammary tumors in female rats were caused by a mechanism that is not relevant to human risk.

Mammary adenocarcinoma aggressiveness was evaluated by multiplicity of primary tumors, onset latency, incidence of metastases, and time to death due to adenocarcinoma. Multiplicity, onset latency and time to death specifically attributed to mammary adenocarcinoma by the study pathologist differed significantly from control only in the lorcaserin high dose (100 mg/kg/day) group. The incidence of metastases to lung, when evaluated as the proportion of animals with an underlying mammary adenocarcinoma, exceeded historical control values only at the lorcaserin mid-dose. The weight of evidence suggests that the mammary adenocarcinomas that occurred in the female rats receiving lorcaserin did not have a greater metastatic potential than the spontaneously occurring mammary adenocarcinoma in control rats.

The PWG, considering incidence and measures of aggressiveness, concluded that mammary adenocarcinoma was treatment related only at the high dose, providing a safety margin of 24 times human exposure for both incidence and aggresiveness.

Mechanism underlying mammary tumors in rats

Mammary tumors occur spontaneously in female rats, with lifetime incidences up to 70% in the Sprague-Dawley (S-D) strain that was used in the lorcaserin carcinogenicity study. S-D rats are also exquisitely sensitive to hormone-induced mammary tumors, especially those associated with prolactin hyperstimulation. In contrast, prolactin is generally considered not relevant to tumorigenesis of human breast cancer, and this tumor has not been definitively shown to result from increased prolactin.[3] 5-HT_2 receptor agonists are known to increase pituitary prolactin release.[4] Arena therefore hypothesized that lorcaserin increased the incidence of mammary tumors in female rats through increased prolactin effects. Limited supportive data were submitted with the original NDA, but were deemed insufficient. Arena conducted additional experiments using intact female rats to evaluate whether lorcaserin at the doses employed in the rat carcinogenicity study caused prolactin-dependent mammary changes.

Acute administration of lorcaserin increased circulating prolactin in intact female rats at all doses used in the 2-year carcinogenicity study (10, 30 and 100 mg/kg). To determine longer term effects, a 90 day experiment was conducted, with weekly assessments at the predetermined t_{max} (time of maximal concentration) for prolactin. With daily dosing, the stimulatory effect on mean circulating prolactin on each day of assessment was diminished after approximately 2 weeks at the high dose, and a stimulatory effect was not seen at the lower doses. However, greater numbers of lorcaserin treated animals in all dose groups intermittently experienced high levels of circulating prolactin than negative controls, and average circulating prolactin over the 90 day experimental period for each animal was elevated by all doses, and significantly so for the low and high dose. In addition, pituitary prolactin content was significantly increased with all lorcaserin doses after 90 days of daily administration Histomorphological changes of the mammary gland that are characteristic of hormonal stimulation were increased significantly by lorcaserin over vehicle control after 90 days of daily dosing. Such changes are known to precede the development of mammary fibroadenoma and mammary adenocarcinoma in rats. In contrast, microscopic changes indicative of a genotoxic carcinogen were not observed. The

histomorphological changes were dependent on the pituitary (blocked by hypophysectomy), and were prolactin-mediated (blocked by a specific prolactin receptor antagonist).

The weight of evidence supports the hypothesis that lorcaserin caused mammary tumors in female rats by increasing prolactin effects on the mammary tissue. This rodent mechanism is not generally thought to represent increased risk of breast cancer in humans.

Complete Response Item 3: Unidentified mode of action and unclear safety margin for lorcaserin-emergent brain astrocytoma

In the 2-year carcinogenicity study, in male but not female rats, brain astrocytoma was increased at high dose and marginally increased at mid dose. In the original NDA, brain exposure in humans was directly extrapolated from animal data to estimate a safety margin. For the Complete Response, human brain exposure was extrapolated from human CSF exposure data. For non-human species, lorcaserin concentrations were directly measured in brain tissue, cerebrospinal fluid (CSF) and plasma at steady state. For humans, lorcaserin concentration versus time curves were constructed for CSF and plasma collected from healthy obese volunteers at steady state. Since the ratio of lorcaserin exposure in brain and CSF was relatively constant across preclinical species (mouse, rat, monkey), this ratio was therefore used to predict human brain exposure from the measured CSF exposure.

Using this approach, lorcaserin exposure in the brain of the male rat at the dose level revealing no evidence of astrocytoma finding (10 mg/kg/day) was approximately 70 times that in the human at the clinically relevant dose of 10 mg BID. Hence, the exposure margin for astrocytoma observed in male rats relative to humans at the maximum recommended dose is ~70.

Complete Response Item 4: The weight loss efficacy of lorcaserin 10 mg twice a day relative to placebo in overweight and obese individuals without type 2 diabetes is marginal

Two phase 3 trials of 7190 obese and overweight patients were submitted with the original lorcaserin NDA (APD356-009, APD356-011). Each of the trials met pre-specified primary efficacy endpoints, and lorcaserin 10 mg twice daily met the FDA's categorical weight loss benchmark for efficacy provided in the *Guidance for Industry Developing Products for Weight Management* (Draft; Revision 1, February 2007: the proportion of patients achieving at least 5% at the end of one year should be at least 35% and approximately twice the placebo rate). Rates of response based upon achievement of at least 5% weight loss at Week 52 were similar in these two trials; in the pooled dataset, 47.1% of lorcaserin BID patients vs. 22.6% of placebo patients achieved this endpoint. A third clinical trial, APD356-010, was submitted with the complete response. This phase 3 trial evaluated the safety and efficacy of lorcaserin for weight management in 604 patients with type 2 diabetes mellitus. Weight loss in the diabetic population is historically more difficult to achieve. Study APD356-010 also met the pre-specified primary efficacy endpoints, and the categorical 5% weight loss met the FDA's benchmark for weight loss efficacy.

In addition to significant weight loss, lorcaserin was associated with statistically and clinically significant improvement in glycemic control in patients with diabetes. At Week 52, from a

baseline of 8.1%, HbA1c decreased 0.9 units with lorcaserin twice daily, compared with 0.4 units in the placebo group ($p<0.001$). Fifty percent of patients on lorcaserin BID achieved HbA1c levels ≤7%, compared with 26% of patients taking placebo. The improvements in glycemic control with lorcaserin occurred despite decreased daily doses of anti-hyperglycemic medications, both absolute and relative to placebo.

Changes from baseline to Week 52 in total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, diastolic blood pressure, heart rate, hsCRP, waist circumference, body fat content, and scores on the Impact of Weight on Quality of Life questionnaire trended favorably with lorcaserin BID relative to placebo. Mean systolic and diastolic blood pressure and heart rate decreased from baseline in the lorcaserin BID group. These findings are consistent with and supportive of the significant decreases relative to placebo in lipids, blood pressure, heart rate, waist circumference, and IWQOL-Lite scores in the pooled analyses of studies APD356-009 and APD356-011.

The generally favorable changes in cardiovascular and metabolic risk factors and in quality of life associated with lorcaserin use in three phase 3 trials are consistent with requirements outlined in the 2007 FDA guidance for industry. In particular, the weight reduction and the robust improvement in glycemic control observed in patients with type 2 diabetes are significant and noteworthy for this patient population.

Complete response Item 5: (In reference to 2 studies of abuse-related behaviors in rats, and the previous recommendation that lorcaserin be placed into Schedule IV of the Controlled Substances Act) Repeating these studies and submitting data in your complete response to this letter may lead to a different recommendation.

Two behavioral studies in rats were repeated after incorporating technical modifications recommended by the FDA.

Rats exhibit stereotypical behaviors in response to 5-HT_{2A} or 5-HT_{2C} stimulation, which can be used as indicators of *in vivo* receptor activation. A study submitted with the original NDA evaluated the effects of lorcaserin and a positive control (DOI) on 5-HT_{2A} and 5-HT_{2C} specific behaviors. The study, which showed that lorcaserin at pharmacological doses preferentially elicited 5-HT_{2C} associated behaviors, was repeated for the complete response using DOM, a schedule I hallucinogen, instead of DOI, a schedule II hallucinogen, as the concurrent positive control. Dexfenfluramine, previously a schedule IV anorexigen, was used as a second positive control that was expected to elicit both 5-HT_{2A} and 5-HT_{2C} behaviors. Lorcaserin elicited predominantly 5-HT_{2C} associated behaviors, and more closely resembled dexfenfluramine than DOM.

A drug discrimination study was conducted to evaluate whether rats trained to recognize DOM generalized the trained behavior to saline or lorcaserin. The experiment submitted with the original NDA did not achieve >80% response rates to DOM throughout the experiment, potentially reducing the reliability of the results. The experiment was therefore repeated with protocol modifications to assure optimal response rates throughout the study. Collectively, these data demonstrated reliable discriminative control between saline and DOM, and showed that, as found with other serotonergic drugs like SSRIs and fenfluramine, lorcaserin occasioned only

partial generalization to the DOM-associated cue. This suggests that the subjective effects of lorcaserin differ qualitatively from DOM.

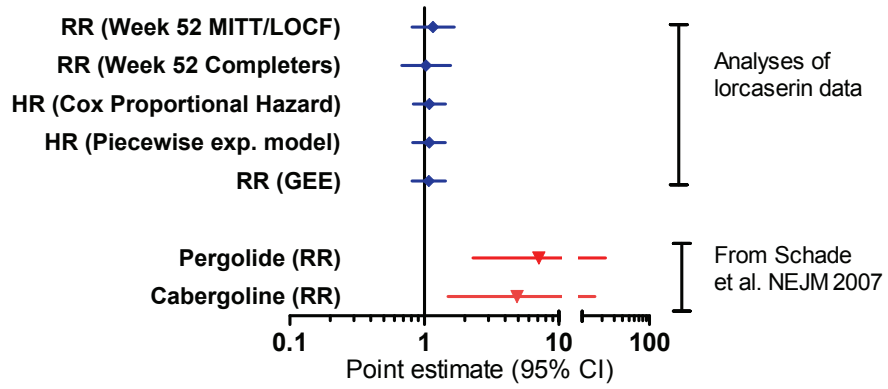
Complete Response Item 6: Include a safety update

Inclusion of study APD356-010 in the NDA did not meaningfully change the adverse event profile established by the initial two trials. The most frequent lorcaserin associated adverse events remained headache, dizziness, nausea, fatigue, and dry mouth. All tended to be mild to moderate in intensity and self-limited with continued lorcaserin use, and only headache occurred with a frequency greater than 5% of that in the placebo group.

Echocardiographic data from the three phase 3 trials, which included ~21,000 echos from ~7800 patients, were pooled and re-analyzed. The primary pre-specified endpoint was incidence of new FDA-defined valvulopathy (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation) from baseline to Week 52, and the primary pre-specified statistical analysis was a non-inferiority analysis of the risk difference between placebo and lorcaserin 10 mg BID, and the pivotal trial program was powered for this endpoint assuming a placebo rate of 2.5% provided by independent DSMB (data safety monitoring board) assessment of the ongoing, lead pivotal trial. At 1 year, 2.04% of patients in the placebo group developed new echocardiographic criteria for valvulopathy, compared to 2.37% of patients in the lorcaserin 10 mg BID group. Lorcaserin was non-inferior to placebo using a risk-difference approach with a pre-specified non-inferiority margin of 1.25% (no greater than 50% of the assumed placebo rate of 2.5%). Applying a risk ratio approach to the Week 52 LOCF data, the relative risk was 1.16 with an upper bound of the 95% confidence interval of 1.67. The relative risk for Week 52 completers was 1.03 with an upper bound of the 95% confidence interval of 1.57. The Week 52 data, however, did not provide adequate numbers of events for a relative risk approach. Supplementary echo analyses were performed using all available echo assessments through 2 years of testing to have adequate power for risk ratio analyses. These analyses were associated with ratio point estimates of 1.08 to 1.09, with upper 95% confidence intervals <1.5 (Figure 5). To provide context, data reported recently for pergolide and cabergoline, two agents known to be associated with cardiac valvular disease in humans are also plotted in Figure 5.[2] In addition, logistic regression analysis of the pooled phase 3 echo data demonstrated a negative association between weight loss and the incidence of valvulopathy at Week 52. The odds ratio for valvulopathy was 1.15 for patients achieving 5% weight loss as compared to a population with stable weight. These data are consistent with Framingham data, and due to differential weight loss, could substantially explain the slight imbalance in incidence of FDA valvulopathy in the two pooled populations, further offsetting the risk that there is any difference in rates between these two groups.[5]

Mean pulmonary artery systolic pressure was not affected by lorcaserin.

Figure 5. Risk Analyses for FDA-defined Valvulopathy; Phase 3 Studies



RR, relative risk; HR, hazard ratio; GEE, generalized estimating equation

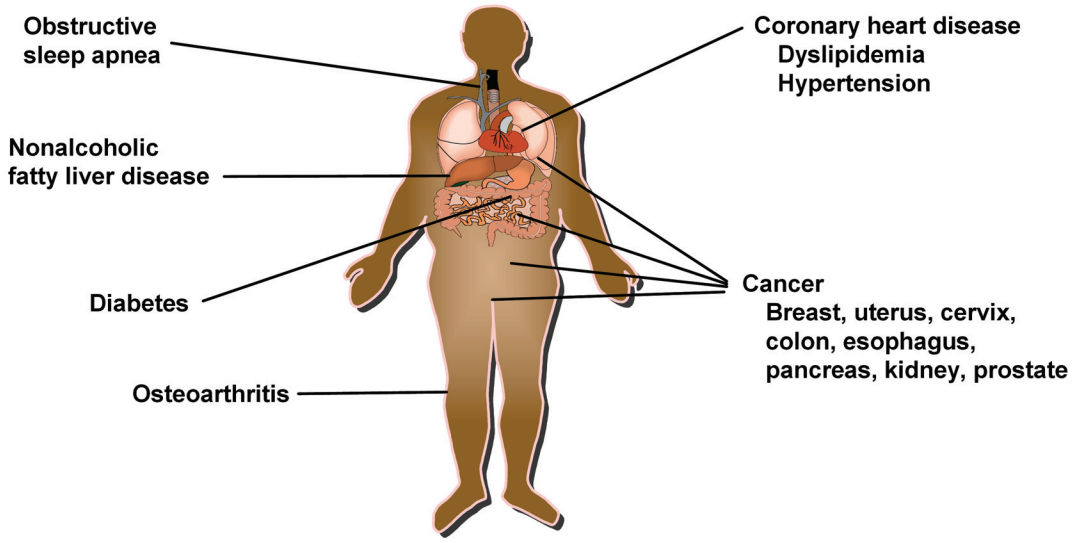
Serum prolactin concentrations measured in studies APD356-010 and APD356-011 were also pooled for re-analysis. The mean changes from baseline at Weeks 4, 12, 24 and 52 in serum prolactin were less than 1 ng/mL in all treatment groups, and lorcaserin did not increase the incidence of hyperprolactinemia. The updated clinical trial safety database did not suggest adverse lorcaserin effects on vital signs, laboratory values or abuse potential.

Inclusion of study APD356-010 in the new drug application strengthens lorcaserin's benefit to risk profile as compared with the original NDA: significant weight loss and improvement in metabolic parameters were demonstrated in patients with type 2 diabetes without new safety findings.

2 INTRODUCTION

Obesity has reached global epidemic proportions as the prevalence has nearly doubled from 20 years ago. Obesity is generally defined as a body mass index (BMI) of 30 kg/m^2 or higher. According to the World Health Organization, more than one billion adults worldwide are overweight, and at least 300 million are obese.[6] In the United States (US) alone, approximately 30% of adults and 15% of children and adolescents are considered obese, and many more are overweight.[7] Obesity is a major risk factor for life-threatening diseases such as type 2 diabetes, heart attack, stroke, and some forms of cancer, including breast and colon cancer (Figure 6), with an estimated 300,000 obesity-related deaths annually in the US.[8, 9] Lifespan is decreased by obesity in women and in men.[10] In fact, an analysis of NHANES data showed that people with BMI $\geq$ 35 kg/m^2 are predicted to lose up to 9-13 years of life as a result of obesity, equivalent to the effects of smoking and underscoring the severity of this epidemic.[10]

Figure 6. Obesity Increases the Risk of Multiple Other Health-related Conditions



Source: Burton BT, Foster WR, Hirsch J, VanItallie TB. Health implications of obesity: NIH consensus development conference. *Int. J. Obes. Relat. Metab. Disord*. 1985;9:155-169.

In an overweight or obese population, modest weight loss can improve existing comorbid conditions or reduce the risk of developing new comorbid conditions, including type 2 diabetes mellitus and hypertension.[11] The Diabetes Prevention Trial demonstrated a continuous decline in the 5-year risk of developing type 2 diabetes with weight loss, such that each kilogram of weight lost by glucose intolerant patients decreased the risk of developing diabetes by 16%. In that study, a 5-kg weight loss was associated with a hazard ratio for new diabetes of 0.42.[12] Moreover, in a 10-year follow up, the benefits of this weight loss on cumulative incidence of diabetes persisted despite significant weight regain.[13] Similarly, modest weight loss has consistently been shown to decrease blood pressure. The TAIM study demonstrated reductions in both systolic (-2.8 mmHg) and diastolic (-2.5 mmHg) blood pressure with a 4.7-kg weight loss

over 6 months.[14] The TONE study in older adults showed decreases in the incidence of new hypertension, a decreased need to resume medications for treatment of hypertension, and decreased cardiovascular complications in patients who lost on average 4 kg over 2 years.[15] In the MRFIT trial, each 1 kg of weight loss predicted a 0.4 mmHg decrease in systolic blood pressure, and a 0.3 mmHg decrease in diastolic blood pressure.[16] Weight loss has also been shown to improve symptoms of osteoarthritis in the knee.[17] Reduction of excess body weight may also decrease the excess mortality that is associated with obesity. In the Swedish Obesity Study, weight loss after bariatric surgery, albeit substantially greater than that associated with pharmacotherapy, was associated with a 24% decrease in mortality over 10.9 years.[18]

Treatment of obese and overweight patients focuses first on lifestyle changes that include diet and exercise modifications. While behavior modification can be very efficacious in some patients, adherence to the prescribed regimens is often poor. This is partly due to unrealistic patient goals and the desire for rapid weight loss with little effort.[7] Pharmacotherapy can play a significant role in weight management programs and is often combined with behavioral changes to enhance weight loss beyond that which is normally achieved with diet and exercise. Indeed, current pharmacotherapies significantly augment weight loss when combined with diet and exercise. Available weight management drugs act centrally to curb appetite and possibly to increase metabolic rate (i.e., phentermine), or to limit the absorption of dietary fat by inhibiting gastric and pancreatic lipases (i.e., orlistat).[7] However, the beneficial effects of available agents are in part offset by side effects that can include increased blood pressure (agents with sympathomimetic activity) or unpleasant gastrointestinal events (orlistat). To enhance treatment, new pharmacotherapeutic approaches should improve tolerability over existing agents while retaining or improving efficacy.

Serotonin was found to decrease food intake and reduce body weight in animals over 4 decades ago. More recently, studies showed that these effects are mediated in part through activation of centrally located serotonin 2C (5-HT_{2C}) receptors. The historical weight management agents fenfluramine and dexfenfluramine corroborated the efficacy of 5-HT_{2C} activation for weight loss in human. These agents, however, lacked specificity; each enhanced serotonin release and blocked its reuptake, leading to non-selective activation of multiple serotonin receptor subtypes.[19-21] Furthermore, their primary metabolite, norfenfluramine, is a very potent 5-HT_{2B} agonist. As a result, fenfluramine use was associated with unacceptable toxicity that included characteristic changes in heart valves that led to echocardiographically apparent aortic and mitral valve insufficiency. The pathogenesis of the heart valve toxicity is comparable to that observed with other agents like ergotamine or pergolide.[2, 22] Serotonin valvulopathy appears to be mediated through activation of serotonin 2B (5-HT_{2B}) receptors located on interstitial cardiac valvular cells. Serotonin 2C receptors are not expressed in heart valves.[23]

Lorcaserin hydrochloride ("lorcaserin") is a selective serotonin 2C (5-HT_{2C}) receptor agonist that reduces body weight by reducing food intake. Lorcaserin was designed to activate 5-HT_{2C} receptors without significant agonism of the 5-HT_{2B} receptor at therapeutic doses. At the same time, the agonist activity of lorcaserin at the serotonin 2A (5-HT_{2A}) receptor, which has been linked to mood and perceptual effects, was minimized. Functional assays indicate that lorcaserin selectivity for the 5-HT_{2C} receptor is approximately 14-fold for the 5-HT_{2A} receptor and 61-fold relative to the 5-HT_{2B} receptor. Furthermore, lorcaserin is only a partial 5-HT_{2A} agonist. Given

that 5-HT_{2C} receptor expression is primarily limited to a few regions of the central nervous system, lorcaserin was predicted to cause weight loss with few unintended pharmacological effects.

Lorcaserin decreases food consumption by selectively mimicking the effects of serotonin at the 5-HT_{2C} receptor. Serotonin decreases food intake by increasing meal-related satiety, reducing pre-meal hunger, and reducing intra-meal food intake.[24, 25] Serotonin acts in the hypothalamus at 5-HT_{2C} receptors, especially those located on POMC neurons, to increase α-melanocyte stimulating hormone (α-MSH) release, and at 5-HT_{1B} receptors on neuropetide Y/agouti-related protein (NPY/AgRP) neurons to decrease AgRP release.[26] α-MSH is a melanocortin-4 receptor (MC-4R) agonist, and AgRP an antagonist. These actions of serotonin therefore activate the MC-4R, a well known modulator of appetite. The neurons that express MC-4R in the hypothalamus communicate with the dorsal vagal complex in the brainstem which in turn relays these signals to the periphery to control food intake and energy balance. Lorcaserin is thought to mimic the hypophagic effect of serotonin at least in part through stimulation of the POMC neurons in the hypothalamus and produces weight loss in rats with repeated administration.[27]

The proposed indication for lorcaserin is as an adjunct to diet and exercise for weight management, including weight loss and maintenance, in obese patients with an initial body mass index $\geq$ 30 kg/m^2, or overweight patients with a body mass index $\geq$ 27 kg/m^2 in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea, type 2 diabetes)

3 CLINICAL WEIGHT LOSS EFFICACY AND SAFETY

Randomized, placebo-controlled efficacy assessments were performed in three Phase 3 studies of obese patients, and overweight patients who had at least 1 weight-related co-morbid condition. The Phase 3 studies provide the primary support for the efficacy and safety of lorcaserin and are the focus of this briefing document. Phase 2 study data guided dose selection and were supportive of the Phase 3 data, and are not presented herein.

Lorcaserin 10 mg BID was superior to placebo for weight loss in each of the three studies, as indicated by three pre-specified measures of categorical or mean weight loss (% of patients achieving ≥5% weight loss, mean weight loss, and % of patients achieving ≥10% weight loss at 1 year). Furthermore, lorcaserin's efficacy met the efficacy benchmark set forth in *2007 draft Guidance for Industry relevant to the development of weight management drugs*, which states that an efficacious weight management drug will provide ≥ 5% weight loss in ≥ 35% patients, and the proportion will be approximately twice that in the placebo group.

3.1 Phase 3 Studies

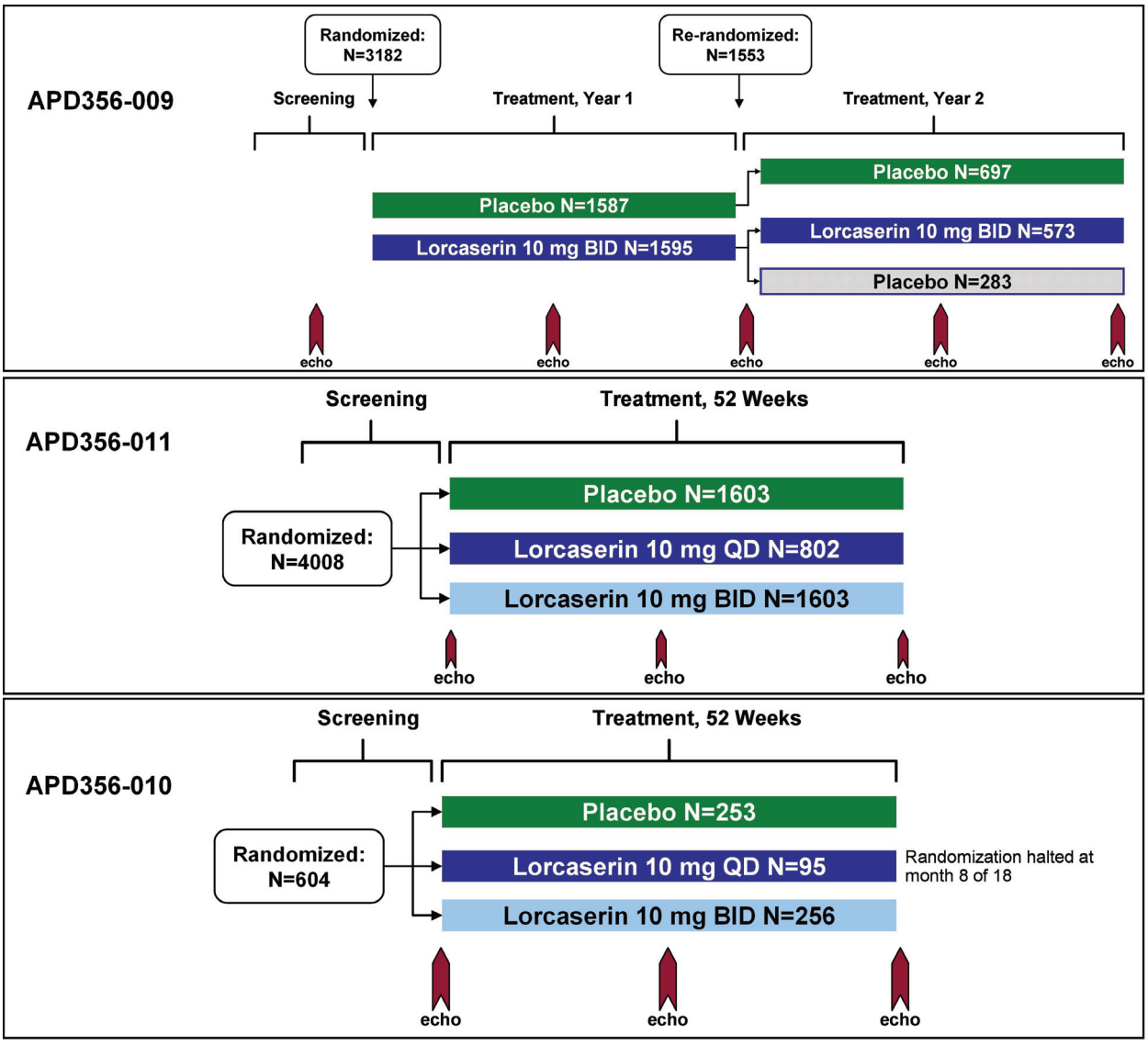
Long-term efficacy was studied in Phase 3 trials: APD356-009 ("BLOOM"), APD356-010 ("BLOOM-DM"), and APD356-011 ("BLOSSOM"). All were adequate and well-controlled ("pivotal") trials that were designed in accordance with the *1997 Guidance for Industry* and the *2007 draft Guidance for Industry relevant to the development of weight management drugs*.

APD356-009 ("BLOOM"; Figure 7) was a 104-week, controlled study that assessed the safety and efficacy of lorcaserin 10 mg BID in overweight and obese patients, with concurrent behavior modification. The primary efficacy objective during Year 1 was to evaluate weight loss; the primary objective during Year 2 was to assess the ability of lorcaserin to maintain body weight loss that was achieved during Year 1. At study start, each patient received randomized, double blind treatment assignments for Year 1 and for Year 2 (all patients were given a new randomization number for Year 2 to assure that patients and study personnel remained blinded to treatment assignments). All patients assigned to placebo during Year 1 (50% of randomized population) remained on placebo in Year 2. Patients assigned to lorcaserin during Year 1 were randomly assigned to stay on lorcaserin during Year 2 (2/3 of Year 1 lorcaserin patients) or to switch to placebo (1/3 of Year 1 lorcaserin patients). Lorcaserin met the pre-specified Year 1 categorical and mean weight loss endpoints, and the Year 2 weight maintenance endpoint.

APD356-010 (BLOOM-DM; Figure 7) was a 52-week, placebo controlled study that evaluated the effect of two lorcaserin doses (10 mg BID and 10 mg QD) on categorical and total weight loss with concurrent behavior modification in 604 patients with type 2 diabetes mellitus managed with oral hypoglycemic agents. Randomization to the 10 mg once daily group was halted by protocol amendment in order to accelerate enrollment, resulting in final group sizes of 253 (placebo), 95 (lorcaserin QD) and 256 (lorcaserin BID). Lorcaserin at both doses met the three pre-defined co-primary efficacy endpoints for efficacy. Greater proportions of patients treated with lorcaserin achieved 5% and 10% categorical weight loss as compared to patients treated with placebo, and patients on lorcaserin achieved a significantly greater mean weight loss.

APD356-011 ("BLOSSOM"; Figure 7) was a 52-week, placebo controlled study that evaluated the effect of two lorcaserin doses (10 mg BID and 10 mg QD) on categorical and total weight loss with concurrent behavior modification. Patients were randomized in a ratio of 2:1:2 to lorcaserin 10 mg BID, 10 mg QD, or placebo. Lorcaserin 10 mg QD and BID met the pre-defined co-primary efficacy endpoints.

Figure 7. Study Designs of Phase 3 Studies



3.2 Objectives and Endpoints

Efficacy endpoints for the Phase 3 clinical trials were consistent with FDA guidance for the development of weight management drugs.[28, 29] The pre-specified primary endpoints in all Phase 3 trials comprised three hierarchically ordered efficacy endpoints, which are referred to herein as "co-primary endpoints":

1. Proportion of patients who lost 5% of baseline body weight at 1 year
2. Mean weight change from baseline to 1 year
3. Proportion of patients who lost 10% of baseline body weight at 1 year

Endpoint 2 was tested only if endpoint 1 reached statistical significance; endpoint 3 was tested only if endpoints 1 and 2 reached statistical significance. Each Phase 3 trial was declared positive after meeting all three primary endpoints.

Loss of as little as 5-10% of bodyweight is associated with a substantial reduction in the risk of developing type 2 diabetes mellitus, and may have beneficial effects in hypertension, dyslipidemia, and quality of life.[30-37] Accordingly, prespecified secondary endpoints included multiple measures of body weight and fat distribution as well as measures of plasma lipids, glycemia and insulin sensitivity, blood pressure, and quality of life. Waist circumference, waist:hip ratio, and body composition were evaluated as indicators of the distribution of weight loss.

3.3 Data Pooling and Presentation

Studies APD356-009 and APD356-011 were designed to include essentially identical, non-diabetic patient populations; according to a pre-specified plan, the efficacy datasets for these studies were pooled for analysis. The prespecified analyses of the pooled dataset included the same 3 ordered primary endpoints that were designated for the individual trials. Analyses of lipids, blood pressure, anthropometric measures, glycemic parameters and quality of life scores (IWQOL-LITE) were among the prespecified secondary endpoints to be analyzed using the pooled data set. Safety data, including adverse events and echocardiographic parameters, were also pooled for analysis.

The patient population in study APD356-010 differed from that in studies APD356-009 and APD356-011 in that all patients had type 2 diabetes. Because diabetes can impact many of the efficacy parameters that were considered, the data from APD356-010 were analyzed separately from studies APD356-009 and APD356-011. For this briefing document, most results for studies APD356-009 and APD356-011 (individually or pooled) and for study APD356-010 are presented side-by-side for review and comparison.

The statistical analyses of echocardiographic data were performed on a pooled dataset from all three studies, as pre-specified.

3.4 Enrollment Criteria

Adults between ages 18 and 65 years at screening were included. Obese patients (BMI $\geq$ 30 kg/m^2), and overweight patients (BMI 27-29.9 kg/m^2) with at least one weight related co-morbid condition were included. Type 2 diabetes was excluded in studies APD356-009 and APD356-011, but required for study APD356-010. The highest allowable BMI was 45 kg/m^2 at screening. Pregnant or lactating women and patients who had undergone prior bariatric surgery were excluded from participation. In the APD356-009 (BLOOM) trial, patients with pre-existing echocardiographic findings that met FDA-defined valvulopathy criteria (mild or greater aortic

regurgitation or moderate or greater mitral regurgitation) were excluded. In contrast, the APD356-010 (BLOOM-DM) and APD356-011 (BLOSSOM) trials had no echocardiographic inclusion/exclusion criteria. Hence, the 4612-patients enrolled in the APD356-010 and APD356-011 trials had a spectrum of echocardiographic findings that should be representative of the target patient population. Patients with hypertension or dyslipidemia were allowed in each trial unless the condition was very poorly controlled according to protocol-specified criteria.

Because their labeling recommends caution when used with other serotonergic agents, selective serotonin reuptake inhibitors (SSRI) and selective norepinephrine reuptake inhibitors (SNRIs) were not allowed in the Phase 3 clinical trials. Patients who were currently taking or had taken an SSRI for treatment of depression within 2 years of screening in the APD356-009 trial and 1 year of screening in the APD356-010 and APD356-011 trials were therefore excluded. Despite this exclusion, approximately 8% of patients enrolled in the pivotal trials had a history of depression.

3.5 Statistical Methods

3.5.1 Analysis Populations

This briefing document focuses on the modified intent to treat (MITT), Completer, and Safety populations. Analyses provided in the NDA included additional analysis populations and imputation methods. The populations presented in the briefing document are as follow:

Safety population: All patients who took at least one dose of study drug.

Modified Intent to Treat (MITT): Included all randomized patients who took at least one dose of study drug and had at least one post-baseline body weight recorded. For the second year of the APD356-009 trial, the MITT2 population included all patients who were re-randomized into the second year of the trial and had at least one post-re-randomization body weight recorded.

Completers: Included all randomized patients who did not withdraw from the study prior to the final scheduled study visit, and who had a body weight recorded at the final scheduled study visit.

Per Protocol (PP): Included all patients who completed Year 1 of the studies without major protocol deviations. This population was constructed to determine results in the subset of the Completer population who had adhered to the protocol as follows: ≥ 80% compliance with study visits and study medication, did not take prohibited medications, and had a Week 52 weight measurement within ±1 week of Week 52.

Per Protocol 2 (PP2): Included all patients who completed Year 2 of study APD356-009 without major protocol deviations. This population was constructed to determine results in the subset of the Completer population who had adhered to the protocol as follows: ≥ 80% compliance with study visits and study medication, did not take prohibited medications, and had a Week 104 weight measurement within ±1 week of Week 104.

Week 52 (Completer + Returning Dropouts; Wk 52/RDP): The Week 52 population was designed to at least partially address the anticipated 40-50% dropout rate typically seen in 1-year

weight management studies. It included Completers AND patients who discontinued prior to Week 52 and returned at the time of the intended Week 52 visit to have body weight measured (Returning Dropouts). The patients were required to have a post-baseline body weight recorded within ±2 weeks of the scheduled Week 52 visit. This population increased the Completer population by ~10%, and included ~60% of the randomized population in studies APD356-009 and APD356-011, and ~69% of randomized patients in APD356-010.

In some analyses, *only* those patients who dropped and returned for the intended Week 52 body weight measurement (Returning Dropouts) were considered—these instances are clearly described.

3.5.2 Analysis of Primary Efficacy Endpoint

PRE-SPECIFIED PRIMARY ANALYSIS

The pre-specified primary analysis used the MITT population with last observation carried forward imputation for missing values (MITT/LOCF).

In the individual studies and in the pre-specified analysis of the pooled datasets for Year 1 of studies APD356-009 and APD356-011, the primary efficacy hypothesis regarding superiority of lorcaserin to placebo for body weight reduction after 52 weeks of treatment consisted of an ordered family of comparisons:

1. proportion of patients who lost at least 5% of their baseline body weight
2. change from baseline in body weight
3. proportion of patients who lost at least 10% of their baseline body weight

An ordered testing procedure was used for the primary efficacy endpoints. Endpoint 2 was tested only if endpoint 1 reached statistical significance; endpoint 3 was tested only if endpoints 1 and 2 reached statistical significance. Each Phase 3 trial was declared positive after meeting all three primary endpoints.

For the analyses of the proportions of patients who lost at least 5% or 10% of baseline body weight, the effect of each dose of lorcaserin was compared to placebo. For individual studies, a logistic regression model with terms for *treatment and baseline body weight* was used; for the pooled Phase 3 analyses, a logistic regression model with terms for *treatment, protocol and baseline body weight* was used. For the analysis of change from baseline in body weight, the ANCOVA model was used to assess the effect of lorcaserin. The ANCOVA model included terms for *treatment and baseline body weight* for data analyses within the individual Phase 3 studies. For the analysis of the pooled Phase 3 dataset, terms for *treatment, protocol, and baseline body weight* were used.

SECONDARY ANALYSES AND SENSITIVITY ANALYSES

Pre-specified secondary analyses used a Completer population in the pooled analysis. Additional analyses were performed using the population of all patients who returned for a Week 52 weight

assessment irrespective of whether they completed Week 52 or discontinued prematurely (Week 52 Population [Completers and the Returning Dropouts]).

Several additional *post-hoc* analyses were performed as "sensitivity analyses" in an attempt to fully explore potential confounding effects of a high dropout rate and of LOCF imputation for missing values, and are included in Appendix 4. These *post-hoc* analyses included using repeated measures analysis of the MITT population, using baseline observation carried forward imputation (BOCF) with a true ITT population (that is, all randomized patients), and using multiple imputation.

3.5.3 Analyses of Secondary Efficacy Data (Anthropometrics and Markers of Cardiovascular Risk)

Each continuous secondary efficacy endpoint was analyzed using the ANCOVA method described above for body weight, substituting the relevant baseline measurement as the covariate. These secondary endpoints were grouped into four families to adjust for multiplicity: lipid family, glycemia family, blood pressure family, and Quality of Life family. If the test of the primary endpoint (proportion of patients who achieved 5% or greater weight loss) was significant, the secondary endpoint families were tested simultaneously at the 0.05 level. Within each family, testing was performed in a conditional manner prioritized in the following order:

APD356-009:

- Lipid family: LDL cholesterol, and then Hochberg procedure for total cholesterol, HDL cholesterol, and triglycerides
- Glycemia family: fasting insulin, fasting glucose, HOMA-IR
- Blood pressure family: systolic blood pressure and diastolic blood pressure
- Quality of life: total score for the IWQOL-LITE questionnaire

APD356-011:

- Lipid family: LDL cholesterol, and then Hochberg procedure for total cholesterol, HDL cholesterol, and triglycerides
- Body Composition: total body fat
- Blood pressure family: systolic blood pressure and diastolic blood pressure
- Quality of life: total score for the IWQOL-LITE questionnaire

Pooled APD356-009 and APD356-011 data analysis:

- Lipid family (triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol)
- Glycemia family (fasting glucose and HbA1c)
- Blood pressure family (systolic blood pressure and diastolic blood pressure)
- Quality of life: total score for the IWQOL-LITE questionnaire

APD356-010:

- Glycemic Parameter Family (HbA1c, fasting glucose, fasting insulin, HOMA-IR)
- Lipid family (triglycerides, HDL cholesterol, LDL cholesterol, total cholesterol)
- BP family (systolic blood pressure, diastolic blood pressure)
- Body composition family (total body fat)
- Quality of Life: total score for the IWQOL-LITE questionnaire

For each family, the endpoints were tested in order, with the following exception for studies APD356-009 and -011: if the first lipid parameter was significant in the individual studies, the Hochberg procedure was used for the remaining lipid parameters. The first endpoint within a family was assessed by comparing lorcaserin 10 mg BID versus placebo. The second endpoint within a family was assessed only if the first endpoint was significant. The third endpoint was assessed only if the second endpoint was significant, and so on through the hierarchy. All comparisons were tested at $\alpha = 0.05$ level (two-sided). A non-significant result for a lorcaserin versus placebo comparison stopped all further testing in that family.

Assumptions for the ANCOVA model were checked via Shapiro-Wilk statistics for normality and Levene's test for homogeneity of variance between the treatment groups using residuals from the ANCOVA model. With the relatively large sample size used in these studies, the inferential conclusions from the parametric ANCOVA model are generally robust to deviations from normality.

3.5.4 Sample Size Calculation

The sample sizes for the Phase 3 studies were determined by the analysis of echocardiographic safety data—not by efficacy considerations. As a result, the studies are "over powered" with respect to the efficacy endpoints. When planning the APD356-009 trial, for example, we predicted that 20% of subjects in the placebo group would achieve a 5% or greater weight loss at Year 1. Based on sample size estimation methods for the comparison of two proportions, with $\alpha = 0.05$, the proposed sample size of 1550 placebo patients and 1550 lorcaserin-treated patients provided greater than 95% power to detect a difference of 5.5 percentage points (i.e., from 20% of patients in the placebo group losing > 5% body weight to 25.5% of patients in the lorcaserin group). This discrepancy between the number of patients needed to establish efficacy and the number required to establish a "reasonable estimation of safety" is acknowledged in the current draft *Guidance for Industry: Developing Products for Weight Management (2007),*[76] which recommends no fewer than 3000 subjects randomized to receive active treatment and no fewer than 1500 randomized to receive placebo for 1 year.

The sample size in the APD356-009 trial was based on a pre-specified non-inferiority analysis that compared the proportion of patients who developed new findings of FDA-defined valvulopathy at 1 year. The sample sizes of APD356-011 and APD356-010 were also based on the echocardiographic endpoint, and were determined using the incidence of FDA-defined valvulopathy derived from the DSMB (Data and Safety Monitoring Board) analysis of echo data from APD356-009.

Arena and the FDA agreed that the pooled databases would be sufficiently large to rule out a 50% increase over the placebo incidence with 80% power and $\alpha = 0.5$. We assumed that 40% of patients would discontinue from the trials, and for APD356-009, we assumed a placebo incidence of FDA-defined valvulopathy of 5%, resulting in a projected 1550 patients per treatment group. The actual 1 year placebo incidence of FDA-defined valvulopathy provided by the DSMB was 2.5%; hence, the sample size of APD356-011 was based on an assumed placebo incidence of 2.5%; the noninferiority margin for the risk difference analysis was pre-specified at 1.25%. With the inclusion of the APD356-010 study in the NDA resubmission, the total number of patients exceeds that calculated during the sample size determination process.

3.6 Overview of Exposure

Table 2 provides the overall study drug exposure during Year 1 of the Phase 3 studies, by daily dose and duration of exposure. A total of 4347 patients in Phase 3 studies were exposed to at least one dose of lorcaserin for up to 1 year; 571 patients continued lorcaserin exposure for up to 2 years.

During Year 1, mean (±SD) duration of treatment with lorcaserin 10 mg BID and 10 mg QD was 264 ± 133 days and 277 ± 129 days, respectively.

During Year 2 of APD356-009, 571 patients were exposed to lorcaserin 10 mg BID for a mean (±SD) of 305 ± 106.5 days (Table 3).

Table 2. Patient Exposure to Lorcaserin during Year 1 in Long-term Controlled Trials: by Dose and by Actual Duration of Treatment

Number of patients	Days of Treatment									Total Number of Patients on Lorcaserin	Duration of Treatment (Days)	
Lorcaserin Dose	1	2 to 7	8 to 14	15 to 28	29 to 90	91 to 180	181 to 360[a]	361 to final Yr 1 visit	Missing[b]		Range	Mean (SD)
10 mg BID	16	23	67	143	402	375	766	1567	92	3451	1-393	263.7 (133.09)
10 mg QD	4	3	14	29	96	84	173	467	26	896	1-400	277.1 (129.16)
Any Dose	20	26	81	172	498	459	939	2034	118	4347	1-400	266.4 (132.39)

[a] Subjects were counted only once. The total exposure during entire study was calculated for each subject.

[b] Subjects with missing exposure have a missing dosing start or stop date or both.

Table 3. Patient Exposure to Study Drug during Year 2 in APD356-009 Trial: by Dose and by Actual Duration of Treatment

	Lorcaserin/Lorcaserin N=571	Lorcaserin/Placebo N=280	Placebo/Placebo N=691
Number of Days on Study Drug during Year 2			
Mean (SD)	304.8 (106.55)	297.8 (108.21)	302.6 (107.32)
Median	359.0	357.0	358.0
Min-Max	1-410	0-408	1-404

3.7 Demographics and Baseline Characteristics

Demographic characteristics of the patient populations studied in Phase 3 are summarized in Table 4. The data for individual studies APD356-009 and APD356-011 are provided in Appendix 4, Table 64. Across all clinical trials (Phase 1 through Phase 3), the evaluation of lorcaserin included a wide range of BMIs (26.7-60 kg/m^2) and body weights (62.6-213 kg). In the Phase 3 trials, approximately 20% of the patients had a BMI of 40 kg/m^2 or greater, while 5.3% of the Phase 3 population had a BMI of 30 kg/m^2 or less. Like most large obesity studies in the US, the majority of participants were women.

The representation of ethnic/racial groups in the clinical trials reflected the target overweight and obese population in the US. According to US Census estimates, 79.8% of the population is Caucasian, 12.8% African American, and 15.4% Hispanic or Latino.[38] National Health and Nutrition Examination Survey (NHANES) data from 1988-1994 estimated the prevalence of overweight and obesity to be 61% in white men and 49.2% in white women. The prevalence is higher in Black women (65.8%), Mexican-American women (65.9%), and Mexican-American men (63.9%).[7]

Forty-four percent of the non-diabetic patients studied in Phase 3 had co-morbid conditions: 22.7% had hypertension, and 30.6% had dyslipidemia. Approximately 10% were tobacco users at the time of randomization. Approximately 8.2% had a history of depression, and 1.2% of non-diabetic patients reported a known history of coronary artery disease. Among the patients with type 2 diabetes, most also had other co-morbid conditions, primarily hypertension and dyslipidemia.

Based on more than 8000 screening and baseline echocardiograms, the sponsor estimates the prevalence of FDA-defined valvulopathy in the population that was screened to be approximately 5%. Pre-existing FDA-defined valvulopathy was an exclusion criterion for study APD356-009, but was allowed in APD356-010 and APD356-011. Hence, when data from the three studies were pooled, 2.7% of the total Phase 3 study population had echocardiographic criteria for FDA-defined valvulopathy at study entry.

Table 4. Demographic Profile of Patients in Pooled Phase 3 Trials APD356-009 and APD356-011 and Study APD356-010: Safety Populations

Demographics		Pooled Studies APD356-009 and APD356-011 Non-diabetic Patients				APD356-010 Patients with Type 2 Diabetes			
		Pooled Placebo (N=3185)	Pooled Lorcaserin 10 mg BID (N=3195)	Lorcaserin 10 mg QD (N=801)	Any Lorcaserin Dose (N=3996)	Placebo (N=252)	Lorcaserin 10 mg BID (N=256)	Lorcaserin 10 mg QD (N=95)	Any Lorcaserin Dose (N=351)
Gender									
	Female	2580 (81.0)	2610 (81.7)	656 (81.9)	3266 (81.7)	137 (54.4)	137 (53.5)	53 (55.8)	190 (54.1)
	Male	605 (19.0)	585 (18.3)	145 (18.1)	730 (18.3)	115 (45.6)	119 (46.5)	42 (44.2)	161 (45.9)
Age									
	N	3185	3195	801	3996	252	256	95	351
	Mean (SD)	44.0 (11.4)	43.8 (11.6)	43.8 (11.7)	43.8 (11.6)	52.0 (9.32)	53.2 (8.26)	53.1 (7.98)	53.2 (8.17)
	Median	44.0	44.0	44.0	44.0	53.0	55.0	54.0	55.0
	Min-Max	18 - 66	18 - 66	18 - 65	18 - 66	21 - 65	30 - 65	26 - 65	26 - 65
	CV	26.0%	26.4%	26.6%	26.4%	17.9%	15.5%	15.0%	15.4%
Age Group									
	18-24	167 (5.2)	185 (5.8)	51 (6.4)	236 (5.9)	2 (0.8)	0	0	0
	25-34	564 (17.7)	555 (17.4)	143 (17.9)	698 (17.5)	8 (3.2)	7 (2.7)	3 (3.2)	10 (2.80)
	35-44	869 (27.3)	871 (27.3)	211 (26.3)	1082 (27.1)	52 (20.6)	37 (14.5)	8 (8.4)	45 (12.8)
	45-54	910 (28.6)	935 (29.3)	224 (28.0)	1159 (29.0)	84 (33.3)	75 (29.3)	41 (43.2)	116 (33.0)
	55-65	674 (21.2)	648 (20.3)	172 (21.5)	820 (20.5)	106 (42.1)	137 (53.5)	43 (45.3)	180 (51.3)
	> 65	1 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)	0	0	0	0
Race									
	White/Caucasian	2110 (66.2)	2161 (67.6)	538 (67.2)	2699 (67.5)	166 (65.9)	150 (58.6)	49 (51.6)	199 (56.7)
	Black/AfAm	617 (19.4)	604 (18.9)	160 (20.0)	764 (19.1)	45 (17.9)	55 (21.5)	26 (27.4)	81 (23.1)
	Asian	19 (0.6)	24 (0.8)	3 (0.4)	27 (0.7)	8 (3.2)	11 (4.3)	3 (3.2)	14 (4.0)
	NAI/AN	14 (0.4)	18 (0.6)	7 (0.9)	25 (0.6)	0	0	0	0
	Hispanic/Latino	394 (12.4)	355 (11.1)	86 (10.7)	441 (11.0)	27 (10.7)	39 (15.2)	17 (17.9)	56 (16.0)
	NH/PI	9 (0.3)	11 (0.3)	4 (0.5)	15 (0.4)	0	0	0	0
	Other	22 (0.7)	22 (0.7)	3 (0.4)	25 (0.6)	6 (2.4)	1 (0.4)	0	1 (0.3)

Table 4. Demographic Profile of Patients in Pooled Phase 3 Trials APD356 009 and APD356 011 and Study APD356 010: Safety Populations (cont.)

	Pooled Studies APD356-009 and APD356-011 Non-diabetic Patients				APD356-010 Patients with Type 2 Diabetes			
Demographics	**Pooled Placebo (N=3185)**	**Pooled Lorcaserin 10 mg BID (N=3195)**	**Lorcaserin 10 mg QD (N=801)**	**Any Lorcaserin Dose (N=3996)**	**Placebo (N=252)**	**Lorcaserin 10 mg BID (N=256)**	**Lorcaserin 10 mg QD (N=95)**	**Any Lorcaserin Dose (N=351)**
Weight (kg)								
N	3185	3195	801	3996	252	256	95	351
Mean (SD)	100.2 (15.9)	100.4 (15.7)	100.1 (16.6)	100.4 (15.9)	102.6 (18.1)	103.7 (17.0)	106.0 (19.4)	104.3 (17.7)
Median	98.7	99.0	97.5	98.7	100.2	101.8	107.3	102.9
Min-Max	62.7 - 165.9	62.6 - 159.3	64.9 - 185.4	62.6 - 185.	53.0 - 158.6	63.3 - 150.6	69.1 - 156.9	63.3 – 156.9
CV	15.9%	15.6%	16.6%	15.8%	17.6%	16.4%	18.3%	16.9%
Height (cm)								
N	3185	3195	801	3996	252	256	95	351
Mean (SD)	166.5 (8.5)	166.5 (8.7)	166.7 (8.8)	166.6 (8.7)	168.8 (10.1)	169.2 (9.6)	170.8 (9.9)	169.6 (9.7)
Median	165.1	165.2	165.5	165.2	168.1	168.9	172.5	170.0
Min-Max	141.0 - 203.2	138.2 - 198.0	148.0 - 206.0	138.2 - 206	139.5 – 193.0	149.0 - 195.1	148.8 - 194.3	148.8 - 195.1
CV	5.1%	5.2%	5.3%	5.2%	6.0%	5.7%	5.8%	5.7%
BMI (kg/m^2)								
N	3185	3195	801	3996	252	256	95	351
Mean (SD)	36.1 (4.2)	36.1 (4.3)	35.9 (4.3)	36.1 (4.3)	35.9 (4.5)	36.1 (4.5)	36.1 (4.8)	36.1 (4.6)
Median	35.6	35.8	35.1	35.6	35.5	36.0	36.6	36.1
Min-Max	26.7 - 46.6	26.7 - 52.5	26.4 - 46.8	26.4 - 52.5	27.2 - 45.0	27.0 - 44.9	28.2 - 45.0	27.0 - 45.0
CV	11.7%	11.8%	11.9%	11.9%	12.6%	12.4%	13.2%	12.6%
BMI Group								
≤ 30	149 (4.7)	169 (5.3)	37 (4.6)	206 (5.2)	24 (9.5)	21 (8.2)	12 (12.6)	33 (9.4)
30 < - ≤ 35	1297 (40.7)	1244 (38.9)	355 (44.3)	1599 (40.0)	88 (34.9)	82 (32.0)	28 (29.5)	110 (31.3)
35 < - ≤ 40	1092 (34.3)	1118 (35.0)	243 (30.3)	1361 (34.1)	86 (34.1)	91 (35.5)	33 (34.7)	124 (35.3)
> 40	647 (20.3)	664 (20.8)	166 (20.7)	830 (20.8)	54 (21.4)	62 (24.2)	22 (23.2)	84 (23.9)

Table 4. Demographic Profile of Patients in Pooled Phase 3 Trials APD356 009 and APD356 011 and Study APD356 010: Safety Populations (cont.)

	Pooled Studies APD356-009 and APD356-011 Non-diabetic Patients				APD356-010 Patients with Type 2 Diabetes			
Demographics	**Pooled Placebo (N=3185)**	**Pooled Lorcaserin 10 mg BID (N=3195)**	**Lorcaserin 10 mg QD (N=801)**	**Any Lorcaserin Dose (N=3996)**	**Placebo (N=252)**	**Lorcaserin 10 mg BID (N=256)**	**Lorcaserin 10 mg QD (N=95)**	**Any Lorcaserin Dose (N=351)**
Presence of Co-morbid Conditions, n(% of patients)								
	1794 (56.3)	1779 (55.4)	479 (59.8)	2258 (56.5)	52 (20.6)	53 (20.7)	18 (19.0)	71 (20.2)
Hypertension[a]	724 (22.7)	722 (22.6)	175 (21.8)	897 (22.4)	153 (60.7)	157 (61.3)	57 (60.0)	214 (61.0)
Dyslipidemia[a]	962 (30.2)	989 (31.0)	218 (27.2)	1207 (30.2)	149 (59.1)	140 (54.7)	46 (48.4)	186 (53.0)
Sleep apnoea[b]	128 (4.0)	144 (4.5)	27 (3.4)	171 (4.3)	35 (13.9)	33 (12.9)	15 (15.8)	48 (13.7)
None CAD/CVD[c]	5.5%/5.7%	4.5%/4.6%			17 (6.8)	18 (7.0)	7 (7.4)	25 (7.1)
HbA1c%								
N	2288	2464	595	3059	252	256	95	351
Mean (SD)	5.6 (0.39)	5.6 (0.38)	5.6 (0.41)	5.6 (0.39)	8.1 (0.84)	8.1 (0.83)	8.1 (0.78)	8.1 (0.81)
Median	5.6	5.6	5.6	5.6	7.9	7.8	7.9	7.9
	4.3 - 6.6	4.1 - 7.0	4.2 - 6.5	4.1 - 7.0	7.0 – 10.0	6.9 - 10.0	7.0 - 10.0	6.9 - 10.0
CV (%)	6.9%	6.8%	7.3%	6.9%	10.5	10.3	9.7	10.1
≥ 9% (n[%])	0 (0%)	0 (0%)	0 (0%)	0 (0%)	45 (17.9)	47 (18.4)	14 (14.7)	61 (17.4)
HbA1c **HbA1c < 9% (n[%])**	2288 (100.0%)	2464 (100.0%)	595 (100.0%)	3059 (100.0%)	207 (82.1)	209 (81.6)	81 (85.3)	290 (82.6)
Min-Max								
Duration of Diabetes (mean [SD], years)[d]					7.0 (5.0)	6.6 (4.5)	6.6 (5.0)	6.6 (4.7)
Diabetes Medication Used (n[%])								
SFU	--	--	--	--	127 (50.4)	129 (50.4)	47 (49.5)	176 (50.1)
Metformin	--	--	--	--	229 (90.9)	236 (92.2)	88 (92.6)	324 (92.3)
	--	--	--	--	104 (41.3)	109 (42.6)	40 (42.1)	149 (42.5)
Presence of FDA-defined Valvulopathy at Baseline								
	3119 (97.9)	3109 (97.3)	774 (96.6)	3879 (97.1)	243 (96.4)	247 (96.5)	86 (90.5)	333 (94.9)
	66 (2.1)	83 (2.6)	31 (3.9)	114 (2.9)	9 (3.6)	9 (3.5)	9 (9.5)	18 (5.1)

Both

[a] From patient reported baseline characteristics (data field in Demographics dataset).

[b] Medical History search terms: *sleep apnoea*

[c] Medical History search terms: Body system 'cardiovascular' AND: *stent*, MI, angina, atherosclero*, coronary, cardiac cath*, *pain, *pressure, infarct*, attack.

[d] Derived from patient-reported onset date for type 2 diabetes in Medical History dataset; using only onset year.

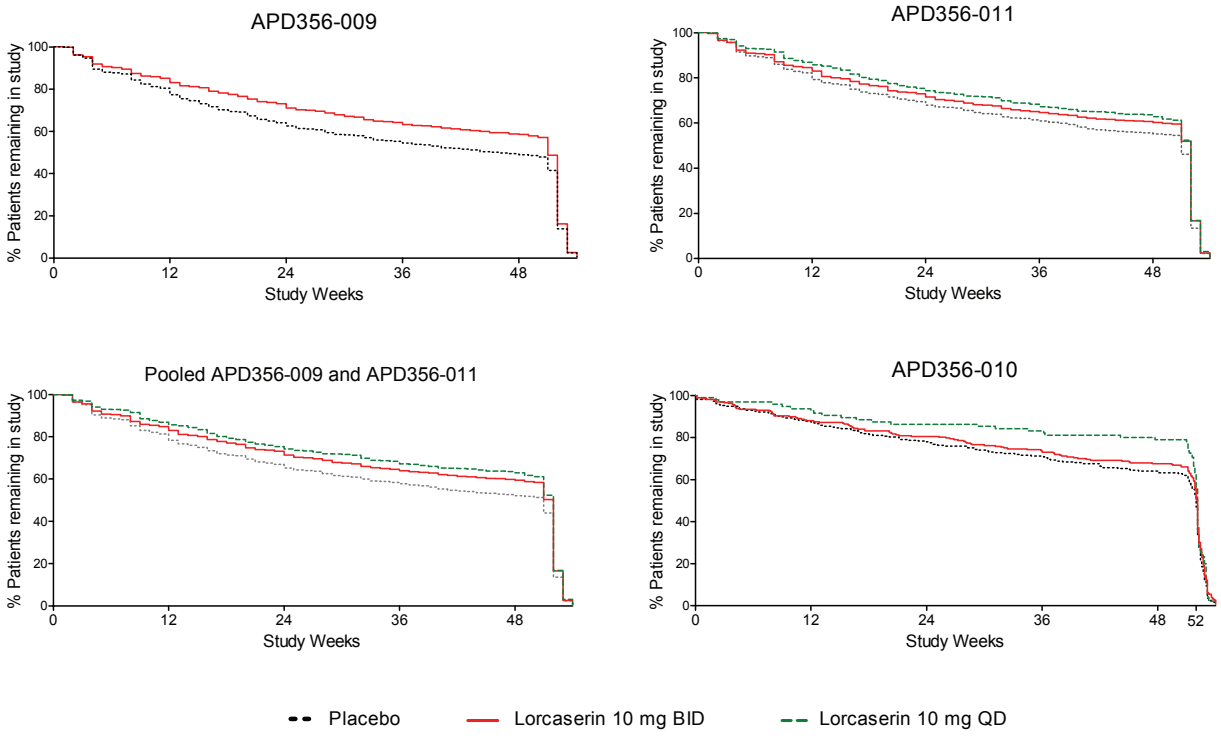
Note: Number of randomized patients in each column is used as the denominator for percentage calculations.

No
Yes
Af Am, African American; NAI/AN, North American Indian/Alaska Native; NH/PI, Native Hawaiian/Pacific Islander; CAD, coronary artery disease; CVD, cardiovascular disease; SFU, sulfonylurea; -- , no data

3.8 Subject Disposition

Of the 7794 patients randomized into Phase 3 trials, 7784 received at least one dose of study medication (Safety Population); 7498 were included in the modified intent to treat (MITT) populations (randomized, took at least one dose of study drug and had at least one post-baseline weight measurement), and 4224 completed 1 year of dosing (Table 5). Study APD356-010 had the highest completion rate, and APD356-011 had a slightly overall higher completion rate than APD356-009. Figure 8 provides Kaplan-Meier curves for the time to discontinuation. Throughout the studies, retention rates were higher in lorcaserin groups as compared to placebo groups. Patients receiving lorcaserin 10 mg BID and 10 mg QD withdrew somewhat more frequently due to adverse events than did patients receiving placebo.

Figure 8. Proportion of Patients Remaining in Study from Baseline to Week 52: Phase 3 Studies



The demographic and baseline characteristics of patients who completed Phase 3 trials and those who discontinued from Phase 3 trials are summarized in Table 5. Some characteristics differed between completers and non-completers; for example, those who completed were on average older than those who dropped out, and slightly more women than men dropped out. However, the trends were the same for patients assigned to lorcaserin and those assigned to placebo. That is, the demographic and baseline characteristics of non-completers were comparable in the placebo and lorcaserin 10 mg BID treatment groups.

Patients in the Phase 3 trials were generally highly compliant with respect to taking study drug while enrolled in the studies. Year 1 compliance was 93.6% in the lorcaserin group and 92.2% in the placebo group in study APD356-009, and 94.9% and 98.9%, respectively, in the APD356-011 study.

Table 5. Patient Disposition by Treatment Group in Phase 3 Trials APD356-009, APD356-010, and APD356-011

	APD356-009		APD356-010			APD356-011			Pooled Analysis: APD356-009 and -011	
	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Placebo
No. of Patients Randomized	1595	1587	95	256	253	802	1603	1603	3198	3190
N (%) of Patients in Safety Population	1593 (99.9)	1584 (99.8)	95 (100)	256 (100)	252 (99.6)	801 (99.9)	1602 (>99.9)	1601 (99.9)	3195 (99.9)	3185 (99.8)
N (%) of Patients Withdrawn Prior to Week 52	712 (44.6)	871 (54.9)	20 (21.1)	87 (34.0)	96 (37.9)	329 (41.0)	686 (42.8)	769 (48.0)	1398 (43.7)	1640 (51.4)
Withdrawal of consent	307 (19.2)	439 (27.7)	8 (8.4)	32 (12.5)	50 (19.8)	162 (20.2)	293 (18.3)	376 (23.5)	600 (18.8)	815 (25.5)
Lack of efficacy	27 (1.7)	88 (5.5)	4 (4.2)	2 (0.8)	5 (2.0)	25 (3.1)	39 (2.4)	62 (3.9)	66 (2.1)	150 (4.7)
Lost to follow-up	191 (12.0)	226 (14.2)	3 (3.2)	20 (7.8)	14 (5.5)	83 (10.3)	198 (12.4)	234 (14.6)	389 (12.2)	460 (14.4)
Adverse event	113 (7.1)	106 (6.7)	6 (6.3)	22 (8.6)	11 (4.3)	50 (6.2)	115 (7.2)	74 (4.6)	228 (7.1)	180 (5.6)
Protocol deviation/ non-compliance	47 (2.9)	44 (2.8)	1 (1.1)	3 (1.2)	10 (4.0)	20 (2.5)	59 (3.7)	49 (3.1)	106 (3.3)	93 (2.9)
Sponsor decision	25 (1.6)	26 (1.6)	1 (1.1)	3 (1.2)	5 (2.0)	10 (1.2)	9 (0.6)	30 (1.9)	34 (1.1)	56 (1.8)
Other discontinuation reason	20 (1.3)	24 (1.5)	1 (1.1)	7 (2.7)	5 (2.0)	0 (0.0)	1 (< 0.1)	0 (0.0)	21 (0.7)	24 (0.8)
PI decision	9 (0.6)	6 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	4 (0.5)	11 (0.7)	6 (0.4)	20 (0.6)	12 (0.4)
N (%) of Patients in MITT Population	1538 (96.4)	1499 (94.5)	94 (98.9)	251 (98.0)	248 (98.0)	771 (96.1)	1561 (97.4)	1541 (96.1)	3097 (96.8)	3037 (95.2)
N (%) of Patients Who Completed 52 Weeks of Study Medication	883 (55.4)	716 (45.1)	75 (78.9)	169 (66.0)	157 (62.1)	473 (59.0)	917 (57.2)	834 (52.0)	1800 (56.3)	1550 (48.6)
N (%) of Patients in Wk 52/RDP Population	1031 (64.6)	901 (56.8)	77 (81.1)	175 (68.4)	165 (65.2)	524 (65.3)	1028 (64.1)	951 (59.3)	2043 (63.9)	1839 (57.6)

3.9 Summary of Efficacy

3.9.1 Primary Efficacy in Phase 3 Studies

The pre-specified co-primary endpoints were as follow:

- Proportion of patients who lost at least 5% of their baseline body weight at Week 52
- Change from baseline in body weight at Week 52
- Proportion of patients who lost at least 10% of their baseline body weight at Week 52

CO-PRIMARY ENDPOINT 1: PROPORTION OF PATIENTS WHO LOST ≥ 5% OF BASELINE BODYWEIGHT AT WEEK 52

Each Phase 3 study and the prespecified pooled analysis of APD356-009 and APD356-011 met the first primary endpoint, with a significantly greater proportion of patients on lorcaserin BID achieving ≥5% weight loss from baseline as compared with placebo (Figure 9, Table 6). Consistent with the FDA Guidance, more than 35% of patients assigned to lorcaserin BID achieved the 5% weight loss benchmark in each study; the proportion of patients achieving this benchmark in the lorcaserin BID group was ≥ twice the proportion in the placebo group.

Figure 9. Proportion of Patients Achieving ≥ 5% Weight Loss after 52 Weeks in Individual and Pooled Phase 3 Studies: MITT Population

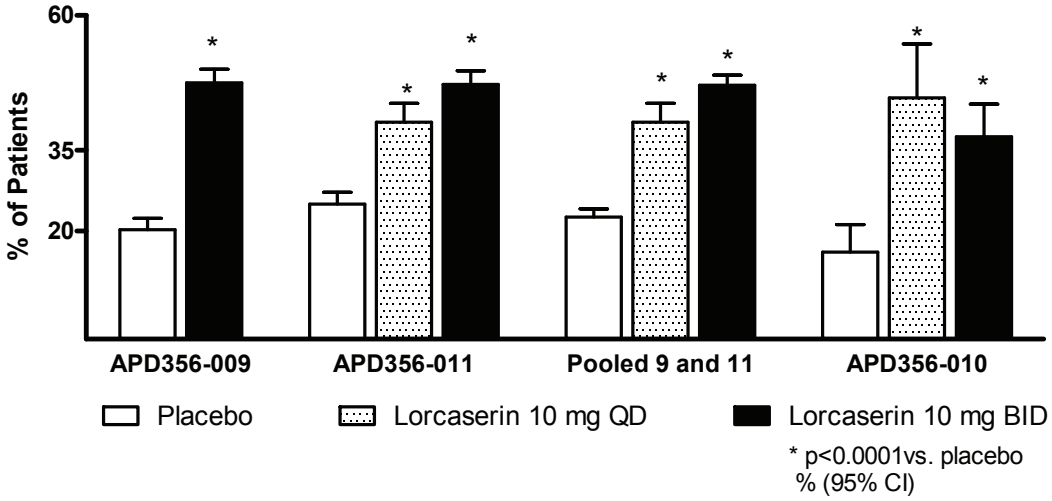


Table 6. Proportion of Patients Achieving ≥ 5% Weight Loss after 52 Weeks of Treatment in Individual and Pooled (APD356-009 and APD356-011) Phase 3 Studies: MITT, Per Protocol/Completer and Returning Dropout/Wk52 Populations

	APD356-009		APD356-011			Pooled (APD356-009 and -011)		APD356-010		
n (%) losing ≥5% weight	**Placebo**	**Lorcaserin 10 mg BID**	**Placebo**	**Lorcaserin 10 mg BID**	**Lorcaserin 10 mg QD**	**Placebo**	**Lorcaserin 10 mg BID**	**Placebo**	**Lorcaserin 10 mg BID**	**Lorcaserin 10 mg QD**
MITT (Co-primary endpoint)										
N	1499	1538	1541	1561	771	3038	3098	248	251	94
n (%)	304 (20.3)	731 (47.5)	385 (25.0)	737 (47.2)	310 (40.2)	687 (22.61)	1460 (47.13)	40 (16.1)	94 (37.5)	42 (44.7)
Difference from Placebo (95% CI)[a]		27.2 (24.0, 30.5)		22.23 (18.94, 25.52)	15.19 (11.11, 19.27)		24.52 (22.22, 26.82)		21.32 (13.78, 28.86)	28.55 (17.51, 39.60)
p-Value[a]		< 0.0001		< 0.0001	< 0.001		< 0.001		< 0.0001	< 0.0001
Per Protocol/Completer[b]										
N	583	737	764	846	418	1529	1775	156	168	75
n (%)	187 (32.1)	489 (66.4)	267 (34.9)	535 (63.2)	222 (53.1)	512 (33.49)	1135 (63.94)	28 (17.9)	75 (44.6)	41 (54.7)
Difference from Placebo (95% CI)[a]		34.3 (29.2, 39.4)		28.29 (23.60, 32.98)	18.16 (12.30, 24.02)		30.44 (27.18, 33.69)		26.69 (17.06, 36.33)	36.72 (23.94, 49.49)
p-Value[a]		< 0.0001		< 0.0001	< 0.001		< 0.001		< 0.0001	< 0.0001
RDP/Wk52										
N	888	1015	951	1028	524	1839	2043	165	175	77
n (%)	267 (30.1)	599 (59.0)	319 (33.5)	603 (58.7)	253 (48.3)	584 (31.76)	1197 (58.59)	32 (19.4)	75 (42.9)	41 (53.2)
Difference from Placebo (95% CI)[a]		28.9 (24.7, 33.2)		25.11 (20.86, 29.36)	14.74 (9.51, 19.96)		26.85 (23.83, 29.86)		23.46 (13.97, 32.96)	33.85 (21.18, 46.53)
p-Value[a]		< 0.0001		< 0.0001	< 0.001		< 0.001		< 0.0001	< 0.0001

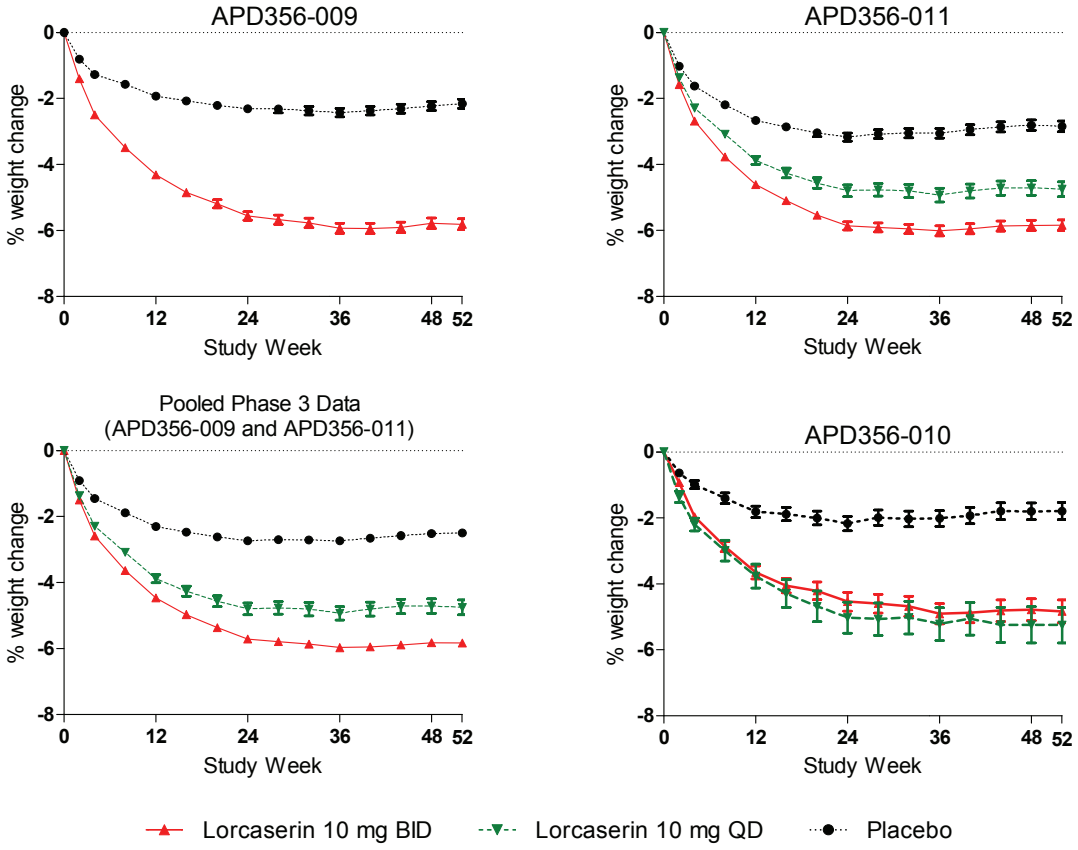
[a] p-value compared to placebo group within same analysis

[b] Per Protocol population in studies APD356-009 and APD356-011; Completer population in pooled analysis and in study APD356-010.

CO-PRIMARY ENDPOINT 2: MEAN CHANGE FROM BASELINE IN BODY WEIGHT AT WEEK 52

Lorcaserin was superior to placebo with respect to the second co-primary endpoint in each individual Phase 3 study and in the pooled analysis (Figure 10, Table 7). Weight loss was observed as early as the first post-baseline visit, and the change from baseline was significantly greater in the lorcaserin BID group than in the placebo group at 2 weeks and thereafter in studies APD356-009 and APD356-011, and at Week 4 and thereafter in study APD356-010. In all analysis populations, non-diabetic patients assigned to placebo or lorcaserin 10 mg BID had greater mean weight loss than did the patients with type 2 diabetes in the corresponding treatment group.

Figure 10. Percent Weight Loss from Baseline to Week 52 in Individual and Pooled (APD356-009 and APD356-011) Phase 3 Studies: MITT Population



Note: APD356-009 and APD356-010, Mean ±SE; APD356-011 and pooled, LS Mean ±SE

Table 7. Mean Weight Loss Change from Baseline at Week 52 in Individual and Pooled (APD356-009 and APD356-011) Phase 3 Studies: MITT, PP/Completer, and RDP/Wk52 Populations

	APD356-009		APD356-011			Pooled -009 and -011		APD356-010		
	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	Placebo
MITT (Co-primary endpoint)										
N	1538	1499	771	1561	1541	3098	3038	94	251	248
Mean baseline[a], kg	100.3 ± 15.69	99.66 ± 15.60	100.11 ± 16.74	100.34 ± 15.65	100.77 ± 16.22	100.36 ± 15.67	100.22 ± 15.92	106.08 ± 19.61	103.52 ± 17.18	102.27 ± 17.99
Mean (±SE) weight change, kg	-5.76 ± 0.16	-2.15 ± 0.14	-4.73 ± 0.23	-5.76 ± 0.16	-2.85 ± 0.16	-5.76 ± 0.11	-2.51 ± 0.11	-5.02 ± 0.57	-4.66 ± 0.37	-1.61 ± 0.37
Difference from Placebo (95% CI)	NR	NR	-1.878 (-2.43, -1.33)	-2.906 (-3.35, -2.46)		3.25 (-3.56, -2.94)		-3.408 (-4.64, -2.18)	-3.053 (-3.96, -2.15)	
p-Value[a]	< 0.0001		< 0.0001	< 0.0001		< 0.001		< 0.0001	< 0.0001	
Mean (±SE) weight change, %	-5.81 ± 0.16	-2.16 ± 0.14	-4.75 ± 0.23	-5.84 ± 0.16	-2.83 ± 0.16	-5.83 ± 0.11	-2.50 ± 0.11	-4.97 ± 0.54	-4.54 ± 0.35	-1.48 ± 0.36
p-Value[b]	< 0.0001		< 0.0001	< 0.0001		< 0.001		< 0.0001	< 0.0001	
Range, kg (%)	-36.0 – 11.7 (-33.3 – 13.3)	-38.2 – 14.1 (-36.3 – 15.5)	NR	NR		-37.20-14.80 (-34.9 – 13.3)	-56.10 – 20.00 (-46.3 – 17.5)	-23.7-7.2 (-18.4-5.4)	-36.1-4.3 (-30.5-4.5)	
Per Protocol/Completer[c]										
N	737	583	418	846	764	1775	1529	75	169	157
Mean baseline[a], kg	100.67 ± 15.99	98.98 ± 15.72	99.26 ± 16.80	100.21 ± 15.75	101.33 ± 16.41	100.51 ± 15.74	100.31 ± 16.16	105.42 ± 19.22	104.73 ± 17.91	101.71 ± 18.27
Mean (±SE) weight change, kg	-8.14 ± 0.26	-3.31 ± 0.28	-6.48 ± 0.36	-7.73 ± 0.25	-3.95 ± 0.27	-7.88 ± 0.17	-3.66 ± 0.18	-6.25 ± 0.65	-5.93 ± 0.49	-2.21 ± 0.38
Difference from Placebo (95% CI)	NR	NR	-2.611 (-3.48, -1.74)	-3.822 (-4.54, -3.11)		-4.23 (-4.71, -3.74)		-3.926 (-5.49, -2.37)	-3.659 (-4.89, -2.42)	
p-Value[a]	< 0.0001		< 0.0001	< 0.0001		< 0.001		< 0.0001	< 0.0001	

Table 7. Mean Weight Loss Change from Baseline at Week 52 in Individual and Pooled (APD356-009 and APD356-011) Phase 3 Studies: MITT, PP/Completer, and RDP/Wk52 Populations (cont.)

	APD356-009		APD356-011			Pooled -009 and -011		APD356-010		
	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	Placebo
Mean (±SE) weight change, %	-8.22 ± 0.26	-3.36 ± 0.28	-6.52 ± 0.35	-7.85 ± 0.25	-3.93 ± 0.25	-7.98 ± 0.17	-3.65 ± 0.17	-6.11 ± 0.62	-5.75 ± 0.46	-2.12 ± 0.36
p-Value[b]	< 0.0001		< 0.0001	< 0.0001		< 0.001				
Range, kg (%)	-36.0 – 11.7 (-33.3 – 13.3)	-38.2 -14.0 (-36.3 – 15.5)	-52.6 – 12.0 (-33.3 – 13.6)	-37.2 – 14.8 (-34.9 -12.4)	-56.1 – 20.0 (-46.2 – 17.5)	-37.2 - 14.8 (-34.9 – 13.3)	-56.1 – 20.0 (-46.3 – 17.5)	-23.7-5.3 (-18.4-4.3)	-36.1-4.3 (-30.5-4.4)	-24.3-16.5 (-18.2-16.5)
RDP/Wk52										
N	1031	901	524	1028	951	2043	1839	77	175	165
Mean baseline[a], kg	100.28 ± 15.96	99.15 ± 15.49	99.43 ± 16.58	100.35 ± 15.61	101.01 ± 16.32	100.30 ± 15.80	100.06 ± 15.95	105.92 ± 19.25	104.39 ± 18.10	101.38 ± 18.20
Mean (±SE) weight change, kg	-6.95 ± 0.23	-2.99 ± 0.22	-5.63 ± 0.33	-7.07 ± 0.23	-3.58 ± 0.23	-7.01 ± 0.16	-3.30 ± 0.16	-6.17 ± 0.63	-5.74 ± 0.48	-2.31 ± 0.37
Difference from Placebo (95% CI)	NR	NR	-2.105 (-2.88, -1.32)	-3.505 (-4.15, -2.86)		-3.70 (-4.15, -3.25)		-3.714 (-5.24, -2.19)	-3.376 (-4.57, -2.18)	
p-Value[b]	< 0.0001		< 0.0001	< 0.0001		< 0.001		< 0.0001	< 0.0001	
Mean (±SE) weight change, %	-7.01 ± 0.23	-2.99 ± 0.22	-5.67 ± 0.32	-7.18 ± 0.23	-3.55 ± 0.22	-7.09 ± 0.16	-3.28 ± 0.16	-6.02 ± 0.61	-5.58 ± 0.45	-2.26 ± 0.36
p-Value[b]	< 0.0001		< 0.0001	< 0.0001		< 0.001		< 0.0001	< 0.0001	
Range, kg (%)	-36.0 – 23.7 (-33.3 – 25.3)	-40.0 – 14.7 (-36.3 -15.9)	-52.6 -12.3 (-33.3 – 14.1)	-37.2 – 21.0 (-34.9 – 18.6)	-56.1 – 20.0 (-46.2 – 17.5)	-37.20 – 23.70 (-34.9- 25.3)	-56.10 – 20.00 (-46.3 – 17.5)	-23.7-5.3 (-18.4-4.3)	-36.1-4.3 (-30.5-4.4)	

[a] APD356-009 and APD356-010: Mean ± SE, APD356-011: Mean ± SD

[b] p-value compared to placebo group within same analysis

[c] Per protocol population analysis: APD356-009 and APD356-011, Completer analysis: Pooled data and APD356-010

MITT = modified intent-to-treat; NR = not reported; PP = Per Protocol; RDP = Returning Dropout population

CO-PRIMARY ENDPOINT 3: PROPORTION OF PATIENTS WHO LOST ≥ 10% OF BASELINE BODYWEIGHT AT WEEK 52

A significantly greater proportion of patients assigned to lorcaserin 10 mg BID lost 10% or more of their baseline body weight at Week 52 as compared to placebo in each individual study and in the pooled Phase 3 analysis (Figure 11, Table 8). As observed with the first and second co-primary endpoints, dose responsive efficacy was observed in patients without type 2 diabetes, but paradoxically, in patients with type 2 diabetes, more patients on the QD dose achieved at least 10% weight loss compared to patients on the BID dose.

Figure 11. Proportion of Patients achieving ≥ 10% Reduction in Body Weight after 52 Weeks of Treatment in Individual and Pooled Phase 3 Studies: MITT Population

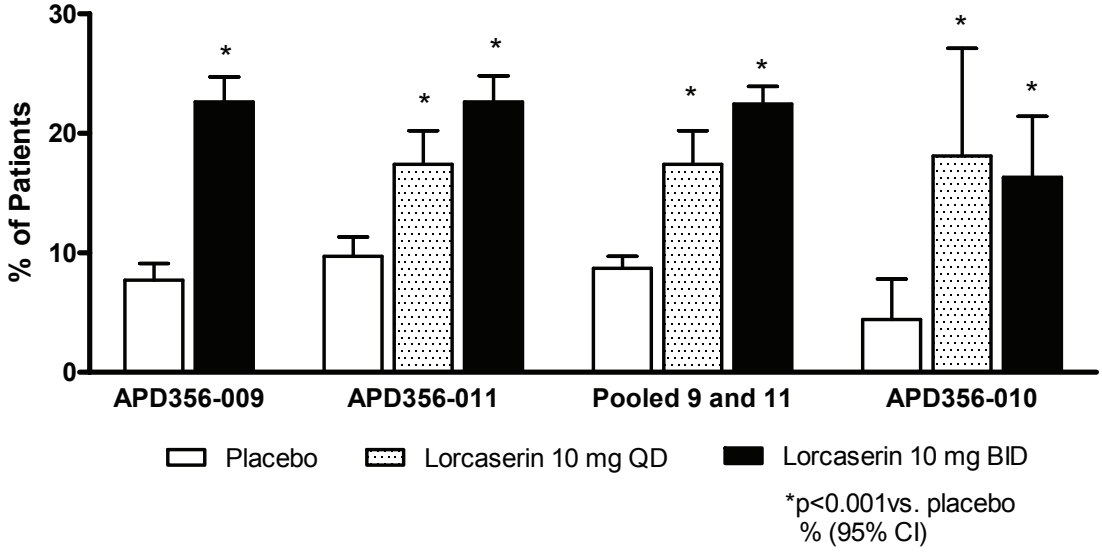


Table 8. Proportion of Patients Achieving ≥ 10% Body Weight Loss after 52 Weeks of Treatment in Individual and Pooled (APD356-009 and APD356-011) Phase 3 Studies: MITT, Per Protocol/Completer, and RDP/Wk52 Populations

	APD356-009		APD356-011			Pooled -009 and -011		APD356-010		
	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	Placebo
MITT										
N	1538	1499	771	1561	1541	3098	3038	94	251	248
n (%)	347 (22.6)	115 (7.7)	134 (17.4)	353 (22.6)	150 (9.7)	695 (22.43)	264 (8.69)	17 (18.1)	41 (16.3)	11 (4.4)
Difference from Placebo (95% CI)	14.9 (12.4, 17.4)		7.63 (4.58, 10.69)	12.88 (10.33, 15.43)		13.75 (11.97, 15.52)		13.65 (5.46, 21.84)	11.90 (6.66, 17.14)	
p-Value[a]	< 0.0001		< 0.0001	< 0.0001		< 0.001		< 0.0001	< 0.0001	
Per Protocol/Completers										
N	737	583	418	846	764	1775	1529	75	168	156
n (%)	267 (36.2)	79 (13.6)	110 (26.3)	297 (35.1)	123 (16.1)	616 (34.70)	224 (14.65)	17 (22.7)	35 (20.8)	9 (5.8)
Difference from Placebo (95% CI)	22.7 (18.2, 27.1)		10.22 (5.26, 15.18)	19.01 (14.87, 23.15)		20.06 (17.23, 22.90)		16.90 (6.74, 27.05)	15.06 (7.92, 22.21)	
p-Value[a]	< 0.0001		< 0.0001	< 0.0001		< 0.001		0.0003	0.0002	
RDP/Wk52										
N			524	1028	951	2043	1839	77	175	165
n (%)	NR	NR	124 (23.7%)	328 (31.9%)	137 (14.4%)	638 (31.23)	248 (13.49)	17 (22.1)	35 (20.0)	11 (6.7)
Difference from Placebo (95% CI)			9.26 (4.99, 13.53)	17.50 (13.88, 21.12)		17.76 (15.21, 20.30)		15.41 (5.40, 25.43)	13.33 (6.29, 20.38)	
p-Value[a]			< 0.0001	< 0.0001		< 0.001		0.0006	0.0004	

[a] p-value compared to placebo group within same analysis
NR = not reported

SENSITIVITY ANALYSES FOR YEAR 1 PRIMARY ENDPOINTS

Muliple steps and analyses were undertaken to accommodate the anticipated large number of dropouts typical of long-term obesity trials. Patients discontinuing from the trial were asked to return at the time of their scheduled Week 52 visit. This increased the proportion of patients with actual Week 52 weight measurements by ~10%, and these data are included in the prespecified RDP/Week 52 analyses presented in the tables above for the 3 co-primary efficacy endpoints.

Additional sensitivity analyses, using alternative imputation methods for missing data, were conducted using the data from individual studies and pooled studies APD356-009 and APD356-011 (lorcaserin 10 mg BID vs. placebo). Categorical and mean weight loss endpoints were analyzed using a repeated measures analysis and multiple imputation with the MITT population. The true ITT population (all randomized patients, even if no study medication was taken) was analyzed using baseline observation carried forward (BOCF) imputation for missing values. Each of the analyses confirmed the results of the primary analysis using the MITT population with LOCF imputation endpoints (Appendix 4). Even with the very conservative ITT/BOCF approach, using all randomized patients and carrying forward baseline weight for those who discontined prior to Week 52, highly statistically significant and meaningful differences were observed for lorcaserin BID as compared to placebo. In these analyses, proportions achieving at least 5% weight loss were 35.7% vs. 16.2% and mean weight losses of 4.4% vs. 1.8% were observed, respectively.

ADDITIONAL ANALYSIS OF YEAR 1 PRIMARY ENDPOINTS

As is true of any weight loss drug, individual responses vary. To determine how the patients most responsive to lorcaserin fared, Week 52 weight loss was determined for the upper quartile of lorcaserin BID and placebo-treated patients using both MITT/LOCF and Completer analyses in pooled phase 3 studies of non-diabetic patients (APD356-009 and -011) and in patients with type 2 diabetes (APD356-010) (Table 9). In the non-diabetic population, the lorcaserin BID quartile with the greatest Week 52 percent weight loss lost on average ~13 kg, or ~29 lbs, by MITT/LOCF analyses and ~16 kg, or ~35 lbs, by Completer analysis. In study APD356-010, the top quartile of lorcaserin BID patients lost on average ~11kg, or ~24 lbs by MITT/LOCF analysis and 13 kg, or ~29 lbs, by Completer analysis. In the placebo groups, similar results were seen in the non-diabetic population and somewhat less weight loss in the diabetic population. These results show a generally similar amount of weight loss for the most responsive patients in both groups, but it is important to note that there are 2-3 times more patients in the most responsive quartile with lorcaserin treatment.

Weight loss for responders (≥5% weight loss) and non-responders is presented in Table 10. A similar pattern of weight loss is observed as in the best responding quartile analyses, and again with twice as many lorcaserin BID as placebo responders. Lorcaserin non-responders also tended to lose more weight than placebo non-responders.

Table 9. Subgroup Analysis for Change from Baseline in Body Weight at Week 52 by Week 52 Percent Change from Baseline Body Weight: Quartile 1

Treatment Mean (SD)	N	Baseline	Week 52	Change from Baseline (kg)
MITT/LOCF				
Pooled Lorcaserin 10 mg BID	1057	98.52 (15.18)	85.65 (14.46)	-12.87 (0.16)
Pooled Placebo	453	99.03 (16.34)	86.49 (14.62)	-12.54 (0.30)
APD356-010 Lorcaserin 10 mg BID	82	102.12 (16.70)	90.81 (15.67)	-11.32 (0.59)
APD356-010 Placebo	29	100.80 (18.22)	90.93 (15.80)	-9.86 (0.78)
Completers				
Pooled Lorcaserin 10 mg BID	602	98.17 (14.82)	82.64 (13.62)	-15.85 (0.20)
Pooled Placebo	220	100.58 (17.26)	84.47 (15.15)	-15.94 (0.38)
APD356-010 Lorcaserin 10 mg BID	54	101.69 (17.44)	88.62 (15.71)	-13.07 (0.77)
APD356-010 Placebo	19	104.26 (19.33)	93.29 (16.87)	-10.97 (0.99)

SD=Standard Deviation; SE=Standard Error;

Pooled 009 and 011 MITT/LOCF:Q1 = -7.16 % , Q2 = -2.89 % , Q3 = -0.13 %; Completers: Q1 = -10.13 % , Q2 = -5.03 % , Q3 = -0.94 %

Study APD356-010: MITT/LOCF: Q1 = -5.9 %, Q2 = -2.8 %, Q3 = -0.4 %; Completers: Q1 = -7.3 %, Q2 = -3.4 %, Q3 = -0.8 %

To further address the study discontinuation issue, a conservative analysis was undertaken which utilized all patients randomized regardless of whether they took study drug or returned for a baseline visit (the ITT population) and which did not require imputation (assumes all dropouts are nonresponders): the proportion of the ITT population who remained in the study for 52 weeks and achieved responder status at this timepoint. In the pooled studies of the non-diabetic patients, 35.7% (1143 of 3198) of patients randomized to lorcaserin 10 mg BID completed the study and were categorized as responders; these patients achieved a mean percent weight loss of 11.2%. In the APD356-010 study, 30.5% of patients randomized to lorcaserin 10 mg BID (78 of 256) completed the study and were categorized as responders; mean percent weight loss in this group was 10.4%. The amount of weight loss achieved by placebo responders was similar, but the proportion of responders was approximately half of that in the lorcaserin BID groups, 16.2% in the pooled non-diabetic patient population (APD356-009 and -011) and 11.5% in the type 2 diabetic population (APD356-010). These results demonstrate that lorcaserin is highly effective in a large subgroup of patients taking the medication (Appendix 4, Table 65 and Table 66, ITT/BOCF).

Table 10. Subgroup Analysis for Percent Change from Baseline in Body Weight at Week 52 by Responder Status (5%): Completers Population

Treatment Mean (SD)	N	Baseline	Week 52	Percent Change from Baseline (%)
Pooled Responders (5%)				
Lorcaserin 10 mg BID	1135	99.17 (15.03)	87.44 (14.79)	-11.90 (0.17)
Placebo	512	99.39 (16.13)	88.45 (15.11)	-10.95 (0.26)
Pooled Non-Responders (5%)				
Lorcaserin 10 mg BID	640	102.88 (16.68)	101.82 (16.76)	-1.03 (0.12)
Placebo	1017	100.78 (16.16)	100.79 (16.51)	0.02 (0.11)
APD356-010 Responders (5%)				
Lorcaserin 10 mg BID	77	102.01 (17.65)	91.00 (16.46)	-10.76 (0.57)
Placebo	29	103.13 (18.71)	93.89 (16.84)	-8.89 (0.59)
APD356-010 Non-Responders (5%)				
Lorcaserin 10 mg BID	91	107.03 (17.91)	105.40 (17.73)	-1.51 (0.25)
Placebo	127	101.39 (18.22)	100.79 (18.27)	-0.57 (0.27)

SD=Standard Deviation; SE=Standard Error;

Lastly, Figure 12 and Table 11 below display the proportions of patients achieving various categorical weight loss levels at Week 52 by both MITT/LOCF and Completer analyses for the combined non-diabetic (APD356-009 and -011) and the diabetic population (APD356-010). More than 80% of lorcaserin BID patients had 0 to 2.4% weight loss from baseline, and at each greater categorical level thereafter, approximately 2-3 times as many lorcaserin BID patients as placebo patients achieved each threshold of weight loss.

Figure 12. Categorical Weight Loss Achieved by Lorcaserin BID and Placebo Patients at Week 52 by MITT/LOCF and Completer Analyses of the Phase 3 Non-diabetic and Diabetic Populations

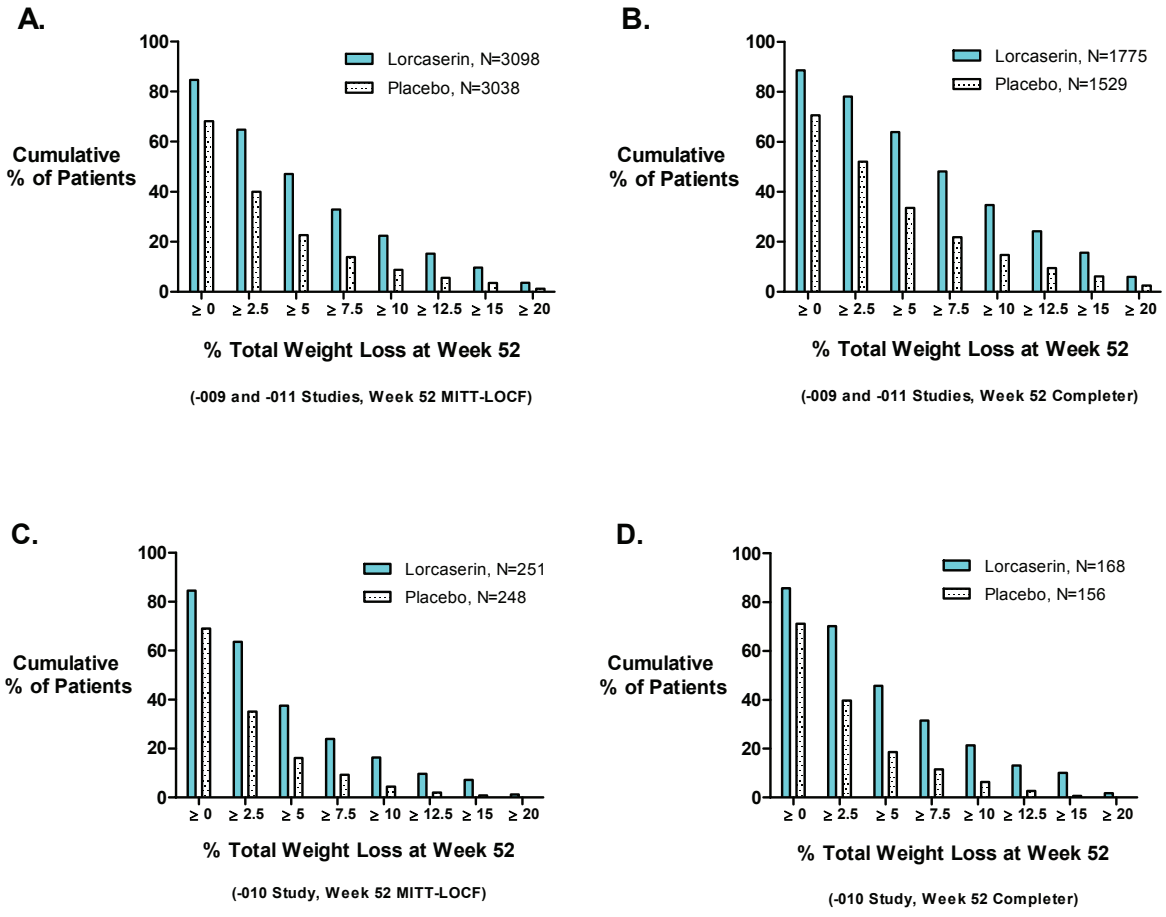


Table 11. Number (%) of Subjects with Total Weight Loss at Week 52

Treatment	N	Total Weight Loss at Week 52 ≥ 0%	≥ 2.5%	≥ 5%	≥ 7.5%	≥ 10%	≥ 12.5%	≥ 15%	≥ 20%
Pooled (APD356-009 and -011)									
					MITT/LOCF				
Lorcaserin 10 mg BID	3098	2625 (84.7)	2009 (64.8)	1460 (47.1)	1018 (32.9)	695 (22.4)	472 (15.2)	298 (9.6)	111 (3.6)
Placebo	3038	2069 (68.1)	1215 (40.0)	687 (22.6)	421 (13.9)	264 (8.7)	168 (5.5)	105 (3.5)	39 (1.3)
					Completers				
Lorcaserin 10 mg BID	1775	1571 (88.5)	1386 (78.1)	1135 (63.9)	854 (48.1)	616 (34.7)	430 (24.2)	279 (15.7)	107 (6.0)
Placebo	1529	1078 (70.5)	796 (52.1)	512 (33.5)	335 (21.9)	224 (14.7)	145 (9.5)	95 (6.2)	38 (2.5)
APD356-010									
					MITT/LOCF				
Lorcaserin 10 mg BID	251	212 (84.5)	160 (63.7)	94 (37.5)	60 (23.9)	41 (16.3)	24 (9.6)	18 (7.2)	3 (1.2)
Placebo	248	171 (69.0)	87 (35.1)	40 (16.1)	23 (9.3)	11 (4.4)	5 (2.0)	2 (0.8)	0 (0)
					Completers				
Lorcaserin 10 mg BID	168	144 (85.7)	118 (70.2)	77 (45.8)	53 (31.5)	36 (21.4)	22 (13.1)	17 (10.1)	3 (1.8)
Placebo	156	111 (71.2)	62 (39.7)	29 (18.6)	18 (11.5)	10 (6.4)	4 (2.6)	1 (0.6)	0 (0)

ANALYSIS OF YEAR 2 PRIMARY ENDPOINT: MAINTENANCE OF WEIGHT LOSS

The primary endpoint for Year 2 in the APD356-009 study was the proportion of patients among the Year 1 lorcaserin subgroup that lost at least 5% of baseline weight at Week 52 who were able to maintain this level of weight loss (at least 5% body weight reduction relative to Baseline) at Week 104. The group that remained on lorcaserin for the full 2 years was compared to the group that was treated with lorcaserin during Year 1 and blindly re-randomized to placebo during Year 2. The primary Year 2 analysis used the MITT2 population, which included all patients who entered Year 2 and had at least one weight measurement subsequent to Week 52. As shown in Table 12 (MITT2), Figure 13 (MITT2) and Figure 14 (Year 2 Per Protocol population), patients who remained on lorcaserin following 1 year of treatment were better able to maintain the weight loss achieved during Year 1 compared with those who switched to placebo. Although all treatment groups regained some weight during Year 2, those who continued to take lorcaserin regained significantly less weight than those who switched to placebo. Moreover, mean weight change from baseline to Week 104 was significantly greater in the group assigned to lorcaserin who completed both years (6.1%, Figure 14) than in the group assigned to placebo that completed 2 years (2.6%) or the group that switched from lorcaserin to placebo after 1 year (4.2%).

Table 12. Proportion of Year 1 Lorcaserin Patients Losing ≥ 5% of Baseline Weight at Week 52 Who Maintained at Least 5% Weight Loss from Baseline at the End of Week 104: APD356-009, MITT2 Population

Treatment	N	n (%) Lost ≥ 5% of Baseline Weight and Maintained at least 5% Weight Loss		
Lorcaserin/Lorcaserin	380	258 (67.9%)		
Lorcaserin/Placebo	175	88 (50.3%)		
Between Treatment Comparison	**Difference in Proportion (%) (95% CI)**	**p-Value**		
		Treatment	**Gender**	**Baseline Body Weight**
Lorc/Lorc vs. Lorc/Pbo	17.6 (8.8, 26.4)	< 0.0001	0.8224	0.8595

Notes: 95% Confidence Interval for difference in proportions were calculated using normal approximation.
p-Values were calculated by using logistic regression model with effects for baseline body weight, treatment and gender.
Lorc = lorcaserin; Pbo = placebo

Figure 13. Change in Body Weight from Baseline to Week 104 in APD356-009: MITT2 Population

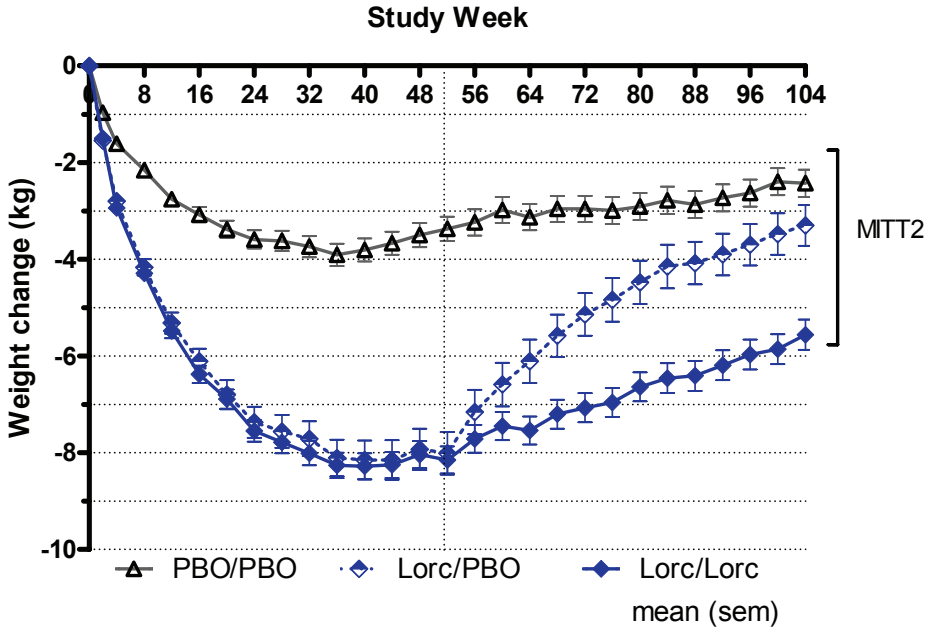
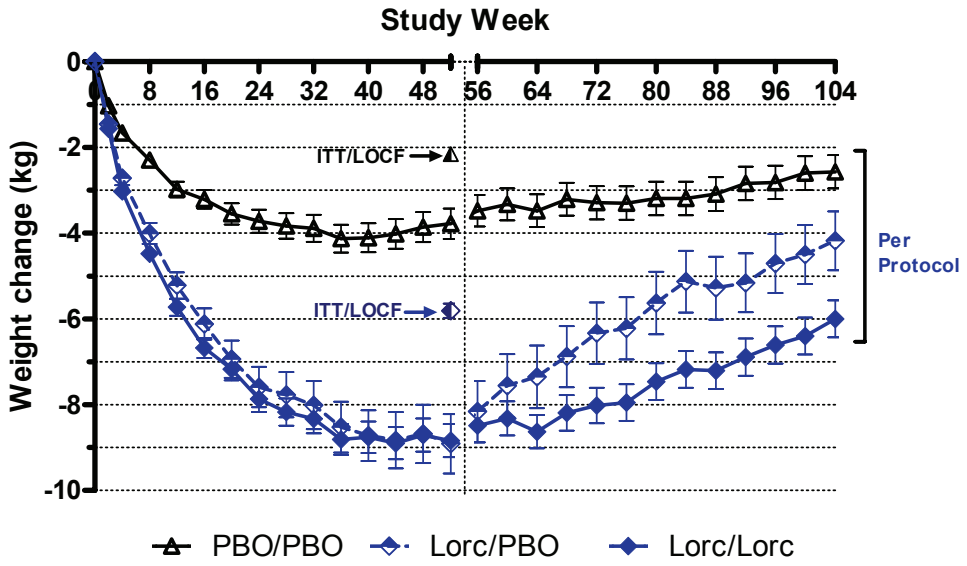


Figure 14. Change in Body Weight from Baseline to Week 104 in APD356-009: PP2 Population



3.9.2 Secondary Efficacy Analyses

3.9.2.1 Secondary Efficacy Parameters in Studies APD356-009 and APD356-011, Non-diabetic Patients

In the pooled Phase 3 dataset from studies APD356-009 and APD356-011, lorcaserin significantly improved anthropometric measures, serum lipid profiles, blood pressure, glycemic parameters, quality of life, and other markers of cardiovascular risk (hsCRP, fibrinogen). Significant improvements were also observed in insulin resistance and hsCRP in study APD356-009, and body fat content decreased significantly in study APD356-011 (Table 13).

Lorcaserin was associated with a 2.1 kg/m^2 LS mean decrease in BMI, compared with a 0.9 unit decrease in the placebo group. Waist circumference, an independent indicator of cardiovascular risk, decreased 6.6 cm in the lorcaserin group and 4 cm in the placebo group ($p<0.001$ for difference in LS means).

Patients on lorcaserin had significantly greater mean decreases in total cholesterol and triglycerides, and a significantly greater mean increase in HDL cholesterol as compared with placebo. LDL cholesterol increased in both treatment groups from baseline to Week 52, but the increase was signifantly less in the lorcaserin group (1.6%) than in the placebo group (2.9%; $p=0.015$). Apolipoproteins A1 (ApoA1) and B (ApoB) were measured in a subset of patients in study APD356-011. Changes from baseline in ApoA1 were not different in the lorcaserin and placebo groups, while ApoB decreased ("improved") signficicantly in the lorcaserin group compared with placebo.

Studies APD356-009 and APD356-011 excluded patients with diabetes; however, the population was insulin resistant, as indicated by baseline HOMA-IR values greater than 1.5. Mean fasting glucose was statistically significantly decreased by lorcaserin (-0.2 mg/dL) compared to placebo (+0.6 mg/dL), and lorcaserin caused a small but statistically significant decrease in HbA1c. The measures of fasting insulin and HOMA-IR may be more meaningful in this non-diabetic population. In study APD356-009, fasting insulin decreased significantly in the lorcaserin group (-3.3 μIU/mL) relative to placebo (-1.3 μIU/mL), resulting in significant improvement in insulin resistance (indicated by HOMA-IR) in the lorcaserin group (-0.4) compared with placebo (-0.2).

Systolic and diastolic blood pressure decreased significantly in the lorcaserin group relative to baseline and relative to placebo. Systolic blood pressure decreased on average 1.8 mmHg in the lorcaserin group and 1.0 mmHg in the placebo group. Diastolic blood pressure decreased 1.6 mmHg with lorcaserin and 1 mmHg with placebo. Heart rate, which was measured as a safety parameter, also decreased relative to baseline and relative to placebo in the lorcaserin group.

Lorcaserin significantly improved quality of life, as indicated by the total (corrected) score on the IWQOL-Lite questionnaire. Potential scores range up to 100 points, with a higher score reflecting a higher quality of life.

Highly sensitive C-reactive protein (hsCRP), measured in the APD356-009 study, was significantly decreased by lorcaserin, as was fibrinogen. Both inflammatory markers are associated with increased cardiovascular risk.

Table 13. Summary of Change from Baseline to Week 52 for Secondary Efficacy Endpoints in Pooled Studies APD356-009 and APD356-011: MITT Population

Parameter Mean	Lorcaserin 10 mg BID			Placebo			p- Value[a]
	N	Baseline mean (sd)	Change LS mean (sem)	N	Baseline mean (sd)	Change LS mean (sem)	
Pooled APD3356-009 and APD356-011 Analyses							
Anthropometric Measures							
BMI (kg/m^2)	3098	36.1 (4.3)	-2.1 (0.0)	3038	36.1 (4.2)	-0.9 (0.0)	< 0.001
Waist circumference (cm)	2830	109.3 (12.1)	-6.6 (0.2)	2721	109.6 (12.2)	-4.0 (0.2)	< 0.001
Lipid Parameters							
Triglycerides (% change)	2882	135.4 (75.7)	-5.3 (0.7)	2780	137.0 (78.5)	-0.5 (0.7)	< 0.001
Total cholesterol (% change)	2882	194.4 (36.1)	-0.9 (0.2)	2780	194.8 (35.6)	0.4 (0.2)	< 0.001
LDL cholesterol (% change)	2869	114.3 (31.2)	1.6 (0.4)	2764	114.1 (29.7)	2.9 (0.4)	0.015
HDL cholesterol (% change)	2882	53.2 (13.3)	1.8 (0.3)	2780	53.5 (13.9)	0.6 (0.3)	0.001
Glycemic Parameters							
Fasting glucose (mg/dL)	2934	92.1 (10.6)	-0.2 (0.2)	2861	92.4 (10.6)	0.6 (0.2)	< 0.001
HbA1c (%)	2466	5.6 (0.4)	-0.12 (0.0)	2290	5.6 (0.4)	-0.05 (0.0)	< 0.001
Blood Pressure							
Systolic (mmHg)	3096	121.4 (11.9)	-1.8 (0.2)	3039	121.5 (11.7)	-1.0 (0.2)	0.007
Diastolic (mmHg)	3096	77.4 (8.1)	-1.6 (0.1)	3039	77.7 (8.1)	-1.0 (0.1)	0.003
Heart Rate[c]	3096	69.5 (8.7)	-1.2 (0.2)	3039	69.5 (8.9)	-0.4 (0.2)	<0.001
IWQOL-Lite total score	2648	74.3 (16.1)	12.0 (0.2)	2466	74.6 (16.0)	10.1 (0.2)	< 0.001
Analyses from Individual Studies							
Fasting insulin (µIU/mL)[b]	1234	15.9 (13.0)	-3.3 (0.4)	1165	15.8 (13.2)	-1.3 (0.4)	0.0002
HOMA-IR (%)[b]	1220	1.9 (1.1)	-0.41 (0.0)	1145	1.9 (1.1)	-0.17 (0.030)	< 0.0001
hsCRP (g/L)	1263	5.5 (0.2)	-1.19 (0.2)	1145	5.4 (0.2)	-0.17 (0.19)	< 0.0001
Fibrinogen (mg/dL)	1123	364.8 (2.2)	-21.5 (2.2)	1011	363.2 (2.3)	-10.6 (2.1)	0.0002
Apolipoprotein A1 (% change)	580	147.3 (24.7)	-0.22 (0.46)	520	147.3 (25.6)	-0.43 (0.489)	0.7604
Apolipoprotein B (% change)	578	91.2 (22.4)	-2.87 (0.66)	518	90.6 (21.2)	1.39 (0.698)	< 0.0001
Total body fat (% change)[b]	85	44.5 (8.1)	-9.9 (1.4)	69	45.0 (9.0)	-4.6 (1.05)	< 0.005

[a] P value for difference in LS means

[b] Mean values provided rather than LS mean

[c] Heart rate was a prespecified safety parameter, but not a prespecified efficacy measure; this is a post-hoc analysis.

3.9.2.2 Secondary Efficacy Parameters in Study APD356-010, Patients with Type 2 Diabetes

Lorcaserin BID was associated with significantly greater decreases in BMI, waist circumference, hip circumference, and percent body fat than placebo (Table 14). The decreases in body fat content of 7.3% with lorcaserin and 2.2% with placebo were accompanied by decreases in waist circumference of 5.5 cm with lorcaserin and 3.3 cm with placebo (p=0.006).

Glycemic control, which is discussed in greater detail below, was significantly improved over placebo with lorcaserin. HbA1c decreased 0.9 units in the lorcaserin group and 0.4 units in the

placebo group ($p<0.0001$). Fasting plasma glucose also decreased significantly more in the lorcaserin group (27.4 mg/dL) than in the placebo group (11.9 mg/dL; $p<0.0001$).

Changes in lipids, diastolic blood pressure, hsCRP, and IWQOL scores trended favorably relative to placebo with lorcaserin BID, but did not reach statistical significance. Although systolic blood pressure decreased from baseline in the lorcaserin group (-0.8 mmHg), the decrease was not greater than that observed in the placebo group (-0.9 mmHg). Of note, the majority of patients in the APD356-010 study were taking concomitant medications for the treatment of hypertension and/or dyslipidemia, which may have confounded the assessment of lorcaserin effects on blood pressure and lipids.

Table 14. Secondary Efficacy Endpoints Change from Baseline at Week 52 in Study APD356-010 (Type 2 Diabetes): MITT Population

Mean (sem) Change from Baseline at Week 52 in:	Lorcaserin 10 mg BID			Placebo			
	N	Baseline Mean (sd)	Change LS mean (sem)	N	Baseline Mean (sd)	Change LS mean (sem)	p-Value[a]
Anthropometric Measures							
BMI (kg/m^2)	251	36.1 (4.5)	-1.6 (0.1)	248	35.8	-0.6 (0.1)	< 0.0001
Waist circumference (cm)	225	115.8 (11.8)	-5.5 (0.5)	224	113.5 (12.6)	-3.3 (0.5)	0.0006
Hip circumference (cm)	225	120.0 (11.0)	-4.1 (0.5)	224	118.9 (12.0)	-2.8 (0.5)	0.0288
Total body fat (% change)	18	46.8 (10.0)	-7.3 (2.5)	23	45.4 (10.8)	-2.2 (1.4)	ND
Lean body mass (kg)	18	58.7 (10.0)	-1.8 (0.7)	23	54.7 (12.5)	-2.3 (0.6)	0.7569
Glycemic Parameters							
HbA1c (%)	238	8.1 (0.9)	-0.9 (0.1)	232	8.0 (0.9)	-0.4 (0.1)	< 0.0001
Fasting plasma glucose (mg/dL)	242	163.6 (48.3)	-27.4 (2.5)	244	160.0 (41.6)	-11.9 (2.5)	< 0.0001
Fasting insulin (µIU/mL)	245	15.0 (10.0)	-3.0 (0.7)	244	16.2 (14.7)	-1.6 (0.7)	0.1203
HOMA-IR	227	2.3 (1.4)	-0.5 (0.1)	217	2.3 (1.4)	-0.2 (0.1)	NC
HOMA-B (%)	227	59.6 (43.1)	9.9 (3.3)	217	60.7 (45.5)	3.4 (3.4)	NC
Lipid Parameters (% change)							
Triglycerides (%)	251	172.1 (103.6)	-10.7 (2.5)	244	163.5 (87.5)	-4.8 (2.5)	0.0541
HDL cholesterol (%)	250	45.3 (11.0)	5.2 (1.0)	244	45.7 (12.7)	1.6 (1.1)	NC
LDL cholesterol (%)	242	95.0 (30.4)	4.2 (2.6)	238	94.6 (30.2)	5.0 (2.6)	NC
Total cholesterol (%)	250	173.5 (35.3)	-0.7 (1.1)	244	172.0 (35.7)	-0.1 (1.2)	NC
Apo A-1 (%)	246	138.9 (21.3)	-0.1 (0.7)	234	138.9 (23.1)	-1.7 (0.8)	0.0836
Apo B (%)	246	86.0 (22.1)	-5.1 (1.4)	234	85.6 (21.6)	-2.1 (1.5)	0.0903
Blood Pressure (mmHg)							
Systolic	251	126.6 (12.7)	-0.8 (0.8)	248	126.5 (13.5)	-0.9 (0.9)	0.8905
Diastolic	251	77.9 (8.0)	-1.1 (0.6)	248	78.7 (7.9)	-0.7 (0.6)	NC
Heart Rate[b]	251	72.3 (9.2)	-2.0 (0.6)	248	72.7 (9.0)	-0.4 (0.6)	0.030
hs-CRP (mg/L)	246	6.6 (9.6)	-1.3 (0.4)	245	5.4 (6.7)	-0.6 (0.4)	0.15
IWQOL-Lite score[c]	224	74.7 (16.2)	11.3 (0.7)	227	74.0 (17.6)	10.2 (0.7)	0.2206

[a] P value for difference in LS means between lorcaserin and placebo

[b] Heart rate was a prespecified safety (not efficacy) parameter, this is a post-hoc analysis.

[c] The reported score is converted to a 1-100 scale. Increases in quality of life score on this scale represent improvement in quality of life.

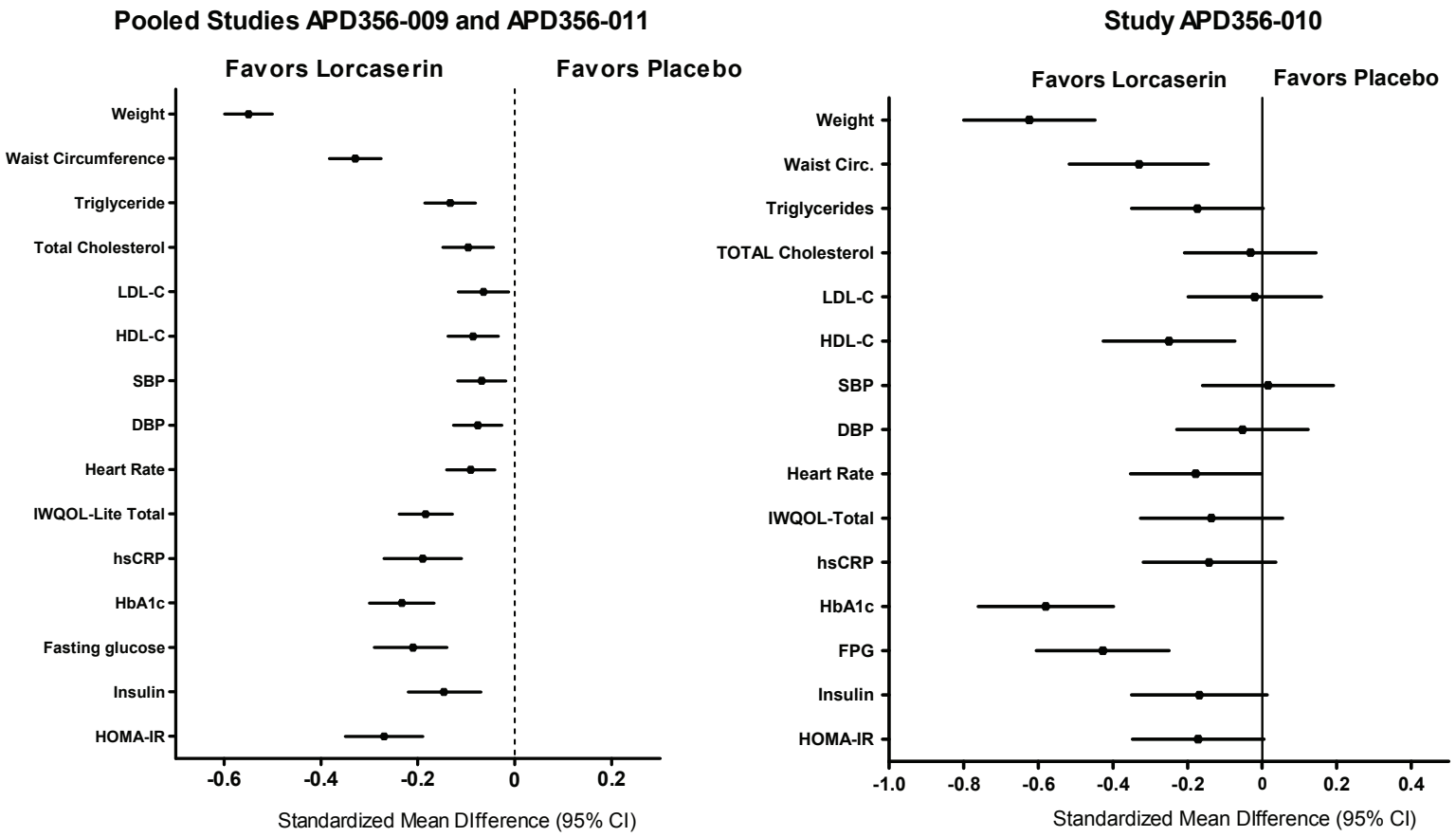
NC = not calculated; statistical testing was not performed as specified by multiplicity testing rule.

3.9.2.3 Summary of Treatment Effects on Efficacy Parameters

The effects of lorcaserin BID relative to placebo on efficacy measures are summarized in Figure 15, which presents the standardized mean differences with 95% confidence intervals for all of the Phase 3 studies. Of note, changes in all parameters directionally favor lorcaserin in studies APD356-009 and APD356-011. Similarly, the majority of changes in study APD356-010 favored lorcaserin. Systolic and diastolic blood pressure decreased by approximately 1 mmHg in both the lorcaserin and placebo groups. The decrease in the lorcaserin BID group (-0.8 mmHg) was slightly less that the decrease with placebo (-0.9 mmHg; Table 14).

Changes in glycemic control among patients with diabetes mellitus are among the key new efficacy analyses provided with the NDA submission. Figure 15 shows the changes in HbA1c, fasting glucose, insulin and insulin resistance to be improved with lorcaserin relative to placebo. These results are described in greater detail in the section that follows.

Figure 15. Standardized Mean Differences (95% CI) for Key Study Endpoints (Lorcaserin 10 mg BID vs. Placebo) in Pooled Studies APD356-009 and APD356-011 and in Study APD356-010



Note: Lipids and body weight are percentage change from baseline. SMD and confidence interval were computed from the least square means of LOCF value at Week 52 and pooled standard deviations produced by ANCOVA model with treatment as factor and adjusted baseline parameter value.

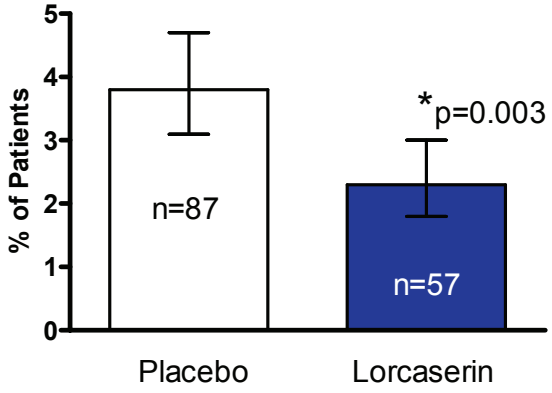
DBP = diastolic blood pressure; FPG = fasting plasma glucose; SBP = systolic blood pressure

3.9.2.4 Effects of Lorcaserin on Glycemic Control in Patients with Type 2 Diabetes Mellitus

DEVELOPMENT OF NEW TYPE 2 DIABETES MELLITUS IN STUDIES APD356-009 AND APD356-011

Approximately 25% of patients randomized into studies APD356-009 and APD356-011 had impaired fasting glucose on the basis of their baseline fasting blood glucose measurement. While few adverse events of "diabetes mellitus" were reported, more than 2% of patients developed biochemical criteria for type 2 diabetes during the trial. Using the definition of HbA1c ≥6.5, the proportion of patients developing new criteria for diabetes was 1.6 fold greater in the placebo as compared with the lorcaserin BID group (Figure 16).

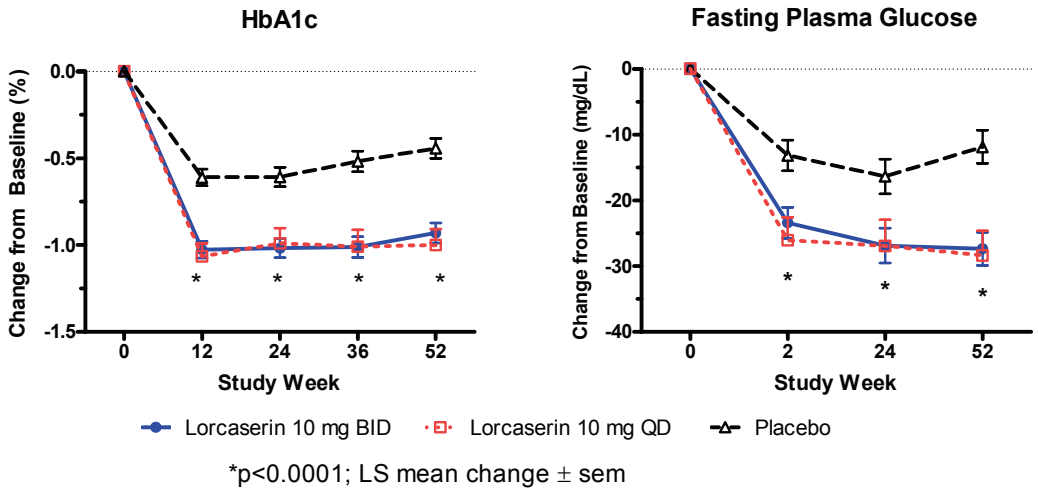
Figure 16. Proportion of Patients with New Diabetes Mellitus (HbA1c ≥6.5) during Studies APD356-009 and APD356-011



EFFECTS OF LORCASERIN ON GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Investigators for study APD356-010 were asked to avoid adjusting anti-hyperglycemic medications during the initial 3 months of the trial unless necessary to assure patient safety. This minimized the confounding effects of medication adjustments on glycemic parameters at the Week 12 time point. Investigators were subsequently allowed to adjust medications according to their clinical judgment. HbA1c and fasting plasma glucose declined in all treatment groups at Week 12, with significantly greater decreases in the lorcaserin groups relative to placebo (Figure 17). Both parameters reached plateaus between Week 12 and Week 52.

Figure 17. Change in HbA1c and Fasting Plasma Glucose by Study Visit in APD356-010: MITT Population with LOCF Imputation



At Baseline, mean HbA1c was 8%. At Week 52, approximately half the patients in the lorcaserin groups had achieved HbA1c values < 7%, the target set by the American Diabetes Association,[39] as compared with 26% of patients assigned to placebo (MITT/LOCF profile, Table 15). Among patients who completed the 52-week trial, the proportion achieving target HbA1c levels was predictably higher, and was significantly greater in the lorcaserin groups than in the placebo group.

Table 15. Proportion of Patients Achieving Target HbA1c of 7% or 6.5% or Target Fasting Glucose by Study Visit in APD356-010: MITT and Completer Populations

Parameter Study Week	MITT/LOCF						Completers					
	Placebo		Lorcaserin 10 mg BID		Lorcaserin 10 mg QD		Placebo		Lorcaserin 10 mg BID		Lorcaserin 10 mg QD	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Patients with HbA1c < 7%												
Baseline	248	20 (8.1)	251	20 (8.0)	94	6 (6.4)	157	12 (7.6)	169	15 (8.9)	75	3 (4.0)
Week 12	230	79 (34.3)	236	132 (55.9)	91	49 (53.8)	156	62 (39.7)	169	105 (62.1)	75	44 (58.7)
Week 52	232	61 (26.3)	238	120 (50.4)	92	48 (52.2)	157	43 (27.4)	169	94 (55.6)	75	42 (56.0)
Patients with HbA1c < 6.5%												
Baseline	248	1 (0.4)	251	1 (0.4)	94	0	157	0	169	0	75	0
Week 12	230	19 (8.3)	236	58 (24.6)	91	22 (24.2)	156	15 (9.6)	169	49 (29.0)	75	19 (25.3)
Week 52	232	20 (8.6)	238	57 (23.9)	92	26 (28.3)	157	13 (8.3)	169	45 (26.6)	75	23 (30.7)
Patients with FPG < 126 mg/dL												
Baseline	245	53 (21.6)	244	47 (19.3)	93	22 (23.7)	156	34 (21.8)	164	31 (18.9)	74	19 (25.7)
Week 52	247	72 (29.1)	249	105 (42.2)	94	42 (44.7)	157	46 (29.3)	168	76 (45.2)	74	35 (47.3)
Patients with FPG < 100 mg/dL												
Baseline	245	13 (5.3)	244	12 (4.9)	93	7 (7.5)	156	8 (5.1)	164	10 (6.1)	74	5 (6.8)
Week 52	247	14 (5.7)	249	35 (14.1)	94	13 (13.8)	157	6 (3.8)	168	27 (16.1)	74	8 (10.8)

Note: Entry criterion was HbA1c of 7-10%; some patients had decreases between Screening and Baseline visits.

Among weight loss responders (those losing ≥ 5% of baseline weight at Week 52), greater reductions in HbA1c were observed than in non-responders (Table 16). Similarly, HbA1c decreased more among patients who began the study with HbA1c ≥ 9% than in those with HbA1c < 9% (Table 16). In each case, lorcaserin was associated with greater reductions in HbA1c than was placebo.

Table 16. HbA1c Change from Baseline at Week 52 by Responder Status and HbA1c Subgroups: MITT Population

Subgroup	Placebo		Lorcaserin 10 mg BID		Lorcaserin 10 mg QD	
	Baseline[a]	Change from Baseline[b]	Baseline[a]	Change from Baseline[b]	Baseline[a]	Change from Baseline[b]
Responders	8.01 (0.73)	-0.44 (0.06)	8.07 (0.80)	-1.45 (0.14)	7.91 (0.82)	-1.29 (0.10)
Non-responders	8.03 (0.95)	-0. 31 (0.07)	8.14 (0.97)	-0.70 (0.09)	8.15 (0.97)	-0.69 (0.14)
Baseline HbA1c:						
< 9%	7.8 (0.7)	-0.20 (0.1)	7.8 (0.7)	-0.76 (0.1)	7.9 (0.7)	-0.94 (0.1)
≥ 9%	9.4 (0.8)	-1.3 (0.2)	9.2 (0.7)	-1.7 (0.2)	9.4 (0.5)	-1.6 (0.3)

[a] Mean (SD)

[b] Mean (SEM)

The use of medications to treat diabetes decreased in patients taking lorcaserin concurrently with the mean improvement in glycemic control (Table 17). In particular, mean daily doses of sulfonylureas and thiazolidinediones decreased 16-24% in the lorcaserin groups, and increased in the placebo group. Metformin use changed little during the trial.

Table 17. Changes in use of Drugs to Treat Type 2 Diabetes Mellitus during the APD356-010 Study: MITT/LOCF

Parameter	Placebo N=252		Lorcaserin 10 mg BID N=256	
	N	n(%)	N	n(%)
Change in total daily dose (n [%])[a]	245		249	
Decrease	--	29 (11.7)	--	43 (17.1)
No change	--	161 (64.9)	--	172 (68.5)
Increase	--	55 (22.2)	--	34 (13.5)
Patients discontinuing all diabetes meds (n [%])	252	1 (0.4)	256	3 (1.2%)
Mean (SD) % daily dose change[b]				
Metformin	219	6.6(40.1)	222	-0.8 (35.9)
SFU	127	6.5 (98.9)	132	-16.0 (63.0)
TZD	61	3.3 (89.0)	57	-16.4 (40.3)
DPP-IV Inhibitors	36	-6.9 (34.1)	23	-4.3 (20.9)
Patients starting new drug by class (n [%])[c]	252		256	
Metformin	--	3 (1.2)	--	3 (1.2)
SFU	--	10 (4.0)	--	9 (3.5)
TZD	--	9 (3.6)	--	3 (1.2)
DPP-IV Inhibitors	--	13 (5.1)	--	10 (3.9)
Patients stopping drug by class (n [%])[c]	252		256	
Metformin	--	0 (0.0)	--	10 (3.9)
SFU	--	8 (3.2)	--	21 (8.2)
TZD	--	4 (1.6)	--	8 (3.1)
DPP-IV Inhibitors	--	3 (1.2)	--	1 (0.4)

[a] Total daily dose of all anti-hyperglycemic agents.

[b] For medications with missing dose, data are omitted.

[c] Refers to initiation of new drug between randomization and final study visit.

SFU = sulfonylureas; TZD = thiazolidinediones; DPP-IV = dipeptidyl peptidase IV; --, not relevant for analysis

To summarize, lorcaserin was associated not only with weight loss among patients with type 2 diabetes, but with significant improvement in glycemic control as well. Patients taking lorcaserin experienced decreases in HbA1c and fasting glucose, with half the lorcaserin group reaching the American Diabetes Association treatment goal of HbA1c $\leq$7. The improvement in glycemia was associated with decreased use of the most common anti-hyperglycemic agents in the trial.

3.9.2.5 Efficacy in Subgroups in Pooled Phase 3 Studies APD356-009 and APD356-011 and in Study APD356-010

Among the non-diabetic patients in studies APD356-009 and APD356-011, all subgroups were more likely to lose ≥ 5% of baseline body weight (Figure 18) when receiving lorcaserin. Comparable weight loss efficacy was observed in men and women, in all racial subgroups, and across the entire BMI range studied (Table 18). The similar weight loss in kg among the body weight quartiles indicates a slightly higher percent weight loss in the lower body weight quartile. This observation is consistent with population PK modeling, which showed a weak negative correlation between body weight and lorcaserin exposure, and a positive correlation between lorcaserin exposure and percent weight loss. Results were similar in study APD356-010, although the confidence intervals are wider in this smaller patient population (Figure 19, Table 18).

Figure 18. Odd Ratios for Achieving ≥ 5% Weight Loss from Baseline to Week 52 in Pooled Studies APD356-009 and APD356-011: MITT/LOCF

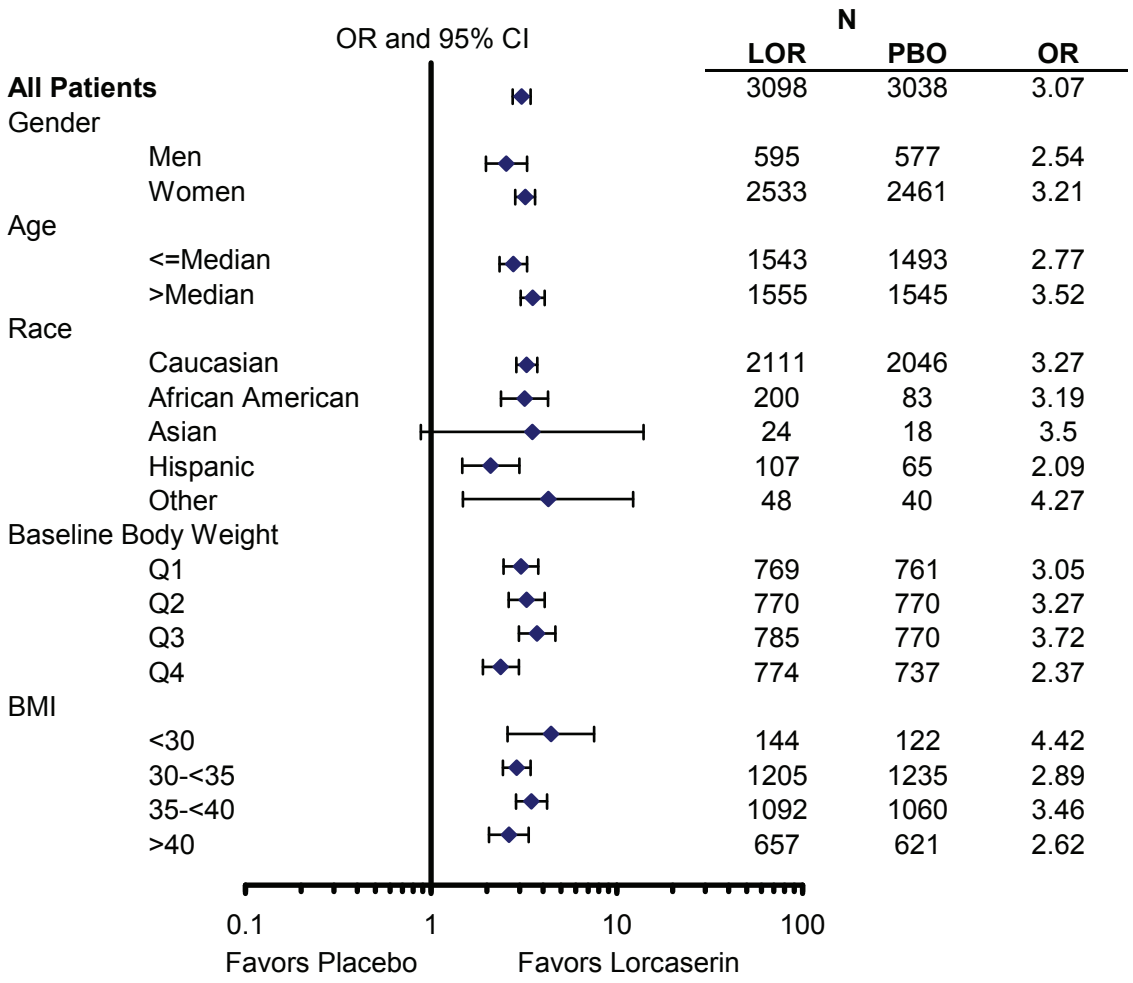


Figure 19. Odd Ratios for Achieving ≥ 5% Weight Loss from Baseline to Week 52 in Study APD356-010: MITT/LOCF

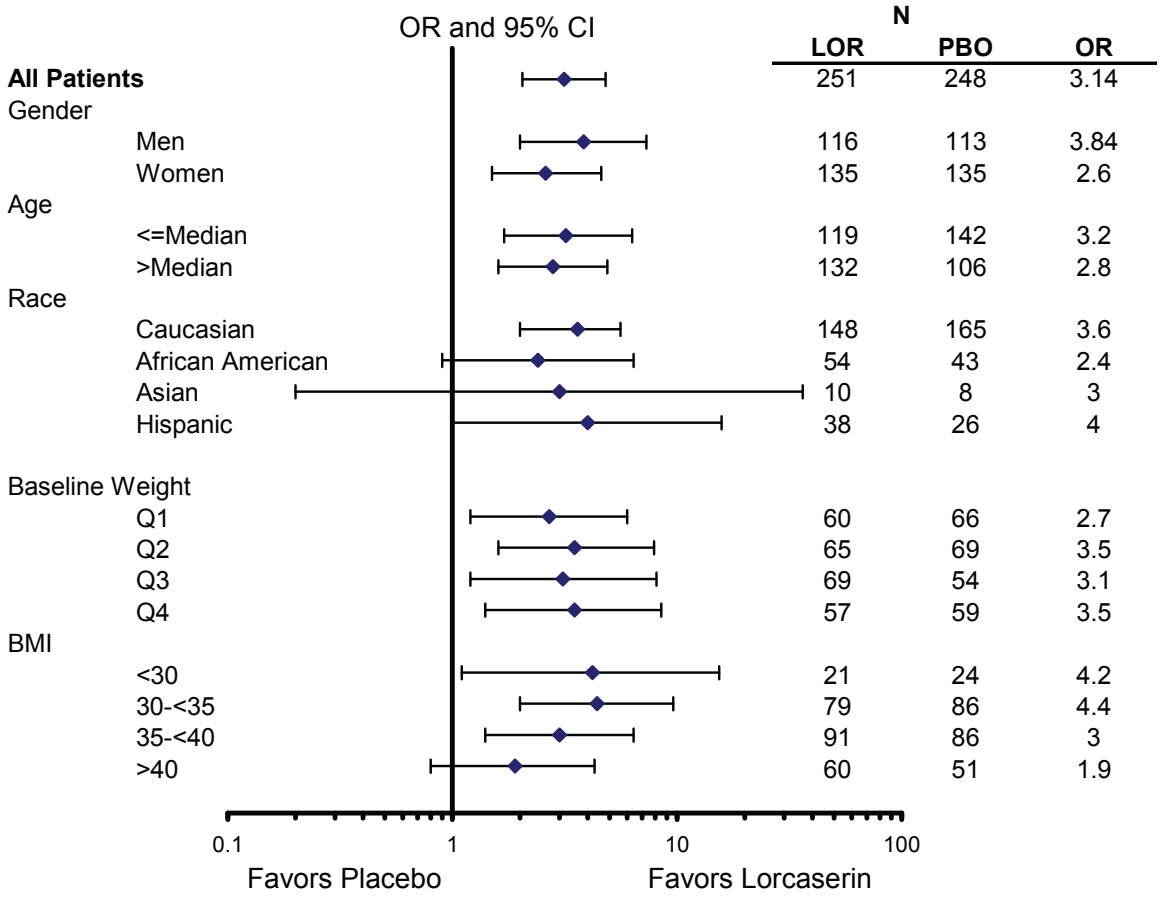


Table 18. Summary of Mean Weight Change from Baseline to Week 52 in Patient Subgroups in Pooled Phase 3 Studies (APD356-009 and APD356-011) and Study APD356-010: MITT/LOCF

	Pooled APD356-009 and APD356-011: Non-Diabetic Patients						APD356-010: Patients with Type 2 Diabetes					
	Placebo			Lorcaserin 10 mg BID			Placebo			Lorcaserin 10 mg BID		
Subgroup	n	Baseline Mean (SD)	Change Mean (SEM)	n	Baseline Mean (SD)	Change Mean (SEM)	n	Baseline Mean (SD)	Change Mean (SEM)	n	Baseline Mean (SD)	Change Mean (SEM)
Gender												
Female	2461	97.0 (14.1)	-2.4 (0.1)	2533	97.3 (14.0)	-5.7 (0.1)	135	95.3 (15.3)	-1.7 (0.3)	135	97.1 (14.5)	-4.7 (0.5)
Male	577	114.1 (15.8)	-3.2 (0.3)	565	114.2 (15.4)	-6.1 (0.3)	113	110.6 (17.5)	-2.0 (0.5)	116	111.0 (17.1)	-5.2 (0.6)
Age												
≤ median[a]	1493	101.5 (16.2)	-1.8 (0.1)	1543	102.2 (15.5)	-4.4 (0.2)	142	103.5 (17.9)	-1.2 (0.3)	119	105.4 (18.8)	-3.7 (0.4)
> median[a]	1545	99.01 (15.6)	-3.2 (0.2)	1555	98.6 (15.6)	-7.1 (0.2)	106	100.6 (18.1)	-2.7 (0.5)	132	101.9 (15.4)	-6.0 (0.6)
Race/ethnicity												
Caucasian	2046	100.8 (16.3)	-3.1 (0.1)	2111	101.0 (16.0)	-6.6 (0.2)	165	104.5 (18.3)	-2.1 (0.3)	148	106.0 (17.1)	-5.5 (0.5)
African American	567	101.0 (14.6)	-1.2 (0.2)	576	102.6 (14.5)	-4.0 (0.2)	43	100.2 (13.8)	-1.4 (0.6)	54	101.8 (16.3)	-4.5 (0.7)
Hispanic/Latino	367	96.2 (14.8)	-1.5 (0.2)	339	93.5 (13.8)	-3.5 (0.3)	26	97.2 (17.5)	-1.6 (0.8)	38	99.3 (16.3)	-3.4 (0.6)
Asian	18	89.9 (14.7)	-2.6 (1.1)	24	88.5 (11.6)	-5.5 (1.1)	8	82.0 (17.3)	-0.6 (1.4)	10	91.1 (20.2)	-4.0 (1.5)
Other	40	102.4 (17.0)	-1.6 (0.7)	48	98.9 (13.6)	-4.8 (0.7)	6	105.2 (22.6)	-2.1 (1.4)	1	114.5[b]	-9.7[b]
Baseline Body Weight Quartile												
Q1 (< 88.3 kg)	761	81.6 (5.1)	-2.2 (0.2)	769	81.8 (5.1)	-5.3 (0.2)	66	81.3 (8.4)	-1.6 (0.4)	60	82.5 (7.2)	-4.6 (0.5)
Q2 (88.3-98.7 kg)	770	93.6 (3.0)	-2.3 (0.2)	770	93.7 (3.0)	-5.7 (0.2)	69	96.8 (2.9)	-1.7 (0.5)	65	96.9 (2.8)	-4.5 (0.7)
Q3 (> 98.7-110.5 kg)	770	104.3 (3.4)	-2.1 (0.2)	785	104.4 (3.4)	-6.0 (0.2)	54	108.1 (3.7)	-1.4 (0.5)	69	108.2 (3.9)	-4.4 (0.7)
Q4 (> 110.5 kg)	737	122.1 (9.9)	-3.4 (0.3)	774	121.4 (9.4)	-6.1 (0.3)	59	126.8 (9.9)	-2.7 (0.7)	57	127.5 (9.7)	-6.5 (1.0)
Baseline BMI Subgroups												
< 30 kg/m^2	122	79.4 (7.5)	-1.8 (0.4)	144	79.4 (8.8)	-5.6 (0.5)	24	79.5 (10.6)	-1.8 (0.8)	21	78.2 (9.6)	-5.0 (0.8)
30 - < 35 kg/m^2	1235	90.6 (10.6)	-2.5 (0.2)	1205	90.7 (10.2)	-5.4 (0.2)	86	93.7 (13.3)	-1.7 (0.4)	79	96.1 (12.0)	-4.7 (0.7)
35 - < 40 kg/m^2	1060	103.4 (11.6)	-2.2 (0.2)	1092	103.6 (11.5)	-5.9 (0.2)	86	106.1 (12.5)	-1.3 (0.4)	91	104.9 (11.6)	-4.5 (0.6)
≥ 40 kg/m^2	621	118.0 (13.3)	-3.2 (0.3)	657	117.2 (12.8)	-6.1 (0.3)	51	120.6 (15.0)	-3.2 (0.8)	60	120.1 (15.4)	-5.8 (0.9)

[a] Median age in APD356-009 and APD356-011, 44 years; median age in APD356-010, 54 years.

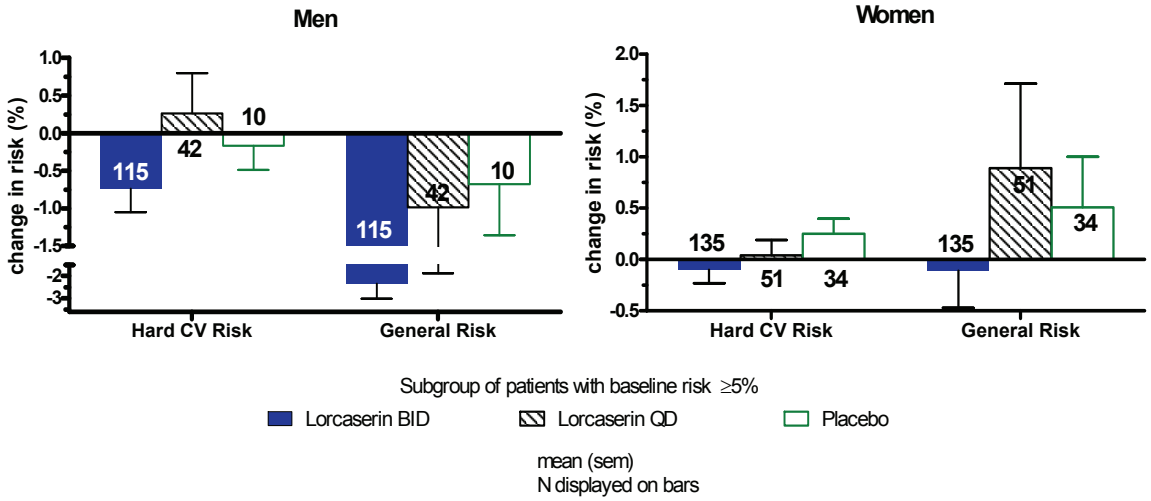
[b] No SD or SEM reported

3.9.3 Application of Framingham Calculators to Predict Effects of Lorcaserin on Long Term Cardiovascular Risk

In each of the phase 3 studies, lorcaserin was associated with changes in multiple parameters that can be predictive of cardiovascular risk. As an exploratory method to predict the long term impact of these changes, Framingham calculators were used. These calculators predict the 10-year risk of "hard"cardiovascular events (related to coronary artery disease) cardiovascular events and "general" cardiovascular events(coronary and cerebrovascular events) based on factors that include sex, age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and smoking status ("hard cardiovascular outcomes"); the "general cardiovascular outcomes" calculator also considers the presence of diabetes.[40-42]

As illustrated in Figure 20 for study APD356-010, lorcaserin twice daily reduced predicted 1-year cardiovascular risk as compared with placebo. The twice daily dose resulted in more favorable "hard cardiovascular risk" and "general cardiovascular risk" predictions than did the once daily dose in men and women with baseline risk ≥ 5%.

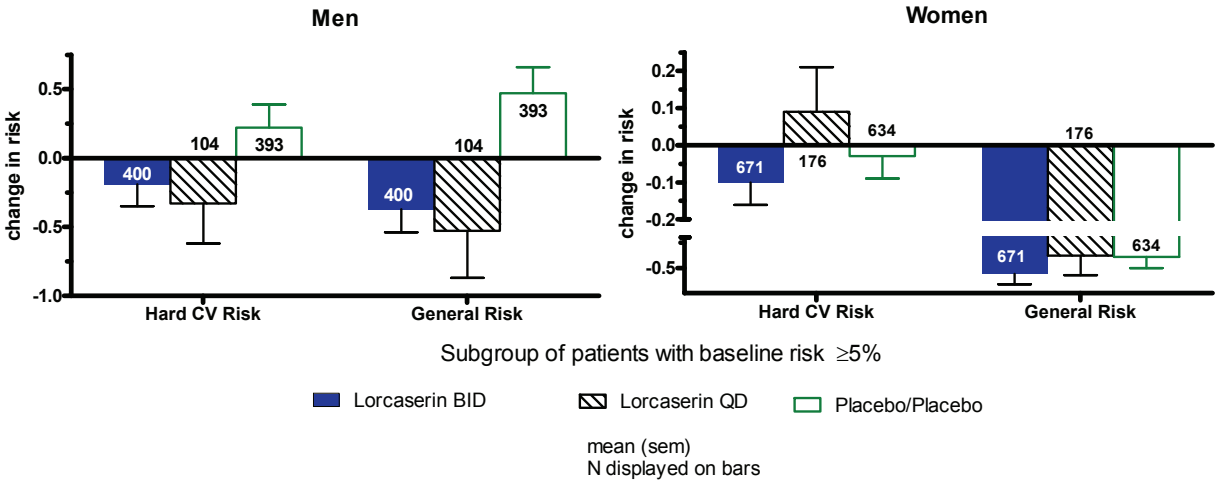
Figure 20. Dose Effect on Framingham Risk Scores in Study APD356-010: MITT/LOCF



Note: Hard CV calculation was based on www.framinghamheartstudy.org/risk/hrdcoronary.html ; General CV calculation was based on www.framinghamheartstudy.org/risk/gencardio.html

Diabetes was exclusionary in studies APD356-009 and APD356-011, but among those patients who had a baseline predicted cardiovascular risk score ≥5%, lorcaserin BID reduced the 10 year "hard CV" or "general CV" predicted risks relative to placebo in men (n= 110) and women (Figure 21). The once daily dose group, which had a smaller sample size than did the twice daily lorcaserin group, was associated with decreased predicted risk compared with placebo in men but not in women.

Figure 21. Dose Effect on Framingham Risk Scores in Pooled Studies APD356-009 and APD356-011: MITT/LOCF



3.9.4 Onset of Action

As illustrated in Figure 10, weight loss was apparent by the first post-baseline time point (2 weeks) and was statistically significantly greater in the lorcaserin groups than in the placebo group.

3.9.5 Maintenance of Long-term Benefit

Weight loss reached a maximum at approximately Week 32-36, and then remained essentially constant until Week 52. Two-year efficacy was assessed in the APD356-009 study. Greater mean body weight loss from baseline to Week 104 was achieved in the lorcaserin/lorcaserin group relative to the placebo/placebo group or the lorcaserin placebo group (Figure 14). Patients who remained on lorcaserin for 2 years were better able to maintain through Year 2 the weight loss achieved during Year 1, as compared to patients who switched to placebo at the end of Year 1. In addition, improvements in many cardiometabolic parameters were maintained in Year 2.

3.9.6 Dosing Recommendations

The recommended lorcaserin dose is 10 mg twice daily. This recommendation is derived from efficacy and safety data (Section 3.10) and from population PK analyses.

Dose-responsive efficacy was demonstrated in Phase 2 studies and in the APD356-011 study, which evaluated lorcaserin at doses of 10 mg once daily and 10 mg twice daily (Figure 9, Figure 10, Figure 11). Consistent with the dose-related weight loss, the effects of lorcaserin on serum lipids, blood pressure, and body composition were also dose-related (Table 20).

In contrast, lorcaserin 10 mg once daily had efficacy comparable to that of lorcaserin twice daily among the patients with type 2 diabetes in study APD356-010 (Figure 9, Figure 10, Figure 11). Changes in anthropometric measures, lipids, glycemic parameters, and blood pressure were

sometimes greater at the once daily dose and sometimes at the twice daily dose in study APD356-010 (Table 14). The reason for the lack of consistent dose-response among the patients with type 2 diabetes is unknown.

Exposure increased with increasing total daily lorcaserin dose (Table 19).

Table 19. Lorcaserin Plasma Concentration (ng/mL) in Study APD356-010: Week 12

Time Point	Mean (SD) Plasma Lorcaserin (ng/mL)	
	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID
Pre-dose	7.1 (6.3)	19.3 (12.4)
2 hours post-dose	32.9 (14.0)	42.8 (16.3)

Table 20. Dose Effect on Secondary Endpoints in Phase 3 Studies APD356-009 and APD356-011: MITT/LOCF

Pooled Studies		Placebo N=3138	Lorcaserin 10 mg QD N=658	Lorcaserin 10 mg BID N=3198
Waist circumference (cm)	Baseline	109.6 (12.17)	108.5 (12.69)	109.3 (12.13)
	Change from Baseline	-4.0 (0.15)	-5.6 (0.32)	-6.5 (0.15)
	p value		< 0.001	< 0.001
BMI (kg/m^2)	Baseline	36.06 (4.21)	35.85 (4.32)	36.11 (4.27)
	Change from Baseline	-0.90 (0.04)	-1.69 (0.09)	-2.09 (0.04)
	p value		< 0.001	< 0.001
Total cholesterol (mg/dL; % change)	Baseline	194.8 (35.60)	194.8 (37.75)	194.35 (36.11)
	Change from Baseline	0.35 (0.25)	-1.41 (0.50)	-0.82 (0.25)
	p value		0.0293	< 0.001
LDL cholesterol (mg/dL; % change)	Baseline	114.1 (29.71)	116.7 (31.97)	114.25 (31.17)
	Change from Baseline	2.96(0.40)	-0.25 (0.73)	1.63 (0.40)
	p value		0.0534	0.015
HDL cholesterol (mg/dL; % change)	Baseline	53.5 (13.93)	51.8 (13.55)	53.24 (13.28)
	Change from Baseline	0.57(0.27)	3.45 (0.66)	1.81 (0.27)
	p value		0.0019	0.001
Triglycerides (mg/dL; % change)	Baseline	137.0 (78.52)	133.3 (77.95)	135.4 (75.67)
	Change from Baseline	-0.57 (0.70)	-5.36 (1.564)	-5.18 (0.73)
	p value		0.0079	< 0.001
Systolic blood Pressure (mmHg)	Baseline	121.51 (11.74)	121.2 (12.12)	121.39 (11.86)
	Change from Baseline	-1.05 (0.21)	-1.1 (0.43)	-1.73 (0.22)
	p value		0.7922	0.007
Diastolic blood pressure (mmHg)	Baseline	77.71 (8.09)	78.0(8.43)	77.44 (8.05)
	Change from Baseline	-1.04 (0.16)	-1.0 (0.32)	-1.50 (0.16)
	p value		0.4151	0.003
Quality of Life (IWQOL-LITE score)	Baseline	74.55 (16.04)	75.50 (15.95)	74.32 (16.13)
	Change from Baseline	10.09 (0.21)	11.32 (0.40)	12.01 (0.20)
	p value		0.005	< 0.001
Analyses for APD356-011 Only		**N=69**	**N=35**	**N=85**
Body fat (kg; % change)	Baseline	45.00 (8.97)	45.68 (9.84)	44.54 (8.05)
	Change from Baseline	-4.61 (1.05)	-6.07 (2.03)	-9.90 (1.39)

Note: Pooled studies: Baseline values are mean (SD); change from baseline values are mean ± SEM.

As discussed in the sections that follow, the safety and tolerability of lorcaserin were comparable with the once daily and twice daily doses in non-diabetic patients and in patients with type 2 diabetes. Hence, tolerability did not clearly favor the lower dose.

Given the clear dose-responsive efficacy among non-diabetic patients, the evidence (albeit limited) that the twice daily dose may have greater benefit than the once daily dose in patients with type 2 diabetes, and the comparable tolerability of the two dose levels, Arena is requesting approval only of the 10 mg twice daily dose.

3.9.7 Efficacy Conclusions

Treatment with lorcaserin resulted in significantly greater weight loss in obese patients and in overweight patients with at least one weight related co-morbid condition, including patients with type 2 diabetes mellitus. Lorcaserin 10 mg BID met the three pre-specified co-primary endpoints in the individual Phase 3 studies and in the analyses of pooled Year 1 data from studies APD356-009 and APD356-011, or pooled data from all three studies:

Studies APD356-009 and APD356-011 (non-diabetic patients, MITT/LOCF):

- 47.1% of patients treated with lorcaserin 10 mg BID achieved the goal of ≥ 5% reduction in body weight after 52 weeks as compared to 22.6% of patients treated with placebo ($p < 0.001$).
- Patients treated with lorcaserin 10 mg BID lost (LS Mean ± SE) 5.8 ± 0.1 kg as compared to 2.5 ± 0.1 kg weight loss in the placebo group ($p < 0.001$).
- 22.4% of patients treated with lorcaserin 10 mg BID achieved the goal of ≥ 10% weight loss from Baseline to Week 52 as compared to 8.7% of the patients from the placebo group ($p < 0.001$).

Study APD356-010 (patients with type 2 diabetes mellitus):

- 37.5% of patients treated with lorcaserin 10 mg BID achieved the goal of ≥ 5% reduction in body weight after 52 weeks as compared to 16.1% of patients treated with placebo ($p < 0.001$).
- Patients treated with lorcaserin 10 mg BID lost (LS Mean ± SE) 5.4 ± 0.6 kg as compared to 1.9 ± 0.3 kg weight loss in the placebo group ($p < 0.001$).
- 16.3% of patients treated with lorcaserin 10 mg BID achieved the goal of ≥ 10% weight loss from Baseline to Week 52 as compared to 4.4% of the patients from the placebo group ($p < 0.001$).

The pre-specified weight maintenance endpoint for Year 2 of the APD356-009 study was also achieved:

- 67.9% of Year 1 lorcaserin patients losing at least 5% of baseline body weight at Week 52 who remained on lorcaserin during Year 2 maintained ≥ 5% weight loss from baseline at Week 104, as compared to 50.3% of patients who were re-randomized to placebo during Year 2 ($p < 0.0001$).

Lorcaserin 10 mg BID had generally favorable effects on cardiovascular risk factors, metabolic parameters and quality of life scores. These effects included the following statistically significant changes in the pooled dataset of non-diabetic patients: decreases in anthropometric measures (BMI, waist circumference), improvements in serum lipid measures, decreases in systolic and

diastolic blood pressure, and improved quality of life scores (IWQOL-Lite). Favorable trends or significant effects were also shown for fasting glucose, fasting insulin, insulin resistance (HOMA-IR), body composition, and inflammatory markers of cardiovascular risk (hsCRP, fibrinogen). In addition, improvements relative to placebo in many of these secondary measures, though lessened, were maintained in Year 2 of the APD356-009 study, where lorcaserin was also associated with significantly greater weight loss from baseline than was placebo.

Among patients with type 2 diabetes mellitus, lorcaserin 10 mg BID had the additional effect of causing statistically and clinically significant improvements in glycemic control that included reduced HbA1c and reduced use of medications used to treat diabetes. The effects of lorcaserin on lipids and blood pressure in this population were small; the small magnitude may be because the majority of patients used concomitant medications for the treatment of hypertension and/or dyslipidemia. Importantly, lorcaserin 10 mg BID was not associated with changes relative to placebo in any parameter in an unfavorable direction. Specifically, lorcaserin did not increase blood pressure or heart rate.

Finally, among all demographic subgroups evaluated (sex, ethnicity, age, starting body weight and BMI), lorcaserin had greater efficacy for weight loss than did placebo.

3.10 Summary of Safety

3.10.1 Overview of Safety Evaluation

Safety evaluations during the clinical development of lorcaserin included standard adverse event monitoring; comprehensive evaluations of clinical laboratory parameters, ECGs, vital signs, and physical examinations; and assessments based on theoretical off-target lorcaserin effects. In addition, because lorcaserin is a centrally acting agent, abuse potential, depression and suicidal ideation, and psychomotor performance were evaluated.

The presentation of adverse events describes treatment-emergent adverse events, which are defined as events that began after the first dose of study drug was taken. Unless otherwise specified, adverse events are presented using Medical Dictionary for Regulatory Activity (MedDRA) terms for organ class and preferred term.

3.10.1.1 Mechanistic Considerations

Lorcaserin is a selective 5-HT_{2C} receptor agonist. In *in vitro* assays, lorcaserin also interacts with the 5-HT_{2A} and 5-HT_{2B} receptors, albeit with lower potency (1/14th and 1/61st that for the 5-HT_{2C}, respectively). Lorcaserin is a partial agonist of the 5-HT_{2A} receptor (25% the activity of serotonin) and a full agonist at the 5-HT_{2B} receptor. Distribution of the 5-HT_{2C} receptor is limited, with minimal or no expression outside the CNS.[43] The primary function of the 5-HT_{2C} receptor is regulation of food intake and body weight. In contrast, both the 5-HT_{2A} and 5-HT_{2B} receptors are expressed in the CNS and peripherally. No significant lorcaserin binding or functional activity was identified at a panel of *in vitro* assays of other G-protein coupled receptors, transporters and ion channels. Given these findings, the safety evaluation program for lorcaserin included, in addition to standard safety assessments, a comprehensive evaluation of effects that could result from activation of 5-HT_{2A} or 5-HT_{2B} receptors.

POTENTIAL CONCERNS RELATED TO 5-HT$_{2B}$ RECEPTOR ACTIVATION

The 5-HT$_{2B}$ receptor is expressed in the heart; activation of this receptor is thought to underlie the valvular heart disease associated with such agents as fenfluramine, ergotamine, and pergolide.[2, 20, 21, 44, 45] A comprehensive echocardiographic monitoring program initiated during Phase 2 was continued through Phase 3 clinical trials to evaluate possible changes in valvular function or morphology. Mulitiple analyses of over ~21,000 echoes from ~7800 patients in the Phase 3 program suggests that at the recommened clinical dose of 10mg twice daily, lorcaserin is not associated with valular heart disease.

POTENTIAL CONCERNS RELATED TO 5-HT$_{2A}$ RECEPTOR ACTIVATION

Activation of the 5-HT$_{2A}$ receptor by some agents can cause alterations in perception and mood.[46, 47] The association between 5-HT$_{2A}$ agonist activity and perceptual effects is not consistent, suggesting that different receptor agonists may signal through alternate pathways that mediate different functions.[48] Although behaviors associated with 5-HT$_{2A}$ activation were not consistently observed in rodent studies of lorcaserin, several types of safety measures related to cognitive function, mood and perception were instituted in the clinical development program. In Phase 1 and/or Phase 2 studies, formal cognitive, mood and motor tests were administered. During Phase 3, mood (in particular, depression) was prospectively evaluated using the Beck Depression Inventory-II. A formal abuse liability clinical study was also conducted (APD356-013). Results from these safety measures suggest that that at the recommended clinical dose of 10 mg twice daily, lorcaserin is not associated with meaningful changes in cognitive function, mood or perception.

POTENTIAL GENERAL CONCERNS RELATED TO SEROTONERGIC AGENTS

Serotonin and some serotonergic agents can increase prolactin release.[49, 50] The effect appears to be an indirect one, and is mediated through both the hypothalamus and the pituitary. 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_{2C}$ receptors have been implicated in serotonin-mediated prolactin release.[50] To monitor for possible lorcaserin effects, serum prolactin was measured pre-dose and post-dose in the single-dose APD356-001A study and in Phase 3 studies APD356-010 and APD356-011. Surveillance for adverse events that could be associated with hyperprolactinemia was also conducted. Serum prolactin concentrations measured in studies APD356-010 and APD356-011 were also pooled for re-analysis. The mean changes from baseline at Weeks 4, 12, 24 and 52 in serum prolactin were less than 1 ng/mL in all treatment groups, and lorcaserin did not increase the incidence of hyperprolactinemia.

The serotonin syndrome is a potentially serious constellation of neuromuscular, autonomic and behavioral symptoms that results from excessive stimulation of central 5-HT$_{1A}$ receptors.[51, 52] Activation of 5-HT$_2$ receptor(s) may also contribute to the syndrome.[51, 52] The symptoms typically arise from overdose of a single serotonergic agent, or combination of two or more agents that increase serotonin release, inhibit serotonin reuptake, or directly activate the relevant serotonin receptors. Labeling of approved serotonergic drugs cautions that with concurrent use of other serotonergic agents, there is a theoretical risk of serotonin syndrome; hence, most serotonergic agents (e.g., SSRIs, SNRIs) were excluded from all clinical trials of lorcaserin although it was later discovered that some patients were taking other serotonergic agents during

the phase 3 program. Specific surveillance to evaluate adverse events that have been associated with the serotonin syndrome was conducted. No cases meeting criteria for serotonin syndrome were reported in the lorcaserin clinical program, however some symptoms of possible serotonergic etiology were reported by patients treated with lorcaserin and placebo during the phase 3 program. The proposed labeling for lorcaserin includes a warning for the theoretical risk of serotonin syndrome and recommends that lorcaserin should only be combined with other agents that affect serotonin pathways only when the benefits clearly outweigh the risks, and advises careful observation of the patient particularly during treatment initiation and concomitant medication dose increases.

3.10.2 Common Treatment Emergent Adverse Events

3.10.2.1 Overview of Adverse Events

This section summarizes adverse events reported in Phase 3 studies. A summary of adverse events reported in single-dose studies is provided in Appendix 5. The single-dose data are provided to illustrate the dose-dependence of adverse events, and the nature of adverse events that were observed at supra-therapeutic doses.

Year 1 data for studies APD356-009 and APD356-011 are presented as a pooled analysis, since the patient populations were comparable. To illustrate dose effects, data for the 10 mg QD dose, which are derived only from the APD356-011 study, are presented alongside the pooled data. Data from the APD356-010 study of weight management in patients with type 2 diabetes were analyzed separately and are presented alongside the pooled data for non-diabetic patients.

Year 2 adverse event data from the APD356-009 study are provided in a separate section that follows the presentation of Phase 3 Year 1 data.

3.10.2.2 Year 1 Adverse Events in Phase 3 Studies

Most patients enrolled in Phase 3 trials reported at least one adverse event during the trials (Table 21). The proportions of non-diabetic patients reporting events were similar among treatment groups, with 82.5% of patients exposed to any dose of lorcaserin and 75.5% of patients on placebo reporting an AE in Year 1. Slightly higher proportions of patients with type 2 diabetes reported at least one adverse event. Across all treatment groups, most of the AEs were mild or moderate in severity; only ~10% of patients experienced an AE that was rated severe.

The most common adverse events in the Phase 3 studies are summarized by MedDRA System Organ Class (SOC) in Table 22 and by MedDRA Preferred Term (PT) in Table 23. The most frequently reported SOC was Infections and Infestations, consistent with Upper Respiratory Tract Infection, Nasopharyngitis and Sinusitis appearing as 3 of the 4 most frequent PT. SOCs with a 50% or greater relative excess of events in the non-diabetic lorcaserin BID group include Nervous System (30.7% of patients versus 19.4%), General (17.2% vs. 10.7%), Eye (4.5% vs. 3.0%), Ear and Labyrinth (3.1% vs. 2.0%), and Cardiac Disorders (2.7% vs. 1.8%). Among patients with type 2 diabetes, Eye Disorders, Immune System, Ear and Labyrinth and Hepatobiliary Disorders met these criteria (Table 22).

Among Preferred Terms, headache was the most frequent in non-diabetic patients and among the most frequent in diabetic patients, and was over-represented in the lorcaserin groups as compared to placebo. PTs that were reported by ≥ 3% of patients and with a 50% or greater relative excess in the lorcaserin BID group as compared to placebo in the pooled studies or in study APD356-010 are summarized in Table 23. The table is ordered by decreasing frequency in the pooled lorcaserin BID group. Few adverse event terms were reported by more than 10% of patients; those that were tended to have comparable incidence among placebo and lorcaserin treated patients. Unique to patients with type 2 diabetes was the high incidence of the preferred term hypoglycaemia, with higher incidence in the lorcaserin BID group. The preferred term includes a broad array of suspected events, documented and undocumented events, and events with or without symptoms. Across all treatment groups, AEs were generally mild or moderate in severity, and infrequently resulted in study discontinuation (range 6-9%).

Table 21. Overall Summary of Treatment-Emergent Adverse Events in APD356-010 and Pooled APD365-009 and APD356-011: Year 1 Safety Population

n(%) of patients	Pooled APD356-009 and APD356-011: Non-Diabetic Patients			APD356-010: Patients with Type 2 Diabetes		
	Placebo N=3185	Lorcaserin 10 mg BID N=3195	Lorcaserin 10 mg QD N=801	Placebo N=252	Lorcaserin 10 mg BID N=256	Lorcaserin 10 mg QD N=95
Number (%) of Patients Reporting AEs	2406 (75.5)	2645 (82.8)	653 (81.5)	213 (84.5)	236 (92.2)	89 (93.7)
N (%) of patients with:						
Drug-related AE	799 (25.1)	1186 (37.1)	267 (33.3)	68 (27.0)	108 (42.2)	38 (40.0)
SAE	73 (2.3)	87 (2.7)	27 (3.4)	17 (6.7)	16 (6.3)	8 (8.4)
Drug-related SAE	6 (0.2)	9 (0.3)	0	3 (1.2)	0	0
Death	2 (0.06)	0	0	0	0	0
Discontinuation/Stop Study Drug due to AE	217 (6.8)	274 (8.6)	60 (7.5)	14 (5.6)	22 (8.6)	7 (7.4)
Discontinuation /Stop Study Drug due to SAE	33 (1.0)	35 (1.1)	7 (0.9)	5 (2.0)	6 (2.3)	4 (4.2)
N (%) of Patients Reporting						
0 AEs	779 (24.5)	550 (17.2)	148 (18.5)	39 (15.5)	20 (7.8)	6 (6.3)
1 AE	602 (18.9)	544 (17.0)	141 (17.6)	46 (18.3)	36 (14.1)	10 (10.5)
> 1 AEs	1804 (56.6)	2101 (65.8)	512 (63.9)	167 (66.3)	200 (78.1)	79 (83.2)
N (%) of Patients Reporting AEs by Maximum Intensity[a]						
Mild	815 (25.6)	888 (27.8)	232 (29.0)	79 (31.3)	93 (36.3)	23 (24.2)
Moderate	1305 (41.0)	1406 (44.0)	333 (41.6)	102 (40.5)	118 (46.1)	52 (54.7)
Severe	285 (8.9)	348 (10.9)	88 (11.0)	32 (12.7)	25 (9.8)	13 (13.7)
N (%) of Patients Reporting AEs by Relationship to Study Treatment[a]						
Probable	161 (5.1)	299 (9.4)	60 (7.5)	11 (4.4)	25 (9.8)	7 (7.4)
Possible	638 (20.0)	887 (27.8)	207 (25.8)	57 (22.6)	83 (32.4)	31 (32.6)
Unlikely	478 (15.0)	453 (14.2)	135 (16.9)	45 (17.9)	41 (16.0)	25 (26.3)
Not Related	1123 (35.3)	1000 (31.3)	251 (31.3)	100 (39.7)	87 (34.0)	26 (27.4)

[a] Patients reporting one or more adverse events are counted once at the maximum intensity and most direct relationship of all adverse events.

Table 22. Summary of Most Frequent Treatment-Emergent Adverse Events Occurring in ≥ 1% Patients by SOC Term in APD356-010 vs. Pooled APD365-009 and APD356-011:Year 1 Safety Population

SOC Term n(%) of patients	Pooled APD356-009 and APD356-011: Non-Diabetic Patients			APD356-010: Patients with Type 2 Diabetes		
	Placebo N=3185	Lorcaserin 10 mg BID N=3195	Lorcaserin 10 mg QD N=801	Placebo N=252	Lorcaserin 10 mg BID N=256	Lorcaserin 10 mg QD N=95
Infections And Infestations	1430 (44.9)	1597 (50.0)	384 (47.9)	140 (55.6)	131 (51.2)	65 (68.4)
Gastrointestinal Disorders	774 (24.3)	1006 (31.5)	226 (28.2)	67 (26.6)	72 (28.1)	33 (34.7)
Nervous System Disorders	619 (19.4)	980 (30.7)	213 (26.6)	50 (19.8)	74 (28.9)	37 (38.9)
Musculoskeletal And Connective Tissue Disorders	627 (19.7)	696 (21.8)	182 (22.7)	83 (32.9)	84 (32.8)	34 (35.8)
General Disorders/Administration Site Conditions	342 (10.7)	548 (17.2)	124 (15.5)	33 (13.1)	49 (19.1)	13 (13.7)
Injury, Poisoning And Procedural Complications	423 (13.3)	479 (15.0)	109 (13.6)	41 (16.3)	46 (18.0)	17 (17.9)
Respiratory, Thoracic And Mediastinal Disorders	408 (12.8)	455 (14.2)	114 (14.2)	48 (19.0)	42 (16.4)	14 (14.7)
Psychiatric Disorders	301 (9.5)	363 (11.4)	83 (10.4)	25 (9.9)	36 (14.1)	15 (15.8)
Skin And Subcutaneous Tissue Disorders	282 (8.9)	315 (9.9)	75 (9.4)	29 (11.5)	32 (12.5)	14 (14.7)
Investigations	209 (6.6)	210 (6.6)	56 (7.0)	27 (10.7)	29 (11.3)	13 (13.7)
Reproductive System And Breast Disorders	151 (4.7)	162 (5.1)	40 (5.0)	10 (4.0)	12 (4.7)	3 (3.2)
Vascular Disorders	126 (4.0)	153 (4.8)	31 (3.9)	13 (5.2)	19 (7.4)	9 (9.5)
Eye Disorders	96 (3.0)	144 (4.5)	32 (4.0)	4 (1.6)	15 (5.9)	2 (2.1)
Metabolism And Nutrition Disorders	127 (4.0)	143 (4.5)	54 (6.7)	65 (25.8)	92 (35.9)	36 (37.9)
Renal And Urinary Disorders	92 (2.9)	130 (4.1)	31 (3.9)	10 (4.0)	15 (5.9)	4 (4.2)
Ear And Labyrinth Disorders	65 (2.0)	99 (3.1)	22 (2.7)	6 (2.4)	10 (3.9)	7 (7.4)
Immune System Disorders	88 (2.8)	89 (2.8)	19 (2.4)	6 (2.4)	11 (4.3)	6 (6.3)
Cardiac Disorders	57 (1.8)	86 (2.7)	15 (1.9)	11 (4.4)	7 (2.7)	4 (4.2)
Neoplasms Benign, Malignant And Unspecified	57 (1.8)	57 (1.8)	19 (2.4)	8 (3.2)	4 (1.6)	3 (3.2)
Blood And Lymphatic System Disorders	39 (1.2)	42 (1.3)	12 (1.5)	6 (2.4)	6 (2.3)	1 (1.1)
Hepatobiliary Disorders	18 (0.6)	27 (0.8)	5 (0.6)	1 (0.4)	3 (1.2)	0
Endocrine Disorders	25 (0.8)	26 (0.8)	4 (0.5)	4 (1.6)	2 (0.8)	1 (1.1)
Social Circumstances	9 (0.3)	5 (0.2)	0	0	2 (0.8)	1 (1.1)
Surgical And Medical Procedures	2 (0.1)	4 (0.1)	1 (0.1)	2 (0.8)	1 (0.4)	1 (1.1)

Note: At each row of summarization, patients reporting more than one event were only counted once.
MedDRA version 12.0 is used as the adverse event coding dictionary.
SOC Terms were sorted by descending order of incidence in pooled lorcaserin BID group.

Table 23. Summary of Treatment-Emergent Adverse Events Occurring in ≥ 3% Patients by Preferred Term in APD356-010 vs. Pooled APD356-009 and APD356-011: Year 1 Safety Population

Preferred Term n(%) of patients	Pooled APD356-009 and APD356-011: Non-Diabetic Patients			APD356-010: Patients with Type 2 Diabetes		
	Placebo N=3185	Lorcaserin 10 mg BID N=3195	Lorcaserin 10 mg QD N=801	Placebo N=252	Lorcaserin 10 mg BID N=256	Lorcaserin 10 mg QD N=95
Headache	321 (10.1)	537 (16.8)	125 (15.6)	18 (7.1)	37 (14.5)	16 (16.8)
Upper respiratory tract infection	391 (12.3)	439 (13.7)	117 (14.6)	37 (14.7)	35 (13.7)	19 (20.0)
Nasopharyngitis	381 (12.0)	414 (13.0)	95 (11.9)	25 (9.9)	29 (11.3)	22 (23.2)
Dizziness	122 (3.8)	270 (8.5)	50 (6.2)	16 (6.3)	18 (7.0)	11 (11.6)
Nausea	170 (5.3)	264 (8.3)	61 (7.6)	20 (7.9)	24 (9.4)	8 (8.4)
Sinusitis	245 (7.7)	236 (7.4)	67 (8.4)	26 (10.3)	16 (6.3)	5 (5.3)
Fatigue	114 (3.6)	229 (7.2)	53 (6.6)	10 (4.0)	19 (7.4)	5 (5.3)
Urinary tract infection	171 (5.4)	207 (6.5)	61 (7.6)	15 (6.0)	23 (9.0)	9 (9.5)
Diarrhoea	179 (5.6)	207 (6.5)	53 (6.6)	19 (7.5)	19 (7.4)	13 (13.7)
Back pain	178 (5.6)	201 (6.3)	55 (6.9)	20 (7.9)	30 (11.7)	8 (8.4)
Constipation	125 (3.9)	186 (5.8)	41 (5.1)	12 (4.8)	11 (4.3)	6 (6.3)
Arthralgia	150 (4.7)	149 (4.7)	34 (4.2)	19 (7.5)	15 (5.9)	10 (10.5)
Influenza	134 (4.2)	138 (4.3)	28 (3.5)	13 (5.2)	15 (5.9)	8 (8.4)
Gastroenteritis viral	101 (3.2)	137 (4.3)	32 (4.0)	11 (4.4)	18 (7.0)	5 (5.3)
Cough	109 (3.4)	136 (4.3)	31 (3.9)	11 (4.4)	21 (8.2)	5 (5.3)
Vomiting	83 (2.6)	122 (3.8)	32 (4.0)	9 (3.6)	9 (3.5)	2 (2.1)
Oropharyngeal pain	80 (2.5)	111 (3.5)	23 (2.9)	12 (4.8)	11 (4.3)	0
Bronchitis	105 (3.3)	104 (3.3)	28 (3.5)	11 (4.4)	8 (3.1)	5 (5.3)
Pain in extremity	95 (3.0)	99 (3.1)	28 (3.5)	17 (6.7)	13 (5.1)	5 (5.3)
Muscle strain	74 (2.3)	98 (3.1)	15 (1.9)	9 (3.6)	10 (3.9)	2 (2.1)
Sinus congestion	78 (2.4)	93 (2.9)	33 (4.1)	12 (4.8)	9 (3.5)	5 (5.3)
Insomnia	97 (3.0)	81 (2.5)	22 (2.7)	6 (2.4)	9 (3.5)	3 (3.2)
Procedural pain	83 (2.6)	72 (2.3)	13 (1.6)	5 (2.0)	13 (5.1)	0
Hypertension	78 (2.4)	70 (2.2)	19 (2.4)	8 (3.2)	13 (5.1)	6 (6.3)
Rash	58 (1.8)	67 (2.1)	10 (1.2)	6 (2.4)	6 (2.3)	4 (4.2)

Table 23. Summary of Treatment-Emergent Adverse Events Occurring in ≥ 3% Patients by Preferred Term in APD356-010 vs. Pooled APD356-009 and APD356-011: Year 1 Safety Population (cont.)

Preferred Term n(%) of patients	Pooled APD356-009 and APD356-011: Non-Diabetic Patients			APD356-010: Patients with Type 2 Diabetes		
	Placebo N=3185	Lorcaserin 10 mg BID N=3195	Placebo N=3185	Lorcaserin 10 mg BID N=3195	Placebo N=3185	Lorcaserin 10 mg BID N=3195
Musculoskeletal pain	43 (1.4)	65 (2.0)	15 (1.9)	10 (4.0)	9 (3.5)	3 (3.2)
Abdominal pain upper	38 (1.2)	61 (1.9)	14 (1.7)	8 (3.2)	2 (0.8)	3 (3.2)
Depression	53 (1.7)	59 (1.8)	9 (1.1)	5 (2.0)	6 (2.3)	5 (5.3)
Gastroenteritis	46 (1.4)	50 (1.6)	19 (2.4)	5 (2.0)	8 (3.1)	5 (5.3)
Anxiety	47 (1.5)	49 (1.5)	15 (1.9)	8 (3.2)	9 (3.5)	2 (2.1)
Oedema peripheral	58 (1.8)	49 (1.5)	12 (1.5)	6 (2.4)	12 (4.7)	1 (1.1)
Contusion	41 (1.3)	49 (1.5)	12 (1.5)	5 (2.0)	5 (2.0)	3 (3.2)
Seasonal allergy	33 (1.0)	49 (1.5)	12 (1.5)	2 (0.8)	8 (3.1)	1 (1.1)
Muscle spasms	53 (1.7)	44 (1.4)	13 (1.6)	9 (3.6)	12 (4.7)	2 (2.1)
Vertigo	21 (0.7)	36 (1.1)	9 (1.1)	2 (0.8)	4 (1.6)	4 (4.2)
Pain	33 (1.0)	32 (1.0)	15 (1.9)	2 (0.8)	2 (0.8)	4 (4.2)
Hypoaesthesia	19 (0.6)	13 (0.4)	7 (0.9)	2 (0.8)	4 (1.6)	3 (3.2)
Herpes zoster	10 (0.3)	11 (0.3)	8 (1.0)	2 (0.8)	0	3 (3.2)
Blood cholesterol increased	7 (0.2)	4 (0.1)	1 (0.1)	0	0	3 (3.2)
Hypoglycaemia	0	2 (0.1)	0	53 (21.0)	75 (29.3)	32 (33.7)
Blood glucose decreased	0	0	0	2 (0.8)	1 (0.4)	3 (3.2)

Note: At each row of summarization, patients reporting more than one event were only counted once.

MedDRA version 12.0 is used as the adverse event coding dictionary.

PTs were sorted by descending order of incidence in the pooled Lorcaserin BID group.

The relative risks associated with each MedDRA System Organ Class and with the most common Preferred Terms (Table 24) were calculated. Headache was the only MedDRA preferred term with a relative risk significantly greater than 1 in all studies. A number of additional terms had RR significantly greater than 1 in pooled studies APD356-009 and APD356-011, with 5 of these terms exceeding 5% incidence (dry mouth, dizziness, fatigue, nausea, and constipation). Hypoglycemia in patients with type 2 diabetes is discussed in greater detail in Section 3.10.2.3, Hypoglycemia in Patients with Type 2 Diabetes.

Table 24. Relative Risk of Adverse Event Preferred Terms Reported by ≥ 1% of Patients in Any Treatment Group and with RR > 1 for Lorcaserin 10 mg BID Group Compared to Placebo during Year 1

	Studies APD356-009 and APD356-011					Study APD356-010 (Type 2 Diabetes)			
Preferred Term	**Relative Risk**	**Lower 95% Confidence Limit**	**Upper 95% Confidence Limit**	**% of Patients in Lorcaserin Group**	**Preferred Term**	**Relative Risk**	**Lower 95% Confidence Limit**	**Upper 95% Confidence Limit**	**% of Patients in Lorcaserin Group**
Chills	5.32	2.23	12.69	1.0	Decreased appetite	5.91	0.72	48.71	2.3
Paraesthesia	2.46	1.35	4.47	1.2	Migraine	4.92	0.58	41.83	2.0
Vision blurred	2.42	1.30	4.50	1.1	Seasonal allergy	3.94	0.84	18.36	3.1
Dry mouth	**2.28**	**1.74**	**2.98**	**5.3**	Musculoskeletal chest pain	3.94	0.44	34.99	1.6
Dizziness	**2.21**	**1.79**	**2.72**	**8.5**	Tension headache	3.94	0.44	34.99	1.6
Somnolence	2.03	1.26	3.27	1.6	Diabetes mellitus	3.45	0.72	16.43	2.7
Fatigue	**2.00**	**1.61**	**2.49**	**7.2**	Asthenia	2.95	0.31	28.20	1.2
Vulvovaginal mycotic infection	1.72	1.12	2.63	1.8	Diverticulitis	2.95	0.31	28.20	1.2
Menorrhagia	1.72	0.96	3.06	1.0	Dysuria	2.95	0.31	28.20	1.2
Vertigo	1.71	1.00	2.92	1.1	Influenza like illness	2.95	0.31	28.20	1.2
Alopecia	1.70	1.10	2.65	1.7	Suicidal ideation	2.95	0.31	28.20	1.2
Tension headache	1.70	0.98	2.94	1.1	Tinea pedis	2.95	0.31	28.20	1.2
Headache	**1.67**	**1.47**	**1.90**	**16.8**	Procedural pain	2.56	0.93	7.07	5.1
Abdominal pain upper	1.60	1.07	2.39	1.9	Stress	2.30	0.60	8.78	2.7
Respiratory tract congestion	1.60	0.91	2.78	1.0	**Headache**	**2.02**	**1.18**	**3.46**	**14.5**
Neck pain	1.57	0.96	2.56	1.3	Alopecia	1.97	0.36	10.65	1.6
Nausea	**1.55**	**1.28**	**1.87**	**8.3**	Hypoaesthesia	1.97	0.36	10.65	1.6
Musculoskeletal pain	1.51	1.03	2.21	2.0	Muscular weakness	1.97	0.36	10.65	1.6
Constipation	**1.48**	**1.19**	**1.85**	**5.8**	Paraesthesia	1.97	0.36	10.65	1.6
Seasonal allergy	1.48	0.95	2.30	1.5	Vertigo	1.97	0.36	10.65	1.6
Haematuria	1.47	0.85	2.55	1.0	Oedema peripheral	1.97	0.75	5.16	4.7
Vomiting	1.47	1.11	1.93	3.8	Cough	1.88	0.93	3.82	8.2

Table 24. Relative Risk of Adverse Event Preferred Terms Reported by ≥ 1% of Patients in Any Treatment Group and with RR > 1 for Lorcaserin 10 mg BID Group Compared to Placebo during Year 1 (cont.)

	Studies APD356-009 and APD356-011					Study APD356-010 (Type 2 Diabetes)			
Preferred Term	**Relative Risk**	**Lower 95% Confidence Limit**	**Upper 95% Confidence Limit**	**% of Patients in Lorcaserin Group**	**Preferred Term**	**Relative Risk**	**Lower 95% Confidence Limit**	**Upper 95% Confidence Limit**	**% of Patients in Lorcaserin Group**
Chest pain	1.41	0.90	2.23	1.4	Fatigue	1.87	0.89	3.94	7.4
Decreased appetite	1.41	0.86	2.29	1.2	Neck pain	1.64	0.40	6.79	2.0
Stress	1.39	0.86	2.25	1.2	Non-cardiac chest pain	1.64	0.40	6.79	2.0
Oropharyngeal pain	1.38	1.04	1.84	3.5	Sciatica	1.64	0.40	6.79	2.0
Pyrexia	1.38	0.85	2.21	1.3	Gastroenteritis viral	1.61	0.78	3.34	7.0
Toothache	1.37	0.89	2.11	1.5	Hypertension	1.60	0.67	3.79	5.1
Gastroenteritis viral	1.35	1.05	1.74	4.3	Gastroenteritis	1.58	0.52	4.75	3.1
Hot flush	1.33	0.83	2.13	1.3	Urinary tract infection	1.51	0.81	2.82	9.0
Muscle strain	1.32	0.98	1.78	3.1	Nephrolithiasis	1.48	0.25	8.76	1.2
Cough	1.24	0.97	1.59	4.3	Somnolence	1.48	0.25	8.76	1.2
Sinus headache	1.23	0.76	1.98	1.2	Back pain	1.48	0.86	2.53	11.7
Migraine	1.23	0.81	1.87	1.5	Insomnia	1.48	0.53	4.09	3.5
Urinary tract infection	1.21	0.99	1.47	6.5	**Hypoglycaemia**	**1.39**	**1.03**	**1.89**	**29.3**
Joint sprain	1.20	0.85	1.69	2.2	Dry mouth	1.31	0.30	5.81	1.6
Contusion	1.19	0.79	1.80	1.5	Muscle spasms	1.31	0.56	3.06	4.7
Sinus congestion	1.19	0.88	1.60	2.9	Pyrexia	1.23	0.33	4.53	2.0
Abdominal discomfort	1.18	0.74	1.87	1.2	Nausea	1.18	0.67	2.08	9.4
Gastrooesophageal reflux disease	1.16	0.72	1.87	1.1	Depression	1.18	0.37	3.82	2.3
Diarrhoea	1.15	0.95	1.40	6.5	Nasopharyngitis	1.14	0.69	1.89	11.3
Pharyngitis streptococcal	1.15	0.78	1.71	1.6	Influenza	1.14	0.55	2.34	5.9
Rash	1.15	0.81	1.63	2.1	Dizziness	1.11	0.58	2.12	7.0

Table 24. Relative Risk of Adverse Event Preferred Terms Reported by ≥ 1% of Patients in Any Treatment Group and with RR > 1 for Lorcaserin 10 mg BID Group Compared to Placebo during Year 1(cont.)

Preferred Term	Studies APD356-009 and APD356-011				Preferred Term	Study APD356-010 (Type 2 Diabetes)			
	Relative Risk	Lower 95% Confidence Limit	Upper 95% Confidence Limit	% of Patients in Lorcaserin Group		Relative Risk	Lower 95% Confidence Limit	Upper 95% Confidence Limit	% of Patients in Lorcaserin Group
Back pain	1.13	0.93	1.37	6.3	Anxiety	1.11	0.43	2.82	3.5
Upper respiratory tract infection	1.12	0.99	1.27	13.7	Muscle strain	1.09	0.45	2.65	3.9
Depression	1.11	0.77	1.60	1.8					
Flatulence	1.09	0.68	1.74	1.1					
Gastroenteritis	1.08	0.73	1.61	1.6					
Nasopharyngitis	1.08	0.95	1.23	13.0					
Blood pressure increased	1.08	0.69	1.71	1.2					
Palpitations	1.06	0.66	1.71	1.1					
Anxiety	1.04	0.70	1.55	1.5					
Pain in extremity	1.04	0.79	1.37	3.1					
Dyspepsia	1.03	0.72	1.49	1.8					
Influenza	1.03	0.81	1.30	4.3					

Note: Terms reported by ≥ 5% of patients and with significantly greater risk in lorcaserin group (lower 95% CI > 1) are in **bold type.**

Terms are ordered by decreasing RR in each study/study group

3.10.2.3 Adverse Events in Subpopulations

DEMOGRAPHIC SUBPOPULATIONS

The most common adverse events and selected adverse events of interest were evaluated by sex (Appendix 5, Table 73), race (Appendix 5, Table 74) and age (Appendix 5, Table 75). In addition, patients were subgrouped by starting BMI (Appendix 5, Table 76 and Table 77) and body weight (Appendix 5, Table 78, Table 79). The events of particular interest were those potentially associated with off-target lorcaserin effects (5-HT_{2A} or 5-HT_{2B}), depression, gallbladder disease (which can be associated with weight loss), and hypoglycemia. The search terms used for each of the adverse event categories are provided in Appendix 5, Section 7.16.

Women generally reported common adverse events (headache, nausea, dizziness) more often than men in all treatment groups; sex did not appear to impact the association of these events with lorcaserin (Appendix 5, Table 73). Among the other events of interest, no drug-gender interaction was evident. Similarly, no drug-race interaction was apparent (Appendix 5, Table 74).

Patients older than the median age generally reported adverse events with lower incidence than did patients younger than the median age (Appendix 5, Table 75). The older patients did not appear to be more sensitive to lorcaserin with respect to the adverse events of interest.

Finally, starting body weight, but not starting BMI, impacted the incidence of some lorcaserin-associated adverse events (Appendix 5, Table 77, Table 78, Table 79, Table 80). Lorcaserin associated headache, nausea and dizziness may have been more prevalent among patients in the lowest body weight quartile.

Overall, the differences in common adverse event rates according to demographic factors were small, and do not justify dose adjustment.

HYPOGLYCEMIA IN PATIENTS WITH TYPE 2 DIABETES

Because weight loss can decrease plasma glucose concentrations among patients with type 2 diabetes, hypoglycemia was monitored by adverse event reporting, by patient self-reporting in "real time" using an interactive voice recognition system (IVRS), and by glucose self-monitoring. Many events of asymptomatic blood glucose values < 70 mg/dL were reported as adverse events. The most meaningful assessment is the analysis of symptomatic events (see shaded row in Table 25). Symptomatic events were more common in patients taking lorcaserin BID (7.4%) and lorcaserin QD (10.5%) than in patients on placebo (6.3%). No patient on lorcaserin experienced severe hypoglycemia; no patient required parenteral agents or medical assistance.

Table 25. Summary of Suspected Hypoglycemia Adverse Events by Protocol-defined Severity and Symptoms in APD356-010

Criteria n (%)	Placebo N=252	Lorcaserin 10 mg BID N=256	Lorcaserin 10 mg QD N=95
Total number of hypoglycemia events reported[a]	**326**	**530**	**317**
Unique events designated symptomatic	55	48	33
Unique events designated asymptomatic	179	302	175
Unique events, unspecified	92	180	109
Number(%) of patients reporting events by symptoms[b]	54 (21.4)	76 (29.7)	33 (34.7)
Symptomatic	16 (6.3)	19 (7.4)	10 (10.5)
Asymptomatic	36 (14.3)	43 (16.8)	20 (21.1)
Unspecified	18 (7.1)	32 (12.5)	14 (14.7)
Number(%) of patients reporting symptomatic events by protocol-defined severity[b,c]			
Mild/moderate	16 (6.3)	19 (7.4)	10 (10.5)
Severe	(1)[d]	0	0
Catastrophic	0	0	0
Subgroup Analysis by Baseline Anti-diabetic Agent: n/N(%) reporting event coded as "hypoglycemia"			
Metformin without SFU	16 (12.6)	10 (10.5)	11 (8.8)
SFU (+/- metformin)	60 (47.6)	23 (24.2)	43 (34.4)

[a] Each event is counted even if multiple events per patient.

[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] Severity as defined in protocol:

- Mild/moderate hypoglycemia:capillary glucose < 65 mg/dL (3.3 mmol/L) and patient is able to treat himself/herself; or, if glucose is not measured, symptoms of hypoglycemia that resolve with administration of oral carbohydrates.
- Severe hypoglycemia: capillary glucose < 50 mg/dL (2.8 mmol/L) 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 results in life-threatening injury to the patient or another person, hospitalization, and/or death.

[d] 1 patient experienced 2 seizures; insufficient data to rule out hypoglycemic episodes as cause.

Note: Summary of suspected hypoglycemia adverse events include PTs "hypoglycemia" and "blood glucose decreased."

3.10.2.4 Time to Onset and Duration of Adverse Events

Some of the most common lorcaserin-related adverse events, headache, dizziness, and nausea, tended to occur early during Year 1, resolved spontaneously with continued study drug use, and typically did not recur at a higher rate in the active group than in the placebo group with continued dosing (examples in Table 26, Figure 22). The common lorcaserin-associated events were most frequent within the initial 2 weeks of the trials; the rates in lorcaserin and placebo groups were similar after about 2 weeks of exposure (headache is provided as an example in Figure 22, where the slopes of the lines are similar for all treatment groups after the initial few

weeks). Depression-related events—although not increased by lorcaserin (narrow definition SMQ) are provided as an example of AEs that occurred at a fairly constant rate throughout the trial (Figure 22). The duration of the most common AEs in the lorcaserin groups of studies APD356-009 and APD356-011 typically was no longer than that in the placebo group (Table 26).

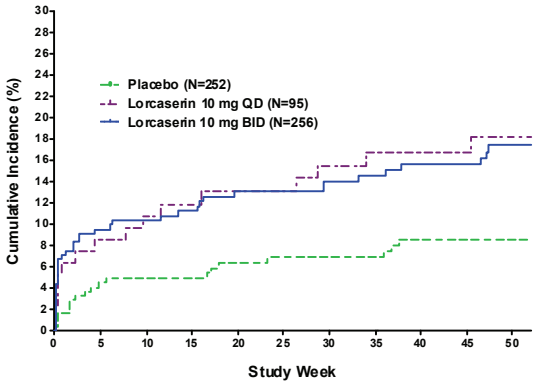
Table 26. Kaplan-Meier Estimated Duration (Days) of Selected Adverse Events Up to 52 Weeks in Phase 3 Studies APD356-009 and APD356-011

Event Category Statistics	Placebo N = 3185	Lorcaserin 10 mg BID N = 3195	Lorcaserin 10 mg QD N = 801
Dizziness			
Total Number of patients with AE	123	273	50
Total Number of events	144	329	60
Median Duration (95% CI), days	7.0 (4, 12)	7.0 (5, 9)	4.0 (2, 6)
Inter-Quartile Range of Duration, days	2.0, 28.0	2.0, 29.0	1.0, 14.0
Headache			
Total Number of patients with AE	337	568	134
Total Number of events	402	716	169
Median Duration (95% CI), days	7.0 (5, 10)	4.0 (4, 6)	4.0 (3, 7)
Inter-Quartile Range of Duration, days	2.0, 39.0	2.0, 25.0	2.0, 29.0
Nausea			
Total Number of patients with AE	170	264	61
Total Number of events	186	301	68
Median Duration (95% CI), days	4.0 (3, 6)	5.0 (4, 5)	5.0 (3, 11)
Inter-Quartile Range of Duration, days	2.0, 16.0	2.0, 18.0	3.0, 20.0

Figure 22. Kaplan-Meier Time to Event Curves for Selected Adverse Events during Year 1 in Phase 3 Studies

APD356-010: Patients with Type 2 Diabetes

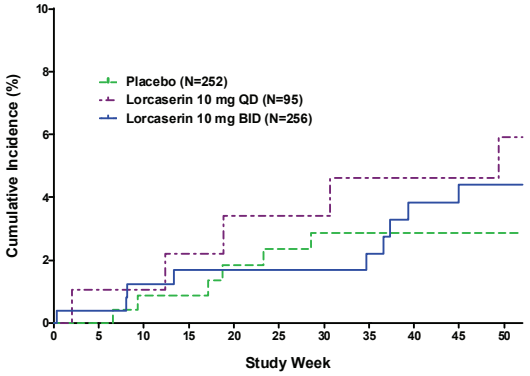
Headache



Number of patients at risk:

Treatment Group	Baseline	Week 24	Week 52
Placebo	252	184	123
Lorcaserin QD	95	70	46
Lorcaserin BID	256	181	115

Depression –Narrow SMQ

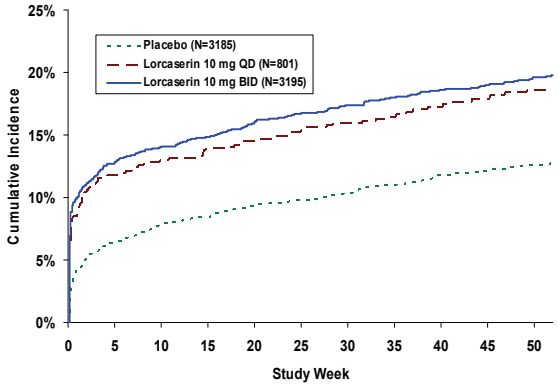


Number of patients at risk:

Treatment Group	Baseline	Week 24	Week 52
Placebo	252	191	131
Lorcaserin QD	95	80	58
Lorcaserin BID	256	203	139

Pooled APD356-009 and -011: Non-Diabetic Patients

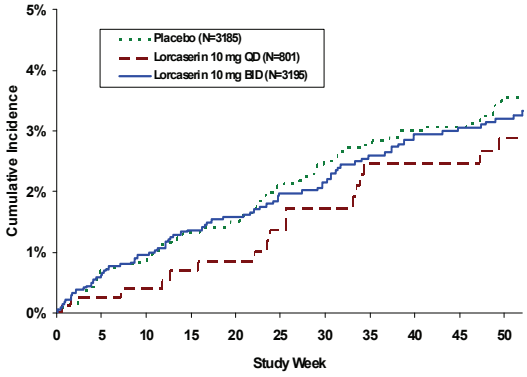
Headache



Number of patients at risk:

Treatment Group	Baseline	Week 24	Week 52
Placebo	3185	1851	1074
Lorcaserin QD	801	498	305
Lorcaserin BID	3195	1912	1195

Depression –Narrow SMQ



Number of patients at risk:

Treatment Group	Baseline	Week 24	Week 52
Placebo	3185	1990	1178
Lorcaserin QD	801	574	360
Lorcaserin BID	3195	2234	1406

3.10.3 Deaths

Two deaths occurred during the clinical development of lorcaserin. Both occurred in patients who were taking placebo at the time of the event, and neither was related to the clinical trial.

One death was reported during Year 2 of the APD356-009 trial, and one death was reported during the APD356-011 trial.

3.10.4 Serious Adverse Events during Exposures up to Year 1

3.10.4.1 Serious Adverse Events in Phase 3 Studies during Year 1

In general, patients with type 2 diabetes experience a higher incidence of serious adverse events (SAEs) across treatment groups than did non-diabetic patients (Table 27). The incidence of SAEs among patients in the placebo and lorcaserin BID group, respectively, was 2.3% and 2.7% among non-diabetic patients and 6.7% and 6.3% among patients with type 2 diabetes. Few events occurred in more that 1 patient; only gallbladder related adverse events, myocardial infarction, cellulitis, and intervertebral disc protrusion were reported by more than 2 patients on lorcaserin BID in either the pooled studies or study APD356-010. In the placebo group, gallbladder related events, ankle fractures, osteoarthritis, breast cancer, and asthma each occurred in more than 2 patients.

Considering all of the Phase 3 studies, few events were consistently more common with lorcaserin than placebo. Excesses of 3 or more patients in the lorcaserin groups were limited to the event terms non-cardiac chest pain and cholecystitis, which occurred in 4 and 5 patients, respectively, on lorcaserin, and 1 and 0 patients on placebo.

An excess of gallbladder-related SAEs in the lorcaserin group compared to the placebo group may be due to the greater weight loss in the lorcaserin group. Cholelithiasis and cholecystitis are associated not only with obesity, but also with weight loss.[53,54]

Table 27. Summary of Most Frequent Serious Adverse Events with Preferred Term Occurring in > 1 Patient in Any Group in Phase 3 Studies: Year 1 Safety Population

System Organ Class Preferred Term	Pooled Studies -009 and -011: Non-Diabetic Patients				APD356-010: Patients with Type 2 Diabetes			
	Placebo (N=3185)	Lorcaserin 10 mg BID (N=3195)	Lorcaserin 10 mg QD (N=801)	Any Lorcaserin Dose (N=3996)	Placebo N=252	Lorcaserin 10 mg BID N=256	Lorcaserin 10 mg QD N=95	Any Lorcaserin Dose N=351
Number (%) of Patients with SAE[a]	73 (2.3)	87 (2.7)	27 (3.4)	114 (2.9)	17 (6.7)	16 (6.3)	8 (8.4)	24 (6.8)
Cardiac Disorders	3 (0.1)	9 (0.3)	1 (0.1)	10 (0.3)	3 (1.2)	1 (0.4)	2 (2.1)	3 (0.9)
Myocardial infarction	0	3 (0.1)	0	3 (0.1)	2 (0.8)	0	0	0
Gastrointestinal Disorders	7 (0.2)	7 (0.2)	5 (0.6)	12 (0.3)	3 (1.2)	0	0	0
Gastritis	1 (< 0.1)	0	2 (0.2)	2 (0.1)	0	0	0	0
Oesophagitis	0	2 (0.1)	0	2 (0.1)	0	0	0	0
Small intestinal obstruction	2 (0.1)	1 (< 0.1)	1 (0.1)	2 (0.1)	0	0	0	0
Appendicitis	2 (0.1)	1 (< 0.1)	0	1 (< 0.1)	0	0	0	0
General Disorders	2 (0.1)	4 (0.1)	1 (0.1)	5 (0.1)	3 (1.2)	3 (1.2)	0	3 (0.9)
Chest pain	2 (0.1)	2 (0.1)	0	2 (0.1)	2 (0.8)	0	0	0
Non-cardiac chest pain	0	1 (< 0.1)	1 (0.1)	2 (0.1)	1 (0.4)	2 (0.8)	0	2 (0.6)
Hepatobiliary Disorders	5 (0.2)	9 (0.3)	2 (0.2)	11 (0.3)	0	1 (0.4)	0	1 (0.3)
Cholecystitis	0	4 (0.1)	0	4 (0.1)	0	1 (0.4)	0	1 (0.3)
Cholelithiasis	3 (0.1)	2 (0.1)	2 (0.2)	4 (0.1)	0	0	0	0
Cholecystitis acute	1 (< 0.1)	2 (0.1)	0	2 (0.1)	0	0	0	0
Infections And Infestations	6 (0.2)	11 (0.3)	1 (0.1)	12 (0.3)	3 (1.2)	3 (1.2)	1 (1.1)	4 (1.1)
Cellulitis (incl. male genital cellulitis)	1 (< 0.1)	3 (0.1)	0	3 (0.1)	2 (0.8)	0	0	0
Diverticulitis	1 (< 0.1)	2 (0.1)	0	2 (0.1)	0	0	0	0
Gastroenteritis	0	1 (<0.1)	0	1 (<0.1)	0	2 (0.8)	0	2 (0.6)
Pneumonia	1 (< 0.1)	2 (0.1)	0	2 (0.1)	0	0	0	0
Injury, Poisoning And Procedural Complications	10 (0.3)	9 (0.3)	5 (0.6)	14 (0.4)	0	0	0	0
Tibia fracture	2 (0.1)	0	1 (0.1)	1 (< 0.1)	0	0	0	0
Ankle fracture	4 (0.1)	0	0	0	0	0	0	0
Joint dislocation	2 (0.1)	0	0	0	0	0	0	0

System Organ Class Preferred Term	Pooled Studies -009 and -011: Non-Diabetic Patients				APD356-010: Patients with Type 2 Diabetes			
	Placebo (N=3185)	Lorcaserin 10 mg BID (N=3195)	Lorcaserin 10 mg QD (N=801)	Any Lorcaserin Dose (N=3996)	Placebo N=252	Lorcaserin 10 mg BID N=256	Lorcaserin 10 mg QD N=95	Any Lorcaserin Dose N=351
Musculoskeletal And Connective Tissue Disorders	13 (0.4)	11 (0.3)	5 (0.6)	16 (0.4)	1 (0.4)	3 (1.2)	0	3 (0.9)
Intervertebral disc protrusion	2 (0.1)	3 (0.1)	0	3 (0.1)	0	1 (0.4)	0	1 (0.3)
Osteoarthritis	5 (0.2)	2 (0.1)	1 (0.1)	3 (0.1)	0	1 (0.4)	0	1 (0.3)
Lumbar spinal stenosis/spinal column stenosis	1 (< 0.1)	0	2 (0.2)	2 (0.1)	1 (0.4)	0	0	0
Neoplasms Benign, Malignant And Unspecified	12 (0.4)	11 (0.3)	4 (0.5)	15 (0.4)	3 (1.2)	2 (0.8)	1 (1.1)	3 (0.9)
Breast cancer	3 (0.1)	2 (0.1)	0	2 (0.1)	0	0	0	0
Lung adenocarcinoma	0	2 (0.1)	0	2 (0.1)	0	0	0	0
Multiple myeloma	0	2 (0.1)	0	2 (0.1)	0	0	0	0
Uterine leiomyoma	2 (0.1)	1 (< 0.1)	1 (0.1)	2 (0.1)	0	1 (0.4)	0	1 (0.3)
Bladder cancer	2 (0.1)	0	0	0	0	0	0	0
Nervous System Disorders	10 (0.3)	7 (0.2)	2 (0.2)	9 (0.2)	1 (0.4)	0	2 (2.1)	2 (0.6)
Syncope	2 (0.1)	2 (0.1)	0	2 (0.1)	0	0	0	0
Cerebrovascular accident	0	0	0	0	0	0	2 (2.1)	2 (0.6)
Reproductive System And Breast Disorders	7 (0.2)	8 (0.3)	2 (0.2)	10 (0.3)	0	0	0	0
Dysmenorrhoea	0	2 (0.1)	0	2 (0.1)	0	0	0	0
Menorrhagia	0	2 (0.1)	0	2 (0.1)	0	0	0	0
Uterine prolapse	2 (0.1)	1 (< 0.1)	0	1 (< 0.1)	0	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	4 (0.1)	6 (0.2)	1 (0.1)	7 (0.2)	1 (0.4)	0	0	0
Dyspnoea	0	2 (0.1)	0	2 (0.1)	0	0	0	0
Pulmonary embolism	1 (< 0.1)	2 (0.1)	0	2 (0.1)	0	0	0	0
Asthma	3 (0.1)	0	0	0	1 (0.4)	0	0	0

[a] At the SOC level, all patients are summarized. At the PT level, terms reported by more than one patient in any treatment arm are presented.

Note: At each level of summarization, patients reporting more than one event were only counted once.

3.10.4.2 Discontinuations due to Adverse Events

Summaries of the most frequent AEs leading to study withdrawal or permanent discontinuation of study drug are tabulated by SOC (Table 28) and by Preferred Term reported by > 0.1% of patients in any group (Table 29) below.

Among non-diabetic patients in studies APD356-009 and APD356-011, withdrawals due to AEs were slightly more frequent in the lorcaserin BID group (8.6% of patients) than the lorcaserin QD (7.5% of patients) and placebo groups (6.8% of patients) (Table 28). The placebo discontinuation rate due to AEs was slightly lower than the placebo discontinuation rates (8.1-9.2%) reported in recent published 1-year obesity trials.[55-57] Lorcaserin was also associated with higher discontinuation incidence than was placebo in study APD356-010 of patients with type 2 diabetes. No single AE preferred term accounted for the excess.

The SOCs (i.e., body systems) most often responsible for early discontinuation, with a rate exceeding 1% in either lorcaserin group, were Nervous System Disorders, Psychiatric Disorders, Gastrointestinal Disorders, and General Disorders. Among patients with type 2 diabetes, Musculoskeletal Disorders also accounted for more than 1% of patients discontinuing early in the lorcaserin BID group. The greatest excess in AEs leading to discontinuation in the lorcaserin BID group as compared to placebo occurred in the General Disorders SOC, Musculoskeletal Disorders, Psychiatric Disorders, and the Nervous System SOC. The effect was not consistently dose related.

At the level of Preferred Terms (Table 29), only headache was associated with a discontinuation rate > 1% among non-diabetic patients: 1.3% of patients assigned to lorcaserin discontinued due to headache, compared to 0.8% of patients assigned to placebo in pooled studies APD356-009 and APD356-011. Depression, nausea and dizziness led to more discontinuations (difference >0.2%) in the lorcaserin BID group than in the placebo group among non-diabetic patients. The lorcaserin QD dose was associated with lower discontinuation rates for depression as compared to placebo, and equivalent rates for nausea and dizziness. Whereas headache was the most common AE leading to study withdrawal in the pooled APD356-009 and APD356-011 studies, no patient withdrew due to a headache in the APD356-010 study. Only dizziness, CVA (cerebrovascular accident) and depression caused more than one patient treated with lorcaserin to discontinue from APD356-010; each term was listed by 2 patients as the cause for study withdrawal.

Overall, discontinuation rates due to AEs were low, and differences between active and placebo groups were small.

Table 28. Adverse Events Leading to Early Discontinuation by System Organ Class in Phase 3 Studies during Year 1: Events Reported by > 0.1% of Patients in Any Group (Pooled APD356-009 and APD356-011) or in > 1 Patient (APD356-010)

SOC n(% of patients)	Pooled Studies APD356-009 and -011: Non-diabetic Patients			Study APD356-010: Patients with Type 2 Diabetes		
	Pooled Placebo (N=3185)	Lorcaserin 10 mg BID (N=3195)	Lorcaserin 10 mg QD (N=801)	Placebo (N=252)	Lorcaserin 10 mg BID (N=256)	Lorcaserin 10 mg QD (N=95)
Number of Patients Discontinued due to AE	**217 (6.8)**	**274 (8.6)**	**60 (7.5)**	**14 (5.6)**	**22 (8.6)**	**7 (7.4)**
Blood And Lymphatic System Disorders	1 (< 0.1)	1 (< 0.1)	1 (0.1)	0	0	0
Cardiac Disorders	13 (0.4)	15 (0.5)	3 (0.4)	0	0	0
Congenital, Familial And Genetic Disorders	1 (< 0.1)	0	0	0	0	0
Ear And Labyrinth Disorders	3 (0.1)	1 (< 0.1)	0	0	0	1 (1.1)
Endocrine Disorders	1 (< 0.1)	0	0	0	0	0
Eye Disorders	9 (0.3)	6 (0.2)	4 (0.5)	0	0	0
Gastrointestinal Disorders	37 (1.2)	37 (1.2)	10 (1.2)	3 (1.2)	1 (0.4)	1 (1.1)
General Disorders And Administration Site Conditions	19 (0.6)	38 (1.2)	4 (0.5)	0	3 (1.2)	0
Hepatobiliary Disorders	2 (0.1)	4 (0.1)	0	0	2 (0.8)	0
Immune System Disorders	2 (0.1)	0	0	0	0	0
Infections And Infestations	13 (0.4)	9 (0.3)	2 (0.2)	1 (0.4)	1 (0.4)	0
Injury, Poisoning And Procedural Complications	7 (0.2)	4 (0.1)	5 (0.6)	1 (0.4)	0	0
Investigations	16 (0.5)	11 (0.3)	4 (0.5)	0	2 (0.8)	0
Metabolism And Nutrition Disorders	3 (0.1)	3 (0.1)	4 (0.5)	0	2 (0.8)	0
Musculoskeletal And Connective Tissue Disorders	9 (0.3)	19 (0.6)	5 (0.6)	0	4 (1.6)	0
Neoplasms Benign, Malignant And Unspecified	11 (0.3)	14 (0.4)	4 (0.5)	2 (0.8)	1 (0.4)	1 (1.1)
Nervous System Disorders	49 (1.5)	84 (2.6)	15 (1.9)	2 (0.8)	5 (2.0)	4 (4.2)
Psychiatric Disorders	36 (1.1)	71 (2.2)	13 (1.6)	3 (1.2)	4 (1.6)	1 (1.1)
Renal And Urinary Disorders	2 (0.1)	2 (0.1)	1 (0.1)	0	1 (0.4)	0
Reproductive System And Breast Disorders	8 (0.3)	9 (0.3)	0	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	7 (0.2)	12 (0.4)	1 (0.1)	1 (0.4)	0	0
Skin And Subcutaneous Tissue Disorders	18 (0.6)	13 (0.4)	4 (0.5)	1 (0.4)	2 (0.8)	0
Vascular Disorders	8 (0.3)	11 (0.3)	1 (0.1)	2 (0.8)	1 (0.4)	1 (1.1)

Note: At each level of summarization, patients reporting more than one event were only counted once.

Table 29. Adverse Events Leading to Early Discontinuation by Preferred Term in Phase 3 Studies during Year 1: Events Reported by > 0.2% of Patients in Any Group (Pooled APD356-009 and APD356-011) or in > 1 Patient (APD356-010)

Preferred Term n(% of patients)	Pooled Studies APD356-009 and -011: Non-diabetic Patients			Study APD356-010: Patients with Type 2 Diabetes		
	Pooled Placebo (N=3185)	Lorcaserin 10 mg BID (N=3195)	Lorcaserin 10 mg QD (N=801)	Placebo (N=252)	Lorcaserin 10 mg BID (N=256)	Lorcaserin 10 mg QD (N=95)
Total Number of Patients	**217 (6.8)**	**274 (8.6)**	**60 (7.5)**	**14 (5.6)**	**22 (8.6)**	**7 (7.4)**
Gastrointestinal Disorders						
Nausea	14 (0.4)	22 (0.7)	3 (0.4)	0	0	1 (1.1)
Constipation	2 (0.1)	3 (0.1)	4 (0.5)	0	1 (0.4)	0
General Disorders						
Fatigue	5 (0.2)	9 (0.3)	3 (0.4)	0	1 (0.4)	0
Chest pain (or non-cardiac chest pain)	3 (0.1)	9 (0.3)	1 (0.1)	0	1 (0.4)	0
Malaise	0	5 (0.2)	0	0	0	0
Musculoskeletal And Connective Tissue Disorders						
Myalgia	0	0	3 (0.4)	0	0	0
Nervous System Disorders						
Headache	24 (0.8)	41 (1.3)	10 (1.2)	0	1 (0.4)	0
Dizziness	6 (0.2)	23 (0.7)	2 (0.2)	0	1 (0.4)	2 (2.1)
Cerebrovascular accident	0	0	0	0	0	2 (2.1)
Psychiatric Disorders						
Depression	16 (0.5)	29 (0.9)	1 (0.1)	0	2 (0.8)	1 (1.1)
Anxiety	8 (0.3)	12 (0.4)	3 (0.4)	2 (0.8)	0	0
Vascular Disorders						
Hypertension	5 (0.2)	8 (0.3)	1 (0.1)	1 (0.4)	0	0

Note: At each level of summarization, patients reporting more than one event were only counted once.

3.10.5 Year 2 Adverse Event Summary for Phase 3 Study APD356-009

Patients who entered Year 2 of the APD356-009 trial were re-randomized in a blinded manner. Patients assigned to lorcaserin 10 mg BID during Year 1 either remained on lorcaserin (2/3 of patients) or were switched to placebo (1/3 of patients). All patients assigned to placebo during Year 1 remained on placebo during Year 2; this was necessary to maximize the statistical power for analysis of Year 2 echocardiographic safety data. Hence, Year 2 adverse events are reported for three treatment groups: placebo/placebo, lorcaserin/lorcaserin, and lorcaserin/placebo. Each adverse event is assigned to the treatment that the patient was taking on the start date of the adverse event.

Headache persisted in having a dose-related excess incidence over placebo (Table 30). Other common adverse events occurred with similar frequencies in all treatment groups.

Table 30. Most Frequent Adverse Events (> 3% of patients) during Year 2: Phase 3 Study APD356-009

Preferred Term n(%)	Placebo/Placebo N=697	Lorcaserin/Lorcaserin N=573	Lorcaserin/Placebo N=283
Nasopharyngitis	88 (12.6)	94 (16.4)	39 (13.8)
Upper respiratory tract infection	112 (16.1)	83 (14.5)	31 (11.0)
Sinusitis	48 (6.9)	49 (8.6)	30 (10.6)
Urinary tract infection	35 (5.0)	41 (7.2)	14 (4.9)
Headache	30 (4.3)	41 (7.2)	18 (6.4)
Arthralgia	43 (6.2)	38 (6.6)	17 (6.0)
Influenza	42 (6.0)	38 (6.6)	14 (4.9)
Back pain	30 (4.3)	34 (5.9)	16 (5.7)
Diarrhoea	30 (4.3)	34 (5.9)	9 (3.2)
Nausea	29 (4.2)	20 (3.5)	9 (3.2)
Insomnia	18 (2.6)	19 (3.3)	11 (3.9)
Gastroenteritis viral	21 (3.0)	18 (3.1)	14 (4.9)
Pharyngolaryngeal pain	18 (2.6)	17 (3.0)	7 (2.5)
Bronchitis	27 (3.9)	16 (2.8)	8 (2.8)
Pain in extremity	24 (3.4)	15 (2.6)	8 (2.8)

Withdrawals due to adverse events were infrequent during Year 2, and differed little among treatment groups (Table 31). Most adverse event terms associated with early terminations were reported by a single patient. The preferred term most frequently associated with withdrawal was depression (4 patients each in the placebo and lorcaserin BID group and 2 patients in the lorcaserin QD group).

Table 31. Adverse Events Leading to Early Discontinuation for > 1 Patient during Year 2: Phase 3 Study APD356-009

Preferred Term n(%)	Placebo/Placebo N=697	Lorcaserin/Lorcaserin N=573	Lorcaserin/Placebo N=283
Patients who withdrew due to AE	**19 (2.7)**	**21 (3.7)**	**12 (4.2)**
Atrial fibrillation	2 (0.3)	0	0
Depression	4 (0.6)	4 (0.7)	2 (0.7)
Headache	0	1 (0.2)	1 (0.4)
Anxiety	1 (0.1)	2 (0.3)	1 (0.4)

Serious adverse events were also less frequent during Year 2 than during Year 1 (Table 32). The majority of events were reported by one patient each; only osteoarthritis (2 vs. 1 patient) and rectocele (2 vs. 0 patients) were reported by more than one patient and were more frequent in the lorcaserin/lorcaserin group than in the placebo group. No evidence of specific late-onset adverse events emerged among patients who were exposed to lorcaserin for up to 2 years.

Table 32. Most Frequent Serious Adverse Events (Lorcaserin/Lorcaserin > Placebo/Placebo) during Year 2: Phase 3 Study APD356-009

Preferred Term n(%)	Placebo/Placebo N=697	Lorcaserin/Lorcaserin N=573	Lorcaserin/Placebo N=283
Osteoarthritis	1 (0.1)	2 (0.3)	1 (0.4)
Rectocele	0	2 (0.3)	0
Enterocele	0	1 (0.2)	0
Biliary dyskinesia	0	1 (0.2)	0
Cholecystitis	0	1 (0.2)	0
Drug hypersensitivity	0	1 (0.2)	0
Diverticulitis	0	1 (0.2)	0
Giardiasis	0	1 (0.2)	0
Osteomyelitis	0	1 (0.2)	0
Concussion	0	1 (0.2)	0
Fibula fracture	0	1 (0.2)	0
Blood pressure increased	0	1 (0.2)	0
Intervertebral disc degeneration	0	1 (0.2)	0
Intervertebral disc disorder	0	1 (0.2)	0
Pituitary tumor benign	0	1 (0.2)	0
Uterine prolapse	0	1 (0.2)	0

3.10.6 Echocardiographic Safety Monitoring

3.10.6.1 Echocardiographic Monitoring

Certain serotonergic drugs are associated with an increased risk of valvular regurgitation through activation of serotonin 2B receptors. This valvulopathy is characterized by thickening and fibrosis of heart valve leaflets, and tends to affect the left-sided valves (aortic and mitral) more

than the right-sided valves (tricuspid and pulmonic). The usual method to identify and quantify valvular regurgitation (or insufficiency) is echocardiography. A 5-level rating scale is applied to the aortic, mitral and tricuspid valves: absent, trace, mild, moderate, severe. Regurgitation of the pulmonic valve is classified simply as absent or present. Some physiological variation in valvular function occurs normally, such that trace insufficiency is often considered "physiological." In addition, there is acquisition and interpretation variability when assessing valvular competency by echocardiography, primarily comprises one category shifts at the lower end of the scale (absent, trace, and mild).[58]

To evaluate potential cardiac valvular toxicity in patients exposed to lorcaserin, serial echocardiograms were performed every 6 months during Phase 3 trials. In total, over 20,000 echoes over 2 years of lorcaserin exposure were obtained. Acquisition and interpretation procedures were highly standardized, with all echocardiograms read at a central core laboratory by expert cardiologists. Each echo was interpreted by two cardiologists who were blinded to treatment assignment, with a third designated adjudicator who was also blinded, resolving any discrepant readings.

In 1997, the FDA established criteria for evaluation of valvular heart disease prevalence in patients exposed to fenfluramine ("fen/phen"); these criteria were adopted for some data analyses in our Phase 3 trials. The criteria are referred to as "FDA-defined valvulopathy," or simply "FDA valvulopathy," and stipulate that significant valvular regurgitation comprises **mild or greater aortic valve regurgitation and/or moderate or greater mitral valve regurgitation**.

3.10.6.2 Analysis of Echocardiographic Safety Data

The primary echocardiographic (echo) safety endpoint for the Phase 3 trials was the proportion of patients who developed new FDA-defined valvulopathy from baseline to Week 52. Additional analyses evaluated other time points and each valve individually. Key analyses included:

- Pre-planned analysis: Analysis of the proportion of patients who developed new echocardiographic criteria for FDA-defined valvulopathy at Week 52, using LOCF imputation for missing Week 52 values
  - Risk difference; confidence intervals reported as 90% and 95%, equivalent to $\alpha = 0.05$ and $\alpha = 0.025$ for 1-sided non-inferiority analyses, respectively (pre-specified as the primary analysis in study protocols: risk difference with 90% CI)
  - Relative risk; confidence intervals reported as 90% and 95% (requested by FDA for safety update: % with 95% CI)
- Three *post-hoc* analyses that use all of the available echocardiographic data through up to 104 weeks of dosing. The pre-specified analyses used only Week 52 data with LOCF imputation, which constituted only 43% of all available echoes and did not contain enough events (FDA valvulopathy) to adequately power risk ratio assessment.
  - The time to first event with a hazard ratio using a piecewise exponential model (PEM)

- The time to first event with a hazard ratio using Cox proportional hazards model (CoxPH)
- The average prevalence ratio across the four 6-month times of assessment through Week 104 using a generalized estimating equation (GEE)

The primary data analysis used a non-inferiority approach based on risk difference to test whether the incidence of FDA-defined valvulopathy in patients treated with lorcaserin was no worse than the incidence in the placebo group. This analysis was performed using a pooled dataset that included echo data from all Phase 3 trials. The total number of patients was intended to be sufficient to rule out an increase in the incidence of valvulopathy 50% greater than placebo, with 80% power at the 5% significance level, and the power in the pooled dataset exceeded 80%. A non-inferiority analysis is a *one*-sided analysis, and evaluates only whether one result is worse than another by a specified margin. The testing scheme is analogous to inspecting a one-sided 95% confidence interval of the form [-inf, UL] for the difference in proportions, and concluding that lorcaserin is not inferior to placebo if the upper limit, UL < half the placebo incidence (which is also the upper limit of the usual *two*-sided 90% confidence interval for the difference in proportion).

In the absence of good incidence data in the literature, the sponsor derived the assumed placebo incidence from an independent interim analysis of the APD356-009 echocardiographic data by a Data Safety Monitoring Board, which informed Arena of the overall 1-year incidence of FDA-defined valvulopathy (2.5%). Arena used the information to determine the final number of patients randomized into the APD356-010 and APD356-011 trials, and to set the noninferiority margin at 1.25%.

As a point of reference when interpreting the results for lorcaserin, a meta-analysis of drugs known to be valvulopathogens estimated the prevalence odds ratio (95% CI) of FDA-defined valvulopathy among patients who used fenfluramine or dexfenfluramine to be 2.2 (1.7-2.7).[59] Pergolide and cabergoline are associated with increased risk of clinically significant valvular regurgitation. In a retrospective analysis of medical records, the incidence-rate ratio (95% CI) of "clinically significant" valvulopathy (aortic, mitral, and/or tricuspid regurgitation) among patients taking pergolide was 7.1 (2.3-22.3) and among those taking cabergoline was 4.9 (1.5-15.6).[2] Other investigators estimated an odds ratio (95% CI) of 4.0 (1.3-12.2) for aortic regurgitation and 3.7 (0.7-19.2) for clinically significant mitral regurgitation with pergolide use.[60] Zanettini, et al. conducted a prevalence echocardiographic study among outpatients taking pergolide or cabergoline, and identified relative risk (95% CI) for moderate or greater mitral regurgitation of 6.3 (1.4-28.3) and 4.6 (0.9-22.8), respectively. The corresponding relative risks for aortic regurgitation were 4.2 (1.2-15.0) and 7.3 (2.2-24.8).[61]

3.10.6.3 Primary Echocardiographic Safety Endpoint

Week 52 echo data from the three Phase 3 studies were pooled. LOCF imputation was used for missing Week 52 echoes; that is, if no Week 52 echo was available, the Week 24 (or early termination) echo was analyzed with the Week 52 data. Note that patients who discontinued prematurely from the trial were asked to return at the time of their intended Week 52 visit to

undergo a final echocardiogram. The patients who discontinued and returned to have an echo performed increased by ~10% the total number of echo pairs evaluated.

In the pooled analysis of all three trials, the 1 year incidence of echocardiographic FDA-defined valvulopathy was 2.04% in the placebo groups and 2.37% in the lorcaserin BID groups. The difference in proportions of 0.33 and its 90% confidence interval was then used to determine whether the non-inferiority criterion was met. Using the pre-planned analysis of pooled Phase 3 echo data, the upper limit of the 90% CI for the difference in proportion is less than the noninferiority margin of 1.25; the 95% CI is also below this margin (Table 33). Hence, lorcaserin BID was non-inferior to placebo using the pre-specified non-inferiority risk difference analysis.

Relative risk at Week 52 was calculated as a secondary analysis, even though the database lacked adequate power for this analysis. To provide 80% power to exclude a 1.5 relative risk using a 2-sided $\alpha = 0.05$ (equivalent to a one sided $\alpha = 0.025$) would require 191 events, and only 116 were observed in this restricted dataset. The point estimate for relative risk (95% CI) of FDA-defined valvulopathy in the lorcaserin BID group using the pooled datasets with LOCF imputation for missing echoes was 1.16 (0.81, 1.67).

Within the individual studies, the 1 year incidences of new valvulopathy in the placebo and lorcaserin BID groups were fairly consistent, with the exception of the placebo group in the APD356-010 trial. In that trial, a single patient (0.5% incidence) assigned to placebo developed new FDA-defined valvulopathy at Week 52, well below the placebo incidences observed in the larger APD356-009 and APD356-011 studies. However, at Week 24 in the APD356-010 trial, the rate was consistent with the rate observed in the other trials: 4 patients (1.9%) in the placebo group met this criteria.

Table 33. Proportion of Patients who Developed New FDA-defined Valvulopathy at Week 52 using LOCF Imputation for Missing Values: Individual Studies and All Three Studies Pooled

Study and Treatment	N	n(%)	Difference in Proportions			Relative Risk			p-value[a]
			Diff.	90% CI	95% CI	RR	90% CI	95% CI	
APD356-009									
Placebo	1194	28 (2.3%)							
Lorcaserin 10 mg BID	1278	34 (2.7%)	0.31	-0.72, 1.34		1.13	0.75, 1.71	0.69, 1.85	0.700
APD356-011									
Placebo	1153	23 (2.0)							
Lorcaserin 10 mg BID	1208	24 (2.0)	-0.01	-0.95, 0.94		1.00	0.62, 1.60	0.57, 1.75	0.999
Lorcaserin 10 mg QD	622	9 (1.4)	-0.55	-1.59, 0.49		0.73	0.38, 1.38	0.34, 1.56	0.460
APD356-010									
Placebo	209	1 (0.5)							
Lorcaserin 10 mg BID	210	6 (2.9)	2.38	0.33, 4.43		5.97	1.02, 35.0	0.73, 49.2	0.122
Lorcaserin 10 mg QD	80	2 (2.5)	2.02	-0.96, 5.00		5.23	0.71, 38.7	0.48, 56.8	0.187
Pooled (three studies)									
Placebo	2553	52 (2.04)							
Lorcaserin 10 mg BID	2696	64 (2.37)	**0.33**	**-0.33, 1.00**	**-0.46, 1.13**	1.16	0.86, 1.57	0.81, 1.67	0.47
Lorcaserin 10 mg QD	702	11 (1.57)	-0.23	-1.21, 0.75	-1.40, 0.94	0.87	0.49, 1.57	0.43, 1.76	0.53

[a] p-value is a comparison between treatment groups and calculated from Fisher's Exact test with no continuity correction.

Note: Last non-missing post baseline observation carried forward. Patients with Baseline FDA-Defined Valvulopathy are excluded.

Primary pre-specified risk difference analysis is **bolded**

3.10.6.4 Additional Analyses of Echocardiographic Data

In addition to Week 52 data, Week 24 data from the Phase 3 dataset and Week 76 and Week 104 data from the APD356-009 study are summarized in Table 34. Among the patients exposed to lorcaserin BID for 1.5 or 2 years in APD356-009, there was no evidence of a time on drug response, and the incidence of FDA-defined valvulopathy was slightly lower than that in the corresponding placebo groups. Week 24 data show incidences for FDA-defined valvulopathy of 1.8-2.5%.

Table 34. Incidence of New FDA Valvulopathy by Echocardiographic Time Point in Phase 3 Studies

	APD356-009		APD356-011		APD356-010		Pooled Phase 3 Studies	
	PBO	Lorcaserin BID	PBO	Lorcaserin BID	PBO	Lorcaserin BID	PBO	Lorcaserin BID
Week 24								
N	1091	1213	1103	1170	206	203	2398	2586
n (%)	21 (1.9)	25 (2.1)	20 (1.8)	27 (2.3)	4 (1.9)	5 (2.5)	45 (1.88)	57 (2.20)
Diff in % (90% CI)		0.1 (-0.8, 1.1)		0.5 (-0.5, 1.5)		0.52 (-1.87, 2.91)		0.33 (-0.33, 0.99)
p-Value[a]		0.8819		0.4621		0.7497		0.48
Week 52								
N	1194	1278	1153	1208	209	210	2553	2696
n (%)	28 (2.3)	34 (2.7)	23 (2.0)	24 (2.0)	1 (0.5)	6 (2.9)	52 (2.04)	64 (2.37)
Diff in % (90% CI)		0.3 (-0.7, 1.4)		-0.01 (-0.9, 0.9)		2.38 (0.33, 4.43)		0.33 (-0.33, 1.00)
p-Value[a]		0.6998		0.9999		0.1219		0.47
Week 76								
N	609	486						
n (%)	19 (3.1)	14 (2.9)						
Week 104								
N	627	500						
n (%)	17 (2.7)	13 (2.6)						

[a] p-Value calculated using Fishers exact test as a secondary analysis.

Note: Last non-missing post baseline observation carried forward; patients with pre-existing FDA valvulopathy are excluded. Upper limit of two-sided 90% CI is equivalent to the upper limit of a one-sided 95% CI.

Diff in % = difference in proportions

The primary analysis of FDA-defined valvulopathy and the analysis summarized in Table 33 used the population of patients who had a baseline echo and at least one post-baseline echo. Last observation carried forward imputation was used for missing echo values. While the analysis of the proportion of patients with an echocardiographic finding at a discrete point in time is informative, it does not fully utilize the available data for each patient. Additional post-hoc analyses were conducted to provide additional insight into the interpretation of the echocardiographic findings. These *post-hoc* analyses utilize all echocardiographic data through Week 104 and include enough events of FDA valvulopathy to provide adequate statistical power (>80%) for risk ratio assessments.

PIECEWISE EXPONENTIAL MODEL

Echocardiographic valvular regurgitation data were evaluated as grouped survival data for the time to first FDA-defined valvulopathy. In the Phase 3 trials, 200 patients experienced an event

of first FDA-defined valvulopathy. The 200 FDA-defined valvulopathy events provide 89% power to detect a hazard ratio of 1.5 at $\alpha = 0.05$ one-sided, and 82% power at $\alpha = 0.025$ one sided. **The hazard ratio from the overall analysis is 1.09 (95% CI, 0.82 to 1.43).**

COX PROPORTIONAL HAZARDS MODEL

An alternative time to event analysis using the Cox proportional hazards (CoxPH) model was also performed. The CoxPH model is a standard tool in survival analysis that models the effect of covariates on the hazard rate but leaves the baseline hazard rate unspecified. A key assumption of the CoxPH model is proportional hazards, that is, the hazard ratio will remain constant over time. This means that the hazard functions for any two individuals at any time point are proportional, not that the risks are the same over time. This approach produced a **hazard ratio of 1.09 (95% CI, 0.83 to 1.44)**.

GEE METHODOLOGY

For the generalized estimating equation (GEE) analysis, all available echo assessments for each patient were used. One record per patient per echocardiogram was used: in each of the Phase 3 studies, echoes were obtained at baseline/screening and then every 6 months. The response variable is the presence or absence of FDA-defined valvulopathy at a given time point. Note that the presence or absence of FDA-defined valvulopathy varies among assessment times rather than always being present after its time of first occurrence. Thus, the GEE method addresses the average prevalence ratio across the four 6-month time intervals from 0 to 104 weeks, with the word "prevalence" applying because the event can appear and disappear over time within the same patient. The **GEE rate ratio is 1.08 (95% CI, 0.81 to 1.44).**

Each of the three supplementary echo assessments used all echoes for each patient from Week 0-104. The resulting number of events (new FDA-defined valvulopathy) provided adequate power for rate ratio analyses, and resulted in upper confidence limits for event rate ratios that were below the target ratio of 1.5. The original pre-planned analysis addressed a risk *difference* in the rate of FDA-defined valvulopathy at the specified time point of 52 weeks. It had adequate power for this purpose, but not enough events for reasonable power to apply to the corresponding relative risk *ratio*. According to these three appropriately powered *post-hoc* analyses, the risk ratio of new FDA-defined valvulopathy was not increased in the lorcaserin BID group by more than 1.5-fold over placebo.

ASSOCIATION BETWEEN WEIGHT OR BMI CHANGE AND INCIDENCE OF FDA-DEFINED VALVULOPATHY

Singh and colleagues analyzed echocardiographic data obtained as part of the Framingham Offspring Study, using a subgroup of patients who had studies of acceptable technical quality and who lacked aortic or mitral stenosis.[5] They evaluated the prevalence and clinical determinants of mitral regurgitation (MR), aortic regurgitation (AR) and tricuspid regurgitation (TR). Singh et al. identified a negative correlation between BMI and MR and between BMI and TR. In other words, as obesity increased, the apparent incidence of MR and TR decreased. The effect of adiposity could be technical (more difficult to detect regurgitation in more obese individuals) or could be related to cardiac structural or hemodynamic factors.

The sponsor hypothesized that weight loss (or decrease in BMI) among overweight or obese individuals—independent of weight loss method-- will cause an apparent increase in the prevalence of FDA-defined valvulopathy when assessed at a point following as compared to a time point preceding weight loss. Details of the logistic regression analysis and results are provided in Appendix 6. Briefly, the analysis was performed first using the placebo group only, and then incorporated the lorcaserin groups, with similar results in the two datasets. The analysis revealed significant negative associations between percent change in body weight or change in BMI and incidence of FDA-defined valvulopathy at Week 52. In other words, the analysis of the pooled Phase 3 data predicted that the apparent incidence of echocardiographic valvulopathy would increase with greater weight loss. The predicted risk of valvulopathy associated with a 5% weight loss is 1.15; the predicted risk associated with a decrease in BMI of 2 kg/m^2 is 1.16. Differential weight loss may therefore contribute to point estimates of risk that slightly exceed unity.

SUMMARY OF FDA-DEFINED VALVULOPATHY RISK ANALYSES

The key analyses of the primary echocardiographic endpoint, proportion of patients who developed FDA-defined valvulopathy, are summarized in Table 35. The analyses with adequate statistical power (CPH, PEM and GEE) exclude a risk of more than 1.5 times placebo. Furthermore, as discussed in the section above, differential weight loss may have contributed to the small differences in risk ratios.

Table 35. Summary of Echocardiographic Analyses for Proportion of Patients with FDA-defined Valvulopathy: Pooled Studies APD356-009, APD356-010, and APD356-011

Method	Data Used	Output	Result	95% CI
Risk Difference; non-inferiority	Week 52, LOCF	Risk difference	0.33	-0.46, 1.13[a]
Relative Risk; non-inferiority	Week 52, LOCF	RR	1.16	0.81, 1.67
Relative Risk; non-inferiority	Week 52, Completer	RR	1.03	0.68, 1.57
Cox Proportional Hazards	Week 0-104	HR	1.09	0.83, 1.44
Piecewise Exponential Model	Week 0-104	HR	1.09	0.82, 1.43
Generalized Estimating Equation	Week 0-104	Rate ratio	1.08	0.81, 1.44

[a] Risk difference: pre-specified non-inferiority margin = 1.25%.

CI = confidence interval; HR = hazard ratio; LOCF = last observation carried forward; RR = relative risk

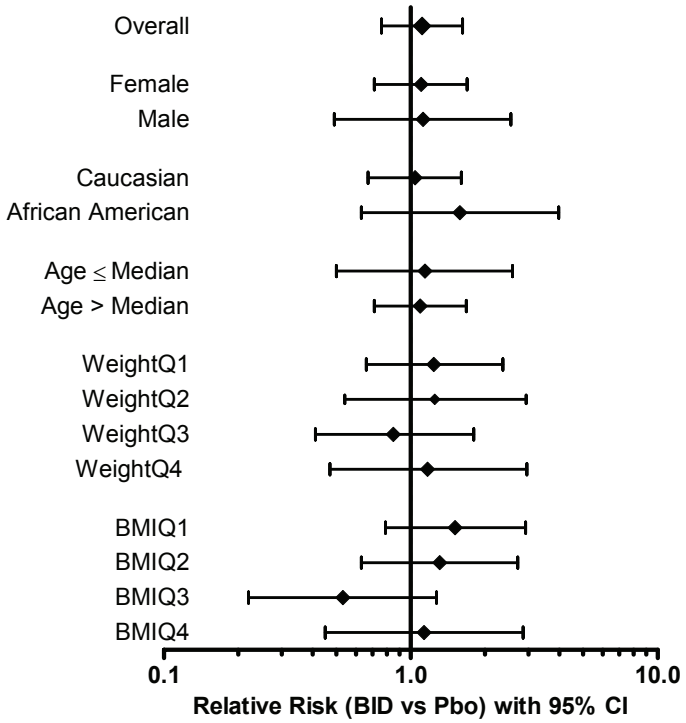
Multiple other observations suggest that there is no difference between rates of valvulopathy between the lorcaserin and placebo groups, including the finding of an imbalance in only one of the two large phase 3 studies, a lack of dose response, and a lack of relative time response (reference/link to appropriate tables in Appendix 5). The incidences of valvulopathy at Week 52 for the placebo and lorcaserin BID groups were 2.3% and 2.7%, respectively, in APD356-009 (3182 patients enrolled) and 2.0% vs. 2.0% in APD356-011 (4008 patients enrolled). In APD356-011, which included the QD dosing, the Week 52 incidence of valvulopathy was 1.4% in this dose group, lower than the 2.0% observed in the placebo and BID groups. And finally, rates of valvulopathy were slightly lower in the lorcaserin BID group than the placebo group

during Year 2 of APD356-009 (Week 76: 3.1% placebo, 2.9% lorcaserin BID; Week 104: 2.7% placebo, 2.6% lorcaserin BID).

FDA-DEFINED VALVULOPATHY IN PATIENT SUBGROUPS

Patient subgroups were evaluated (Figure 23). Gender, race and starting body weight did not appear to impact relative risk.

Figure 23. Relative Risk of New FDA-defined Valvulopathy at Year 1 in Patient Subgroups in Pooled Phase 3 Studies



3.10.6.5 Analysis of Individual Heart Valves

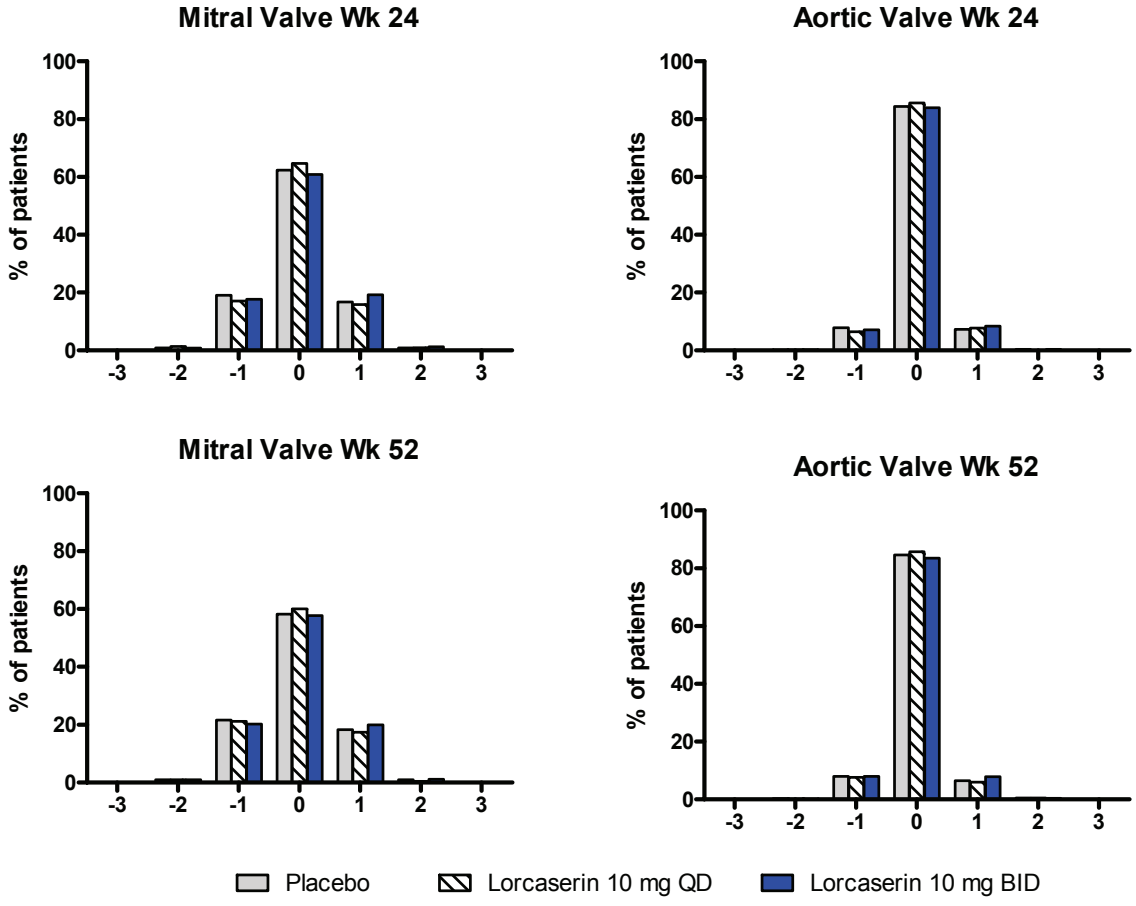
Numerical categorical changes from baseline in regurgitant scores at the aortic and mitral valves at Week 24 and Week 52 are shown in Figure 24 below. Shifts at all heart valves are provided in Appendix 5, in Table 82; and by graphical presentations of the shifts, provided for the entire pooled phase 3 population and by patients with and without FDA valvulopathy at baseline (Figure 49, Figure 50 and Figure 51). In addition, the proportion of shifts constituted by severity classification (e.g., absent to trace, mild to absent, etc.) are displayed in Figure 52.

General observations related to shifts in regurgitant scores include the following: Among all patients or patients without pre-existing FDA-defined valvulopathy, most regurgitant scores did not changes from baseline to Week 52; most changes that did occur were a decrease or increase of 1 category, generally within the spectrum of absent, trace, and mild. Overall, increases and

decreases occurred with similar frequencies across treatment groups. Scores changed less at the aortic valve as compared to the mitral in both treatment groups, and the patterns for all valves are similar across treatment groups.

The APD356-011 and APD356-010 studies included patients who met echocardiographic FDA-defined valvulopathy criteria at baseline. Approximately 4.5% of randomized patients in each study met these criteria, such that approximately 2.7% of the entire Phase 3 population met FDA-defined valvulopathy criteria at baseline. For the aortic, mitral and tricuspid valves, patients with baseline FDA-defined valvulopathy showed a trend opposite that of patients without and that of the overall population: among those with pre-existing valvulopathy, a smaller proportion of patients on lorcaserin BID had increases in valvular regurgitant score.

Figure 24. Shifts in Echocardiographic Regurgitant Scores for Aortic and Mitral Valves, Pooled Phase 3 Studies APD356-009, -011 and -010: All Patients



3.10.6.6 Pulmonary Artery Pressure

Pulmonary artery systolic pressure (PASP) was estimated from echocardiograms, and was analyzed using the pooled dataset from Phase 3 studies APD356-009, APD356-010, and APD356-011 (Table 36, Table 37 and Table 38). Pulmonary hypertension is defined as a directly measured (catheter) mean pulmonary artery pressure of >25 mmHg at rest. Note that, as expected, it was not possible to estimate PASP due to technical limitations (no/inadequate tricuspid valve regurgitant jet) in more than half of echocardiographic studies. Only those echoes with PASP estimates are included in these analyses. A normal estimated PASP was defined as <35 mmHg and an estimated PASP of 50 mmHg, representing at least a 10 mmHg increase from baseline, required further evaluation. Mean increases in PASP ≥ 15 mmHg at Week 52 were slightly more frequent in the lorcaserin BID group than in the placebo group (Table 37); the mean changes were very small, and few of the increases led to elevated PASP (Table 38). Three patients assigned to lorcaserin who had Week 52 PASP ≥ 50 mmHg are discussed below.

Table 36. Analysis of Change from Baseline in PASP at Week 52 in Pooled Studies APD356-009, APD356-010, and APD356-011: Safety Population

mmHg	Pooled Placebo	Pooled Lorcaserin 10 mg QD	Pooled Lorcaserin 10 mg BID
N	1195	349	1278
Baseline PASP (mean [SD])	25.3 (5.0)	25.1 (5.0)	25.7 (5.2)
Change from Baseline (LS mean [SEM])	0.1 (0.2)	0.1 (0.3)	0.2 (0.2)
p-Value		0.786	0.471

Note: Last observation carried forward (LOCF) method used to estimate missing parameters.

Table 37. Number (%) of Patients with Given Increases in PASP from Baseline at Week 24 and at Week 52 in Pooled Studies APD356-009, APD356-010, and APD356-011: Safety Population

Change from Baseline in PASP	Pooled Placebo	Pooled Lorcaserin 10 mg QD	Pooled Lorcaserin 10 mg BID
Week 24	(N=995)	(N=305)	(N=1105)
Patients with **increases** from baseline of			
≥ 10 mmHg	33 (3.32)	7 (2.30)	42 (3.80)
≥ 15 mmHg	8 (0.80)	2 (0.66)	10 (0.90)
≥ 20 mmHg	2 (0.20)	1 (0.33)	2 (0.18)
≥ 25 mmHg	0 (0.00)	1 (0.33)	0 (0.00)
Week 52	(N=1195)	(N=349)	(N=1278)
Patients with **increases** from baseline of			
≥ 10 mmHg	43 (3.60)	10 (2.87)	37 (2.90)
≥ 15 mmHg	7 (0.59)	5 (1.43)	13 (1.02)
≥ 20 mmHg	1 (0.08)	3 (0.86)	4 (0.31)
≥ 25 mmHg	0 (0.00)	1 (0.29)	1 (0.08)

Note: Last observation carried forward (LOCF) method used to estimate missing parameters. Number of Patients who have non-missing PASP at Baseline and at Week 24 or at Baseline and at Week 52 in each treatment group is used as the denominator for percentages calculations.

Table 38. Number (%) of Patients with PASP ≥ Various Thresholds at Week 24 and at Week 52 in Pooled Studies APD356-009, APD356-010, and APD356-011: Safety Population

Change from Baseline in PASP	Pooled Placebo	Pooled Lorcaserin 10 mg QD	Pooled Lorcaserin 10 mg BID
Week 24	(N=1379)	(N=407)	(N=1605)
Patients with PASP			
≥ 35 mmHg	36 (2.61)	9 (2.21)	38 (2.37)
≥ 40 mmHg	5 (0.36)	2 (0.49)	4 (0.25)
≥ 45 mmHg	1 (0.07)	1 (0.25)	0 (0.00)
≥ 50 mmHg	0 (0.00)	1 (0.25)	0 (0.00)
≥ 55 mmHg	0 (0.00)	1 (0.25)	0 (0.00)
≥ 60 mmHg	0 (0.00)	1 (0.25)	0 (0.00)
Week 52	(N=1753)	(N=507)	(N=1968)
Patients with PASP			
≥ 35 mmHg	33 (1.88)	11 (2.17)	42 (2.13)
≥ 40 mmHg	3 (0.17)	5 (0.99)	5 (0.25)
≥ 45 mmHg	1 (0.06)	1 (0.20)	2 (0.10)
≥ 50 mmHg	0 (0.00)	1 (0.20)	2 (0.10)
≥ 55 mmHg	0 (0.00)	1 (0.20)	0 (0.00)
≥ 60 mmHg	0 (0.00)	1 (0.20)	0 (0.00)

Note: Last observation carried forward (LOCF) method used to estimate missing parameters. Number of patients who have non-missing PASP at Baseline and at Week 24 or at Baseline and at Week 52 in each treatment group is used as the denominator for percentages calculations.

The following patients had Week 52 PASP ≥ 50 mmHg *and* an increase from baseline of ≥ 15 mmHg:

Patient 2145-S080 (lorcaserin 10 mg BID): The patient was a 53-year old African American woman with a non-contributory medical history; social history was significant for ~30-year smoking history. PASP was 31.5 mmHg at Baseline, 37.2 mmHg at Week 24, and 53.5 mmHg at Week 52. This event was reported as an adverse event. The patient was referred to a cardiologist not affiliated with the clinical trial. The cardiologist noted that the patient complained of exertional dyspnea and may have had symptoms of obstructive sleep apnea. He recommended a workup that included a treadmill stress test and a sleep study. The stress test was negative; the sleep study documented obstructive sleep apnea. The consulting physician attributed the pulmonary hypertension to the sleep apnea, and did not recommend additional diagnostic testing.

Patient 145-S094 (lorcaserin 10 mg BID): The patient was a 51-year old Caucasian woman with non-contributory medical and social history. PASP was 36.3 mmHg at Baseline, 39.7 mmHg at Week 24, and 34.5 mmHg at early termination (at Month 9, due to scheduling conflict). The patient returned according to protocol at the time of her scheduled Week 52 visit for a follow-up echocardiogram, which showed a PASP of 54.5 mmHg. This event was reported as an adverse event. The patient was referred to a cardiologist external to the clinical trial. He reported that she was asymptomatic and reported no significant physical findings.

He performed a diagnostic transthoracic echocardiogram that showed no evidence of elevated pulmonary artery pressure; estimated RV systolic pressure was 33 mmHg. No further workup was recommended.

Patient 1158-S019 (lorcaserin 10 mg QD): The patient was a 66-year old African American woman with a medical history that included type 2 diabetes, hypertension, hyperlipidemia, shortness of breath, right breast cancer s/p *radiation* and chemotherapy (2002), stable angina, COPD (according to medical records, but not recorded in study medical history database), chronic gastritis, GERD, and endoscopic colon polyp removal associated with a bout of gastrointestinal bleeding and consequent anemia (2007). Her social history was relevant for ongoing cigarette use (~1.5 ppd, duration unknown). She stopped working in 2007 due to weakness and fatigue. Concomitant medications included metformin, pioglitazone, glimepiride, ASA, metoprolol, enalapril, hydrochlorothiazide, atorvastatin, ranitidine, albuterol, calcium, iron, NTG, capsaicin cream, and naproxen. PASP at baseline was 25.1 mmHg, 61.7 mmHg at Week 24, and 76.2 mmHg at Week 52. The patient was referred to a cardiologist who measured her RV pressure at 65 mmHg following the Week 24 study echo and at 52 mmHg following the Week 52 study echo (patient completed the study). The consulting cardiologist offered no specific diagnosis or etiology for the elevated pressure, and did not recommend changes to her management. Approximately 6 months after the patient completed the study, the consulting cardiologist conducted cardiac stress testing (positive) followed by coronary angiography (pulmonary artery pressure 60 mmHg). Coronary artery bypass surgery was performed. One year after completing the study, the patient died at home. No autopsy was performed.

Two additional patients in the APD356-010 study (1 placebo, 1 lorcaserin) had post-baseline PASP values > 40 mmHg (and > baseline value) at Week 24 but not at Week 52. Values for the placebo patient (**1146-S043, Placebo**) were 32.9 mmHg, 43.5 mmHg, and 34.3 mmHg at Baseline, Week 24, and Week 52, respectively. Values for the lorcaserin patient (**1131-S017, Lorcaserin BID**) were 33.2 mmHg, 40.8 mmHg, and 30.1 mmHg at Baseline, Week 24, and Week 52, respectively.

3.10.7 Evaluation of Depression and Suicidal Ideation in Phase 3 Studies

3.10.7.1 Depression

MEDICAL HISTORY OF DEPRESSION PRIOR TO STUDY PARTICIPATION.

Depression and related disorders are common in obese and overweight people. Prevalence estimates range from 6.7% to over 15% in individuals classified as obese, as compared to prevalence rates of 2.8% to 7.4% for normal weight people.[62, 63] Moreover, obese individuals who are not currently depressed are at roughly twice the risk as normal weight individuals of developing depression in the future.[64] Given these figures and lorcaserin's central mechanism of action, depression was assessed during the clinical trials.

Approximately 8% of non-diabetic patients enrolled in Phase 3 studies had a history of depression or a related mood disorder. Two patients reported a history of suicide attempt (1

assigned to lorcaserin QD, 1 to lorcaserin BID). Among randomized patients with type 2 diabetes in study APD356-010, 6.3% reported a medical history of depression.

ADVERSE EVENTS RELATED TO DEPRESSION

Adverse events belonging to the Depression SMQ and the Suicide/self-injury SMQ for Phase 3 trials are presented in Table 39. The frequencies of AEs within the narrow Depression SMQ were similar among the treatment groups in non-diabetic patients and in the pooled analysis. The events were slightly overrepresented in the lorcaserin groups of patients with type 2 diabetes in study APD356-010, although the differences between groups comprised only 1-2 patients. No individual preferred term within the Narrow SMQ appeared to be overrepresented in any treatment group. In contrast, broad depression SMQ terms were reported more often by patients assigned to lorcaserin, and more often led to study discontinuation as compared to placebo. The small difference arose mainly from PTs “Disturbance in attention,” “memory impairment” and “initial insomnia.”

Table 39. Summary of AEs Belonging to Depression Standard MedDRA Queries (SMQ) from Phase 3 Trials

		Pooled Studies APD356-009 and -011: Non-diabetic Patients			Study APD356-010: Patients with Type 2 Diabetes			All Phase 3 Studies Pooled		
	Preferred Term	Placebo N=3185	Lorcaserin 10 mg BID N=3195	Lorcaserin 10 mg QD N=801	Placebo (N=252)	Lorcaserin 10 mg BID (N=256)	Lorcaserin 10 mg QD (N=95)	Placebo (N=3437)	Lorcaserin 10 mg BID (N=3451)	Lorcaserin 10 mg QD (N=896)
Narrow SMQ	Depression	53 (1.7)	59 (1.8)	9 (1.1)	5 (2.0)	6 (2.3)	5 (5.3)	58 (1.7)	65 (1.9)	14 (1.6)
	Depressed mood	23 (0.7)	20 (0.6)	7 (0.9)	0	2 (0.8)	0	23 (0.7)	22 (0.6)	7 (0.8)
	Depressive symptom	1 (< 0.1)	2 (0.1)	0	0	0	0	1 (<0.1)	2 (0.1)	0
	Major depression	1 (< 0.1)	0	0	0	1 (0.4)	0	1 (<0.1)	1 (<0.1)	0
	Decreased interest	0	1 (< 0.1)	0	1 (0.4)	0	0	1 (<0.1)	1 (<0.1)	0
	Dysthymic disorder	0	0	1 (0.1)	0	0	0	0	0	1 (0.1)
	Feeling of despair	1 (< 0.1)	0	0	0	0	0	1 (<0.1)	0	0
	TOTAL NARROW SMQ	**78 (2.4)**	**81 (2.5)**	**17 (2.1)**	**6 (2.4)**	**9 (3.5)**	**5 (5.3)**	**84 (2.4)**	**90 (2.6)**	**22 (2.5)**
Broad Depression SMQ	Disturbance in attention	9 (0.3)	20 (0.6)	2 (0.2)	0	1 (0.4)	0	9 (0.3)	21 (0.6)	2 (0.2)
	Mood swings	5 (0.2)	5 (0.2)	2 (0.2)	0	0	0	5 (0.1)	5 (0.1)	2 (0.2)
	Initial Insomnia	4 (0.1)	13 (0.4)	2 (0.2)	0	0	0	4 (0.1)	13 (0.4)	2 (0.1)
	Crying	4 (0.1)	6 (0.2)	0	0	0	0	4 (0.1)	6 (0.2)	0
	Middle insomnia	5 (0.2)	1 (< 0.1)	0	0	0	1 (1.1)	5 (0.1)	1 (<0.1)	1 (0.1)
	Memory impairment	5 (0.2)	22 (0.7)	0	0	2 (0.8)	0	5 (0.1)	24 (0.7)	0
	Poor quality sleep	4 (0.1)	3 (0.1)	1 (0.1)	0	0	0	4 (0.1)	3 (0.1)	1 (0.1)
	Affect lability	1 (< 0.1)	4 (0.1)	1 (0.1)	0	0	0	1 (<0.1)	4 (0.1)	1 (0.1)
	Apathy	3 (0.1)	2 (0.1)	1 (0.1)	0	0	0	3 (0.1)	2 (0.1)	1 (0.1)
	Dyssomnia	1 (< 0.1)	0	0	0	0	0	1 (<0.1)	0	0
	Hypersomnia	3 (0.1)	7 (0.2)	0	0	0	0	3 (0.1)	7 (0.2)	0
	Mood altered	0	5 (0.2)	1 (0.1)	0	0	0	0	5 (0.1)	1 (0.1)
	Psychomotor hyperactivity	0	3 (0.1)	1 (0.1)	0	0	0	0	3 (0.1)	1 (0.1)
	Psychomotor retardation	0	2 (0.1)	0	0	0	0	0	2 (0.1)	0
	Tearfulness	0	0	0	1 (0.4)	0	0	1 (<0.1)	2 (0.1)	0
	Terminal Insomnia	3 (0.1)	1 (< 0.1)	1 (0.1)	0	0	0	3 (0.1)	1 (<0.1)	1 (0.1)
	TOTAL BROAD SMQ	**44 (1.4)**	**86 (2.7)**	**15 (1.9)**	**1 (0.4)**	**3 (1.2)**	**1 (1.1)**	**45 (1.3)**	**89 (2.6)**	**16 (1.8)**
	BROAD + NARROW	**115 (3.6)**	**155 (4.9)**	**25 (3.1)**	**7 (2.8)**	**12 (4.7)**	**6 (6.3)**	**122 (3.5)**	**166 (4.8)**	**31 (3.5)**

Note: Denominator for each column is number of patients in safety population. Some patients reported more than one term; hence, total may be smaller than sum of individual terms.

STUDY WITHDRAWALS DUE TO AEs RELATED TO DEPRESSION IN PHASE 3 STUDIES

Within all Phase 3 studies, 47 (1.4%) AEs within the broad + narrow Depression SMQ led to study withdrawal or permanent discontinuation of study drug during Year 1 in the lorcaserin BID group, 7 (0.8%) in the lorcaserin QD group and 24 (0.7%) in the placebo group (Table 40). Four patients assigned to placebo, 4 assigned to lorcaserin, and 3 patients re-randomized from lorcaserin to placebo discontinued due to the AE during Year 2 in the APD356-009 trial. For both treatment groups, the rate of discontinuation due to depression–related AE terms was low.

The incidence of event terms in the *narrow* depression SMQ did not differ among treatment groups, but withdrawals due to these events were more frequent in lorcaserin than placebo patients. Broad depression SMQ terms were reported more often by patients assigned to lorcaserin than placebo, and more often led to study discontinuation in lorcaserin-treated patients.

Table 40. Summary of Depression-related Adverse Events (Broad + Narrow SMQ) Leading to Study Withdrawal or Permanent Discontinuation of Study Drug during Year 1

	Pooled Studies APD356-009 and APD356-011: Non-diabetic Patients			Study APD356-010: Patients with Type 2 Diabetes		
SMQ Preferred Term	**Pooled Placebo (N=3185)**	**Pooled Lorcaserin 10 mg BID (N=3195)**	**Lorcaserin 10 mg QD (N=801)**	**Placebo (N=252)**	**Lorcaserin 10 mg BID (N=256)**	**Lorcaserin 10 mg QD (N=95)**
Number of Patients Reported with Event[a]	24 (0.8)	42 (1.3)	6 (0.7)	0	4 (1.6)	1 (1.1)
SMQ: Depression Narrow	**18 (0.6)**	**35 (1.1)**	**2 (0.2)**	**0**	**3 (1.2)**	**1 (1.1)**
Depression	16 (0.5)	29 (0.9)	1 (0.1)	0	2 (0.8)	1 (1.1)
Depressed mood	2 (0.1)	6 (0.2)	1 (0.1)	0	0	0
Major Depression	0	0	0	0	1 (0.4)	0
SMQ: Depression Broad	**6 (0.2)**	**8 (0.3)**	**4 (0.5)**	**0**	**1 (0.4)**	**0**
Disturbance in attention	1 (< 0.1)	4 (0.1)	1 (0.1)	0	1 (0.4)	0
Mood swings	2 (0.1)	1 (< 0.1)	1 (0.1)	0	0	0
Memory impairment	2 (0.1)	1 (< 0.1)	0	0	0	0
Crying	1 (< 0.1)	1 (< 0.1)	0	0	0	0
Apathy	0	0	1 (0.1)	0	0	0
Psychomotor retardation	0	1 (< 0.1)	0	0	0	0
Substance abuse	0	0	1 (0.1)	0	0	0

Note: Includes permanent discontinuation of study drug or withdrawal from study during Year 1.
[a] Number (%) of patients; denominator is safety population

In summary, lorcaserin did not increase the incidence of depression *per se*, but did increase the frequency of study withdrawal due to depression related AEs. Lorcaserin did increase the incidence of certain terms included in the broad depression SMQ, mainly those related to

memory and attention. The latter events tended to be self-limited and rarely led to study withdrawal.

BECK DEPRESSION INVENTORY-II (BDI-II) SCORES

The BDI-II questionnaire, comprised of 21 questions scored from 0-3, was administered at screening and at 9 subsequent time points in the APD356-009 study, and at screening and 3 subsequent time points in the APD356-010 and -011 studies. Patients with mild or greater depression scores at screening were excluded to avoid the possibility that their depression could spontaneously worsen, necessitating treatment with SSRIs/SNRIs and removal from the study. This instrument evaluates the severity of clinical depression as follows:

Total score
0-13: minimal depression
14-19: mild depression
20-28: moderate depression
29-63: severe depression

Mean changes in total BDI-II score were similar between treatment groups at each time point, and similar score shifts were observed in both groups (Table 41, Figure 25).

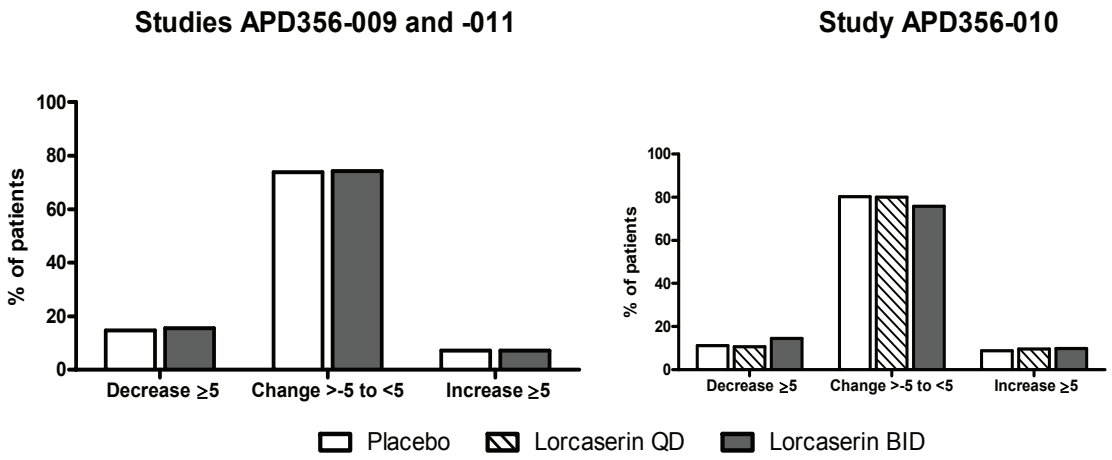
Table 41. Beck Depression Inventory II Total Scores, Change from Baseline: Safety Population

	Pooled Studies APD356-009 and APD356-011 Non-diabetic Patients			Study APD356-010: Patients with Type 2 Diabetes		
	Pooled Placebo	Pooled Lorcaserin 10 mg BID	Lorcaserin 10 mg QD[a]	Placebo	Lorcaserin 10 mg BID	Lorcaserin 10 mg QD
Week 4						
N	2843	2931	750	240	248	93
Baseline, Mean (sd)	4.0 (4.0)	4.1 (4.1)	3.8 (4.0)	4.1 (3.6)	4.4 (4.3)	4.1 (4.5)
Change from Baseline, LS Mean (sem)	-1.0 (0.1)	-0.8 (0.1)	-1.1 (0.1)	-0.3 (0.3)	0.1 (0.3)	-0.1 (0.4)
Week 24						
N	2901	2981	754	242	250	93
Baseline, Mean (sd)	4.1 (4.1)	4.1 (4.1)	3.8 (4.0)	4.0 (3.6)	4.4 (4.3)	4.1 (4.5)
Change from Baseline, LS Mean (sem)	-0.7 (0.1)	-0.9 (0.1)[b]	-0.6 (0.1)	-0.1 (0.3)	0.1 (0.3)	0.5 (0.5)
Week 52						
N	2905	2981	754	242	93	250
Baseline, Mean (sd)	4.1 (4.1)	4.1 (4.1)	3.8 (4.0)	4.0 (3.6)	4.1 (4.5)	4.4 (4.3)
Change from Baseline, LS Mean (sem)	-0.8 (0.1)	-0.9 (0.1)[b]	-0.6 (0.2)	-0.3 (0.3)	-0.1 (0.4)	0 (0.5)

[a] Data from study APD356-011 only

[b] P<0.001 versus placebo

Figure 25. Change in Total BDI-II Scores from Baseline to Week 52 in Pooled Phase 3 Studies



SUICIDAL IDEATION

The BDI-II was used to monitor suicidal ideation in all Phase 3 studies. Question #9 of this instrument asks about suicidal thoughts:

9. Suicidal Thoughts or Wishes

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

Investigators were encouraged to report as adverse events any response >0 to BDI-II item #9. Indeed, almost all adverse events coded to the Preferred Term suicidal ideation were reported in response to a BDI-II answer on question #9 that indicated passive suicidal thoughts (Table 42). One report in the placebo group and 1 report in the lorcaserin BID group arose from a patient's spontaneous report of suicidal thoughts that were not associated with the BDI-II instrument. One patient taking placebo and 1 patient taking lorcaserin attempted suicide, each with drug ingestion (not study drug).

In summary, the incidence of suicidal ideation was similar in placebo and lorcaserin treatment groups.

Table 42. Summary of Adverse Events Related to Suicidal Ideation in Study APD356-010 and Pooled Studies APD356-009 and -011

N=	Pooled Studies APD356-009 and APD356-011: Non-diabetic Patients			Study APD356-010: Patients with Type 2 Diabetes			All Studies Pooled		
	Pooled Placebo (N=3185)	Pooled Lorcaserin 10 mg BID (N=3195)	Lorcaserin 10 mg QD (N=801)	Placebo (N=252)	Lorcaserin 10 mg BID (N=256)	Lorcaserin 10 mg QD (N=95)	Placebo 3437	Lorcaserin 10 mg BID 3451	Lorcaserin 10 mg QD 896
AEs based on post-baseline BDI-II score	28 (0.9)	34 (1.1)	6 (0.7)	1 (0.4)	3 (1.2)	2 (2.1)	29 (0.8)	37 (1.1)	8 (0.9)
AEs based on spontaneous reports	1 (<0.1)	1 (<0.1)	0	0	0	0	1 (<0.1)	1 (<0.1)	0
AEs of suicidal *behavior*[b]	1 (<0.1)[a]	1 (<0.1)	0	0	0	0	1 (<0.1)[a]	1 (<0.1)	0

Loc, lorcaserin; PBO, placebo

[a] One patient in study APD356-009 attempted suicide while on placebo in Year 2 (Study Day 495); she had been assigned to lorcaserin during Year 1.

[b] Includes 1 suicide attempt and 1 intentional overdose

3.10.8 Analysis of Breast Cancer Risk and Circulating Prolactin

3.10.8.1 Adverse Events of Breast Cancer

In the 2-year carcinogenicity study of high-dose lorcaserin in rats, a lorcaserin-related increase in the incidence of mammary neoplasms was observed. A safety margin of 24 was established for malignant adenocarcinoma, and mechanistic experiments demonstrated that the mammary tumors observed in rats are most likely prolactin-dependent. Although drug-induced prolactin dependent mammary tumors in rats are unlikely to predict increased risk of breast cancer in humans,[3] a post-hoc analysis of breast neoplasms in the clinical trials of lorcaserin was performed, and serum prolactin was measured.

The adverse events related to breast cancer reported in the Phase 3 trials are summarized in Table 43. No adverse events of breast cancer were reported in study APD356-010.

Table 43. Summary of Adverse Events Related to Breast Cancer in Pooled Phase 3 Studies: Year 1, All Women in Safety Population

Preferred Term n(%)	Placebo N=2717	Lorcaserin 10 mg QD N=709	Lorcaserin 10 mg BID N=2747
Total Patient-years[a]	2418	564	2698
Breast cancer	4 (0.1)	0	4 (0.1)
Breast cancer in situ	0	1 (0.1)	1 (<0.1)

[a] Time to event was defined as from date of randomization to date of first event reported, or censored at the last day of study.

During Year 2 of the APD356-009 trial, 1 (0.4%) patient in the lorcaserin/placebo group reported an AE of breast cancer. This was in addition to the events summarized in Table 43.

3.10.8.2 Serum Prolactin Analyses

Serum prolactin concentrations were measured in approximately 1/3 of patients enrolled in the APD356-011 study and all patients enrolled in APD356-010. Samples were collected pre-dose and 2 hours post-dose at Baseline, and at Weeks 12, 24, and 52. Pre-dose morning prolactin concentrations increased less than 1 ng/mL in the lorcaserin groups post-baseline, with small decreases (0.1-0.2 ng/mL) in the placebo group at weeks 24 and 52 (Table 44). A small decrease in mean serum prolactin from pre-dose to 2 hours post dose of ~1 ng/mL was observed in the placebo group throughout the study (Table 45). In the lorcaserin BID group, a small increase from pre- to post-dose of <0.5 ng/mL was noted on Day 1; at subsequent weeks, lesser decreases from pre- to post-dose were observed in the lorcaserin BID group than in the placebo group.

Table 44. Change from Baseline in Pre-dose Prolactin in Pooled Studies APD356-010 and APD356-011

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

[a] Upper limits of normal: Women, 25 ng/mL; men, 17 ng/mL

Table 45. Summary Statistics for Serum Prolactin and Change from Pre- to Post-Dose in Pooled Studies APD356-010 and -011: All Patients

			Prolactin concentrations (ng/mL)[a]				
			Pre-Dose	Post-Dose	PRL delta (Post-Dose minus Pre-Dose)		
Visit	Treatment Group	N	Mean (SD)	Mean (SD)	Mean (SD)	Median	Min, Max
Day 1	Placebo	760	8.95 (10.03)	7.78 (8.93)	-1.17 (4.45)	-0.45	-86.20, 21.70
	Lorcaserin 10 mg QD	340	8.58 (6.25)	8.74 (6.44)	0.16 (3.35)	0.00	-15.00, 42.10
	Lorcaserin 10 mg BID	796	8.57 (7.15)	8.81 (7.00)	0.24 (3.82)	0.10	-57.60, 22.00
Week 12	Placebo	494	8.28 (5.98)	7.08 (5.21)	-1.21 (3.09)	-0.80	-30.00, 17.10
	Lorcaserin 10 mg QD	225	9.03 (6.63)	8.50 (5.93)	-0.53 (4.24)	-0.20	-27.90, 24.50
	Lorcaserin 10 mg BID	537	8.76 (6.50)	8.39 (6.51)	-0.38 (3.09)	-0.40	-16.60, 21.00
Week 24	Placebo	441	8.10 (5.94)	6.96 (5.12)	-1.15 (3.96)	-0.60	-55.00, 23.00
	Lorcaserin 10 mg QD	214	9.29 (8.71)	8.86 (8.15)	-0.43 (3.91)	-0.10	-34.00, 15.30
	Lorcaserin 10 mg BID	482	8.49 (6.67)	8.15 (6.55)	-0.34 (3.50)	-0.20	-20.70, 23.60
Week 52	Placebo	357	8.08 (6.74)	6.92 (5.57)	-1.16 (4.19)	-0.50	-62.90, 13.60
	Lorcaserin 10 mg QD	181	8.99 (6.77)	8.32 (5.58)	-0.67 (3.81)	-0.30	-28.50, 9.60
	Lorcaserin 10 mg BID	408	8.87 (7.51)	8.40 (6.81)	-0.47 (3.46)	-0.20	-30.40, 17.10

[a] Upper limits of normal: Women, 25 ng/mL; men, 17 ng/mL

3.10.9 Pregnancy and Lactation

Lorcaserin has not been systematically studied in pregnant or lactating women. Within the Phase 3 clinical program, women who became pregnant were withdrawn from the study immediately. Among the 54 women who conceived during trial participation, all women assigned to lorcaserin who gave birth had healthy babies (Table 46). No women enrolled in study APD356-010 became pregnant.

Table 46. Summary of Pregnancies in Pooled Phase 3 Trials (APD356-009 and -011)

	Lorcaserin (any dose) N=3996	Placebo N=3185
Patient pregnancies, n (% of women)	30 (0.8)	24 (0.8)
Partner Pregnancies	4	1
Outcomes (for patient pregnancies), n (% of pregnancies)		
Healthy baby	14 (0.47)	4 (0.17)
Miscarriage/SA	2 (0.07)	6 (0.25)
Elective abortion	9 (0.30))	11 (0.46)
Unknown	5 (0.17)	3 (0.13)
Duration of exposure (days)		
Mean (sd)	203 (126)	195 (197)
Range	12 – 453	2 – 737
Median	207	114

Note: Duration of exposure calculations based upon patient phone queries.

SA, Spontaneous abortion

3.10.10 Laboratory Evaluations

No adverse lorcaserin related effects on clinical chemistry, hematology or urinalysis parameter were identified.

In particular, no Hy's law cases for changes in liver function tests were observed. To the contrary, small decreases in population mean values for transaminases and alkaline phosphatase (AP) that were greater in the lorcaserin 10 mg BID group (BL and W52 means) than the placebo group (BL and W52 means) were observed. Creatinine clearance calculated using ideal body weight increased slightly in the lorcaserin 10 mg BID (BL and W52 means) and decreased slightly in placebo groups (BL and W52 means).

3.10.11 Vital Signs

In Phase 3 studies, blood pressure was evaluated both as an efficacy endpoint, using the MITT population with LOCF imputation, and as a safety endpoint, using the safety population of all patients who received study drug. Heart rate was evaluated only as a safety endpoint using observed case analysis. In the pooled dataset from patients without diabetes, lorcaserin BID and QD exerted no effects on vital signs other than the weight-related decreases in blood pressure and heart rate by either observed case or MITT/LOCF analysis (Figure 26, Table 47). In single dose studies, lorcaserin had no acute effect on blood pressure.

Figure 26. Mean Change from Baseline in Blood Pressure and Heart Rate in Studies APD356-009 and -011: Safety Population (observed case)

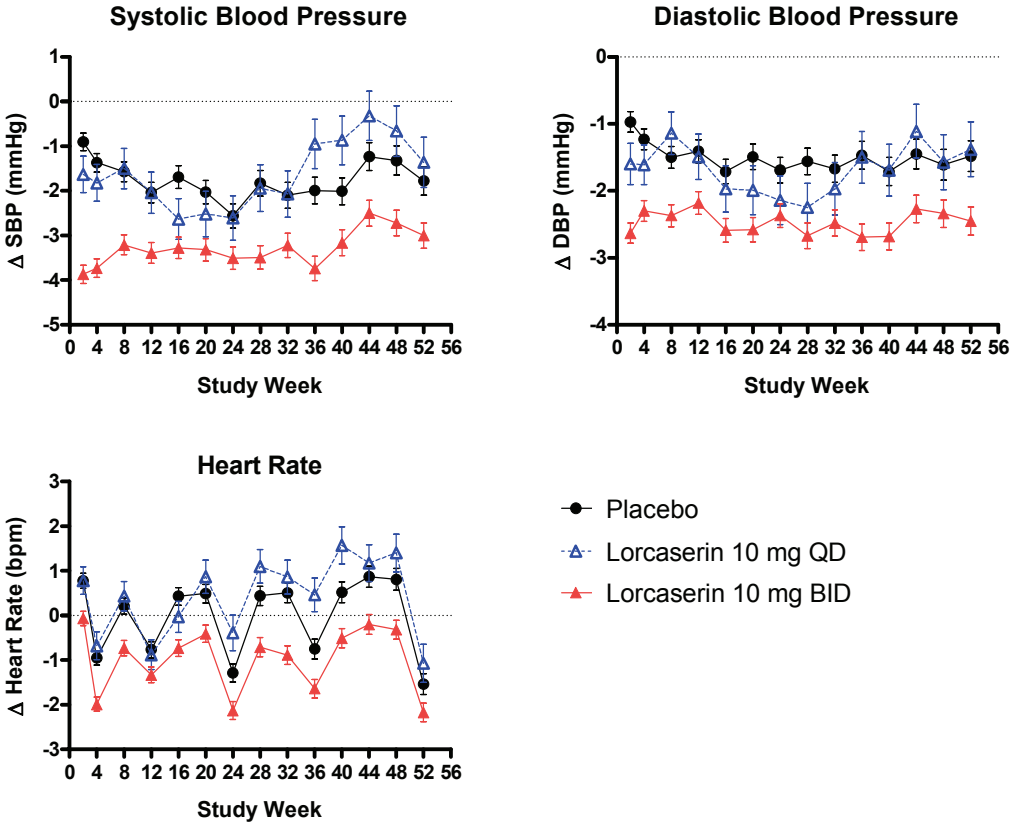


Table 47. Summary of Blood Pressure and Heart Rate Changes from Baseline to Week 52 in Pooled Phase 3 Studies APD356-009 and APD356-011: MITT/LOCF Population

Parameter Treatment	N	Baseline Mean (SD)	Week 52 Mean (SD)	Change from Baseline Mean (SEM)
Systolic BP (mm Hg)				
Placebo	3039	121.51 (11.74)	120.46 (12.46)	-1.05 (0.21)
Lorcaserin 10 mg QD[b]	771	121.20 (12.22)	120.20 (12.50)	-1.10 (0.43)
Lorcaserin 10 mg BID	3096	121.39 (11.86)	119.66 (12.66)	-1.73 (0.22)
Diastolic BP (mm Hg)				
Placebo	3039	77.71 (8.09)	76.67 (8.75)	-1.04 (0.16)
Lorcaserin 10 mg QD[b]	771	78.00 (8.33)	76.90 (8.89)	-1.00 (0.32)
Lorcaserin 10 mg BID	3096	77.44 (8.05)	75.94 (8.70)	-1.50 (0.16)
Heart Rate				
Placebo	3039	69.47 (8.88)	69.04 (9.46)	-0.43 (0.17)
Lorcaserin 10 mg QD[b]	771	69.08 (8.83)	68.67 (9.60)	-0.42 (0.33)
Lorcaserin 10 mg BID	3096	69.47 (8.73)	68.29 (9.53)	-1.18 (0.16)

[a] Lorcaserin QD data from study APD356-011 only

Among the patients with type 2 diabetes in study APD356-010, blood pressure changes were less consistent than in the larger studies of non-diabetic patients (Table 48). Lorcaserin BID was associated with mean decreases in systolic and diastolic blood pressure at Week 52 by either observed case or MITT/LOCF analysis, but in the lorcaserin QD group, blood pressure increased slightly relative to placebo in both analyses at Week 52 (Figure 27, Table 48). However, diastolic and systolic pressures were generally below baseline at other time points (Figure 27). Mean heart rate decreased slightly with both lorcaserin doses.

An analysis of categorical blood pressure levels for all Phase 3 studies showed no effect of lorcaserin to increase systolic or diastolic blood pressure or heart rate (Table 49). Supportive of these findings, lorcaserin BID was found to significantly reduce 24 hour urinary norepinephrine content, by approximatately 50% as compared to placebo, at Week1 and 8 in a 2-month mechanism of action clinical study, Study APD356-014 (Figure 28).

Figure 27. Mean Change from Baseline in Blood Pressure and Heart Rate in Study APD356-010: Safety Population

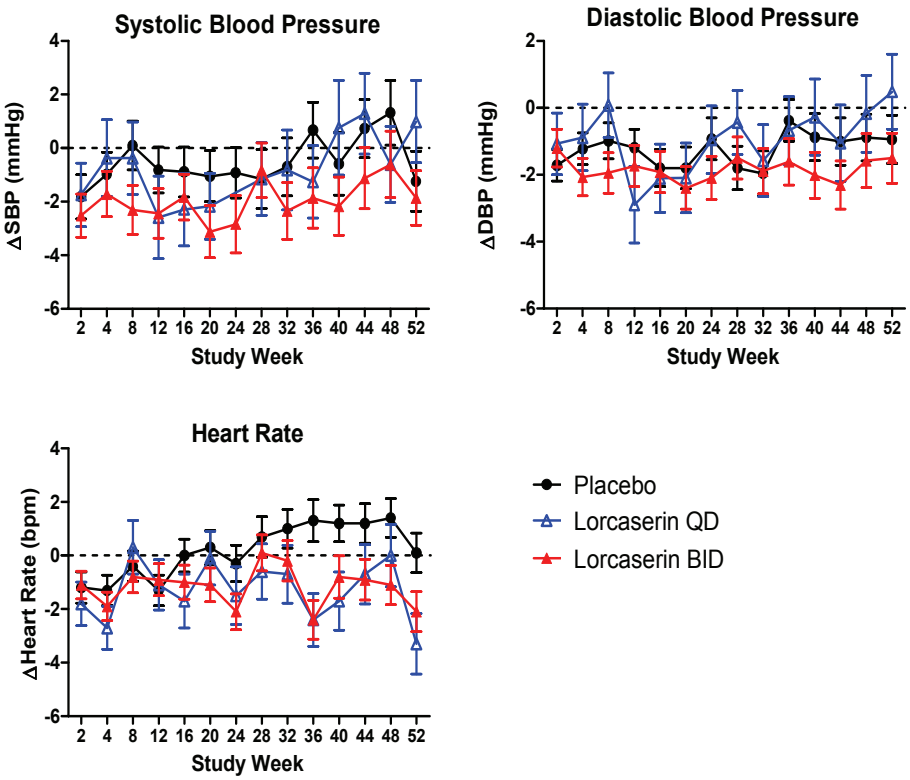


Table 48. Summary of Blood Pressure and Heart Rate Change from Baseline to Week 52 in Phase 3 Study APD356-010

Parameter Treatment	N	Baseline Mean (SD)	Week 52 Mean (SD)	Change from Baseline Mean (SEM)
Systolic BP (mm Hg)[a]				
Placebo	248	126.5 (13.5)	125.6 (13.4)	-0.9 (0.9)
Lorcaserin 10 mg QD	94	126.5 (11.4)	127.1 (12.9)	0.6 (1.4)
Lorcaserin 10 mg BID	251	126.6 (12.7)	125.8 (12.5)	-0.8 (0.9)
Diastolic BP (mm Hg)[a]				
Placebo	248	78.7 (7.9)	77.5 (8.2)	-1.2 (0.6)
Lorcaserin 10 mg QD	94	78.1 (9.3)	78.2 (8.5)	0.1 (1.0)
Lorcaserin 10 mg BID	251	77.9 (8.0)	76.8 (8.9)	-1.1 (0.6)
Heart Rate[b]				
Placebo	248	72.68 (9.00)	72.42 (10.03)	-0.27 (0.57)
Lorcaserin 10 mg QD	94	72.85 (8.48)	70.00 (9.95)	-2.85 (1.04)
Lorcaserin 10 mg BID	251	72.33 (9.20)	70.60 (9.10)	-1.73 (0.59)

Population: MITT/LOCF

[a] Heart rate determined in Safety population (observed case)

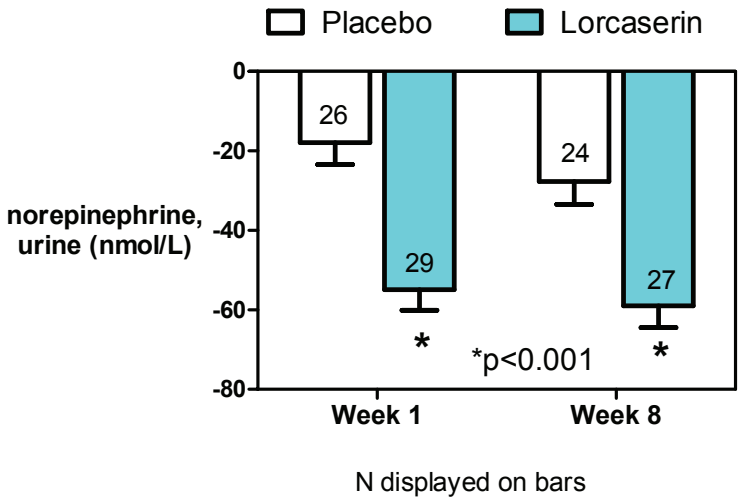
Table 49. Assessment of Categorical Blood Pressure and Heart Rate Values at Any Time during Phase 3 Study APD356-010 and Pooled Studies APD356-009 and -011: Safety Population

Parameter N[a](%) of patients	Pooled Studies APD356-009 and -011: Non-diabetic Patients			Study APD356-010: Patients with Type 2 Diabetes		
	Placebo N=3038	Lorcaserin 10 mg BID N=3095	Lorcaserin 10 mg QD N=771	Placebo N=248	Lorcaserin 10 mg BID N=235	Lorcaserin 10 mg QD N=90
Systolic BP (mm Hg)						
<80	9 (0.3)	14 (0.5)	5 (0.6)	0	0	0
80-84	15 (0.5)	17 (0.5)	4 (0.5)	0	1 (0.4)	0
85-89	42 (1.4)	56 (1.8)	12 (1.6)	2 (0.8)	1 (0.4)	1 (1.1)
120-139	2540 (83.6)	2517 (81.3)	660 (85.6)	225 (90.7)	235 (93.6)	90 (95.7)
140-159	701 (23.1)	650 (21.0)	215 (27.9)	122 (49.2)	120 (47.8)	44 (46.8)
≥160	74 (2.4)	53 (1.7)	16 (2.1)	20 (8.1)	20 (8.0)	7 (7.4)
Diastolic BP (mm Hg)						
<60	292 (9.6)	393 (12.7)	78 (10.1)	24 (9.7)	30 (12.0)	11 (11.7)
80-89	2284 (75.2)	2211 (71.4)	601 (78.0)	207 (83.5)	204 (81.3)	79 (84.0)
90-99	708 (23.3)	624 (20.3)	205 (26.6)	79 (31.9)	74 (29.5)	30 (31.9)
≥100	68 (2.2)	69 (2.2)	26 (3.4)	8 (3.2)	8 (3.2)	4 (4.3)
Heart Rate (bpm)						
<45	23 (0.8)	37 (1.2)	5 (0.5)	3 (1.2)	2 (0.8)	1 (1.1)
45-49	101 (3.3)	176 (5.7)	35 (4.5)	4 (1.6)	8 (3.2)	3 (3.2)
50-54	421 (13.9)	574 (18.5)	126 (16.3)	17 (6.9)	26 (10.4)	12 (12.8)
101-115	47 (1.5)	30 (1.0)	9 (1.2)	1 (0.4)	6 (2.4)	6 (6.4)
116-130	5 (0.2)	0	0	2 (0.8)	0	0
>130	0	0	0	0	0	0

Abbreviations: BP = blood pressure; mm Hg = millimeters of mercury; bpm = beats per minute

[a] Number of patients with non-missing baseline test, and at least one non-missing post-baseline test. Used as denominator for percentages in a category

Figure 28. Change in 24 Hour Urinary Norepinephrine Content from Baseline: APD356-014 Mechanism of Action Study



3.10.12 Safety in Special Populations

In patients with severe renal impairment or end stage renal disease requiring hemodialysis, the *N*-carbamoyl glucuronide of lorcaserin (M5) and the sulfamate of lorcaserin (M1), but not lorcaserin itself, accumulated significantly. Although no specific toxicity of these metabolites was identified, the predicted continuing accumulation with daily dosing prompts us to recommend that lorcaserin not be administered to patients with creatinine clearance (Cockcroft-Gault estimation based on ideal body weight) ≤30 mL/min.

3.10.13 Drug Interactions

Lorcaserin is a weak to moderate inhibitor of CYP2D6 in man at the maximum recommended dose of 10 mg twice daily. However, the magnitude of inhibition, demonstrated using the sensitive CYP2D6 substrate dextromethorphan, is insufficient to merit dose adjustments.

The co-administration of lorcaserin and dextromethorphan to healthy subjects altered the PK of dextromethorphan. The percent ratios of the geometric means of dextromethorphan C_{max}, AUC_{0-t} and AUC_{0-inf} were 177%, 205% and 206%, respectively, following co-administration as compared to dextromethorphan alone. The 90% CI calculated for the percent ratios of the geometric means of C_{max}, AUC_{0-t}, and AUC_{0-inf} were above the 80% − 125% range. According to FDA draft guidance, lorcaserin is a weak to moderate inhibitor of CYP2D6.

The drug-drug interaction study results indicated that lorcaserin slightly increased circulating dextromethorphan concentrations through weak to moderate inhibition of CYP2D6. The high inter-individual variability in CYP2D6 activity in the general population is predicted to impact CYP2D6 substrate metabolism substantially more than would lorcaserin. At the extreme, poor CYP2D6 metabolizers, which comprise 6-10% of the Caucasian population,[65] can experience

dextromethorphan exposures over 100 times those of extensive metabolizers.[66] Hence, population variability is expected to far exceed lorcaserin effects on drugs metabolized by CYP2D6. Therefore, the ~2 fold increase in dextromethorphan exposure associated with the proposed clinical dose of lorcaserin does not justify a recommendation of dose adjustment when lorcaserin is administered with CYP2D6 substrates.

3.10.14 Clinical Safety Conclusions

The most common adverse events reported by more patients on lorcaserin than placebo were headache, dizziness, nausea, fatigue, and dry mouth. All of these events tended to be mild or moderate and self-limited, and none tended to recur during continued dosing once the initial event had resolved. Serious adverse events were infrequent, and occurred in similar numbers of patients on active treatment and placebo.

Across all parameters that were monitored, the safety and tolerability of the 10 mg QD and 10 mg BID doses were comparable. No patient subgroup was identified in which the lower dose was preferable or substantially better tolerated that the twice-daily dose. Hence, given the greater efficacy of the 10 mg BID dose in the overall Phase 3 population, the recommended clinical dose is 10 mg BID.

The echocardiographic safety monitoring program provided point estimates of lorcaserin-associated risk that ranged from 1.03 (Week 52 Completer population) to 1.16 (Week 52 LOCF analysis), and ruled out a 50% or greater increase in the risk of clinically significant valvulopathy. A post-hoc analysis of the data also predicted a slightly higher incidence of FDA-defined valvulopathy in a group with greater weight loss than the placebo reference group.

Lorcaserin 10 mg BID did not increase blood pressure or heart rate; rather, significant decreases were observed with lorcaserin BID in studies APD356-009 and -011, consistent with the weight loss that occurred.

A thorough ECG/QT study and more than 15,000 ECGs collected in Phase 3 studies demonstrated that lorcaserin does not prolong the QTc interval, and confirmed that lorcaserin does not increase heart rate.

Systematic review of all clinical studies and a formal abuse liability clinical trial showed that lorcaserin has very low potential for abuse as a recreational drug. Indeed, supratherapeutic doses of lorcaserin were associated with subject-reported aversive effects.

Pre-specified reviews of depression-related adverse events and BDI-II responses in Phase 3 studies showed no increase in the incidence or severity of depression or suicidal ideation. Similarly, lorcaserin did not increase the incidence of anxiety or other mood disorders, and showed no evidence of 5-HT_{2A}-mediated perceptual or cognitive effects.

Lorcaserin was not associated with increased incidence of breast cancer during Phase 3 clinical trials. No clinically meaningful increases in mean serum prolactin were observed in men or women taking lorcaserin.

Based on the results of a study of the pharmacokinetics of lorcaserin and its metabolites in subjects with renal impairment, Arena will recommend that lorcaserin not be used in patients with severe renal impairment. In patients with calculated (Cockcroft-Gault) creatinine clearance ≤30 mL/min, lorcaserin metabolites M1 and M5 (but not lorcaserin itself) accumulated. In the absence of long-term studies demonstrating that lorcaserin is safe in patients with severe or end stage renal disease, lorcaserin should not be used in patients with a creatinine clearance ≤30 mL/min.

4 COMPLETE RESPONSE ITEMS

4.1 CRL Item 1: Diagnostic Uncertainty in the Classification of Mammary Masses in Female Rats

During the conduct of a 2 year carcinogenicity study in rats, Arena identified an increase in the number of female animals with mammary masses in lorcaserin dose groups relative to vehicle control. Arena notified the FDA, which requested that periodic progress reports be provided throughout the remainder of the study. In compliance with the request, Arena provided bimonthly preliminary, non-peer-reviewed pathology reads from a single pathologist for tissues from female rats. As is typical during study conduct and a peer review process, changes in some mammary tumor diagnoses occurred between the interim non-peer-reviewed interpretations and the final study report that was submitted with the original NDA. Because of these changes, the FDA questioned the certainty of mammary tumor diagnoses and asked that the mammary tissues from the female rat carcinogenicity study be re-adjudicated in a blinded fashion by an independent pathology working group (PWG).

This section briefly reviews the genotoxicity and carcinogenicity data submitted with the original NDA, and the revised data for female mammary gland derived from the PWG re-adjudication. Section 4 provides additional analyses of tumor aggressiveness and the mechanism underlying the benign mammary fibroadenomas and mammary adenocarcinomas observed in female rats.

The discussion includes references to exposure margins, which are used to help evaluate the relevance of animal toxicology findings to humans. Exposure margins refer to the ratio of lorcaserin exposure in the rat at a given dose for a particular safety finding relative to the exposure in humans at the maximum recommended dose of 10 mg twice daily. The term refers to plasma lorcaserin concentration timecourse profiles in relation to mammary gland findings or to brain lorcaserin concentration timecourse profiles in discussions relating to astrocytoma findings, both expressed in units of AUC.

4.1.1 Genotoxicity

The genotoxic potential of lorcaserin was evaluated in a standard battery of tests consisting of an *in vitro* Ames bacterial reverse mutation assay and a chromosome aberration test in Chinese hamster ovary (CHO) cells up to the limits of toxicity, and an *ex vivo* micronucleus assay in rats at doses up to 250 mg/kg. Results from all three assays were negative, indicating that lorcaserin is not genotoxic.

4.1.2 Carcinogenesis

The carcinogenic potential of lorcaserin was evaluated in a 2-year study in mice and a 2-year study in rats.

2-YEAR CARCINOGENICITY STUDY IN MICE

In a mouse carcinogenicity study doses of 5, 25, and 50 mg/kg/day were evaluated. A 100 mg/kg/day dose was eliminated on study Day 16 due to a high rate of mortality. Survival

rates were similar among all treatment groups at the final doses. At the highest dose of 50 mg/kg/day, lorcaserin exposures relative to human at 10 mg BID were 7 and 4 (males and females, respectively), and lorcaserin sulfamate (M1 metabolite) exposures were 66 and 74 (males and females, respectively) times M1 exposure in humans at 10 mg BID. Neither treatment-related toxicity nor carcinogenic effects were observed. **Treatment-related neoplasms were not found at any dose**.

2-YEAR CARCINOGENICITY STUDY IN RATS

A rat carcinogenicity study evaluated lorcaserin doses of 10, 30, and 100 mg/kg/day. The plasma exposure multiples of lorcaserin at the highest dose (100 mg/kg/day) were 55 (males) and 82 (females) times the human exposure at 10 mg BID. Plasma exposure margins for lorcaserin sulfamate (M1), the major circulating metabolite, were 136 (males) and 225 (females) times M1 exposure in humans at 10 mg BID. Based upon structure (a stable sulfamate conjugate of a non-genotoxic parent), M1 is not expected to be genotoxic. Direct evidence of this absence of genotoxicity is provided by the *in vivo* rat micronucleus assay, which used lorcaserin doses of up to 250 mg/kg. M1 exposures were more than 10 times lorcaserin exposures in all preclinical species studied.

Significant general toxicity was observed in males at the 100 mg/kg/day dose, as indicated by weight loss and debilitation. Body weight loss of greater than 10% relative to vehicle control occurred at Week 51, reaching 28% at Week 99. Additional indicators of general toxicity included general poor health and excess mortality; because of these findings, the FDA requested that the male high-dose group be terminated at Week 100. In light of the general toxicity, which can confound interpretation of the carcinogenic potential of a test article, data from this dose in males should be interpreted with caution.

Female Rat Carcinogenicity Study Findings

In female rats, mammary tumor incidence increased with lorcaserin administration. The study report provided with the original lorcaserin NDA showed significant increases in benign and malignant mammary tumors relative to vehicle controls. As part of the Complete Response Letter, the FDA asked that the data for female rat mammary tumors be re-evaluated. The re-analyses focused on malignant mammary adenocarcinoma and benign mammary fibroadenoma, and also addressed lung metastases derived from mammary adenocarcinoma.

The results of the 2-year carcinogenicity study of female S-D rats presented with the original lorcaserin NDA were the product of the standard practice: one pathologist provided initial interpretations of tissue sections, and a second pathologist provided a peer review of the diagnostic findings. According to standard practice in the field, both pathologists were aware of the treatment assignments in the study. The results showed a lorcaserin-related increase in mammary neoplasms. To assure that benign and malignant mammary neoplasms were distinguished with certainty, the FDA recommended a blinded re-adjudication of the mammary tissues by an independent panel of pathologists.

A panel of five pathologists was convened after vetting the members with the FDA. Each independently read all tissue sections derived from female rat mammary tissue, skin and lung (to detect metastases). All slides were blinded to treatment assignment. The five independent sets of

diagnoses were compared. In cases for which the diagnoses were not unanimous, the five pathologists viewed the relevant slide using a multi-headed microscope, and agreed upon a final diagnosis. These definitive diagnoses were entered into the study database and the data were re-analyzed. The five initial independent diagnoses were unanimous for 92.5% of mammary adenocarcinomas and for 97.1% of benign mammary fibroadenomas. The findings from the original report and from the PWG re-adjudication are summarized in Table 50.

Changes in mammary tumor diagnoses of adenocarcinoma and benign fibroadenoma shifted in both directions with the re-adjudication. The net outcome was a reduction in diagnoses of adenocarcinoma in all treatment groups, with corresponding increases in the diagnoses of benign fibroadenoma and adenoma. The overall statistical conclusions were similar in the original report and the PWG re-adjudication report. The PWG re-adjudication concluded that mammary adenocarcinoma was increased over control at the highest dose of 100 mg/kg/day, but not at the mid or low doses (Table 50); benign mammary fibroadenoma was significantly increased over control at all lorcaserin doses.

Table 50. Mammary Neoplasm Incidence in Female Rats

	Original Report				PWG Re-adjudication			
Dose (mg/kg/day)	**0**	**10**	**30**	**100**	**0**	**10**	**30**	**100**
Number of Female Rats	**65**	**65**	**65**	**75**	**65**	**65**	**65**	**75**
Mammary Gland:								
Mammary Adenocarcinoma	28	34	35	60	26	21	24	51
Percent incidence	43.08%	52.31%	53.85%	80%	40%	32.31%	36.92%	68%
Fisher Exact Test P value	--	0.3800	0.2923	<0.0001	--	0.4655	0.8570	0.0012
Multiplicity, n	nd	nd	nd	nd	7	6	6	17
Multiplicity, %	nd	nd	nd	nd	10.77%	9.23%	9.23%	22.67%
Onset rate (p value)	<0.0001				<0.0001			
Peto Test (p value)	0.9025				0.5135			
Mammary Fibroadenoma	20	47	53	45	24	54	55	51
Percent incidence	30.77%	72.31%	81.54%	60%	36.92%	83.08%	84.62%	68.00%
Fisher Exact Test P value	--	<0.0001	<0.0001	0.0007	--	<0.0001	<0.0001	0.0003
Multiplicity, n	nd	nd	nd	nd	7	39	51	41
Multiplicity, %	nd	nd	nd	nd	10.77%	60.0%	78.46%	54.67%
Onset rate (p value)	<0.0001				<0.0001			
Peto Test (p value)	0.9952				0.6479			
Mammary Adenoma					1	2	5	4
Percent incidence	0	0	0	0	1.54%	3.08%	7.69%	5.33%
Fisher Exact Test (p value)					--	1.0000	0.2078	0.3725
Onset rate (p value)	nd	nd	nd	nd	0.3260			
Peto Test (p value)	nd	nd	nd	nd	0.1905			
Mammary Carcinosarcoma	0	0	0	1	0	0	0	1
Percent incidence	0%	0%	0%	1.33%	0%	0%	0%	1.33%
Fisher Exact Test (p value)	--	--	--	--	--	1.0000	1.0000	1.0000
Lung:								
Carcinoma, secondary[a]	0	4	9	6	0	3	4	2
Adenocarcinoma, secondary[b]	nd	nd	nd	nd	0	1	5	5

nd, not determined

[a] Carcinoma, secondary in the original report refers to tumors of both mammary and non-mammary origin

[b] Adenocarcinoma, secondary refers only to tumors of mammary gland origin. Carcinoma, secondary in the PWG re-adjudication refers only to tumors not of mammary gland origin

A key distinction between the original report and the re-adjudication is diagnostic certainty: the PWG reached unanimous initial consensus in >90% of cases. Given this level of certainty, combining the malignant mammary adenocarcinomas and the benign mammary fibroadenomas for statistical analyses cannot be justified. Indeed, the National Toxicology Program guidelines

only support combining tumor types when their histomorphogenesis is similar.[67] Mammary adenocarcinoma and mammary fibroadenoma in the rat, as in the human, have distinct cellular origins, and are genotypically different. The PWG supported only separate statistical analyses of the two tumor types.

The PWG analyses support a safety margin of 24 for mammary adenocarcinoma. That is, the plasma lorcaserin exposure in rats at the highest dose not associated with mammary adenocarcinoma (30 mg/kg/day) is 24 times the plasma exposure in humans taking the maximum recommended dose of 10 mg twice daily. Because benign mammary fibroadenoma was increased at all lorcaserin doses tested, a safety margin was not established for fibroadenoma.

The PWG also examined lung tissue in an effort to identify metastases from mammary adenocarcinoma, and to distinguish metastases from other primary locations. In the original report, all secondary (metastatic) lung masses were grouped together (Table 50). The PWG unanimously diagnosed metastatic mammary tumors in the lungs of 1, 5 and 5 animals at the low, mid and high dose, respectively, compared with none in the vehicle control group. The PWG deemed the finding to be "equivocal," since (1) the incidence of mammary adenocarcinoma was numerically less than the control group at the low and mid dose, and (2) the incidences at the low and high doses were within the historical control range for lung metastases among S-D rats with a primary mammary adenocarcinoma (TX11024).

Summary of CRL Item 1

The PWG re-adjudicated all mammary and associated tissues from the 2 year carcinogenicity study of female S-D rats. The process provided clear diagnoses for mammary adenocarcinoma and benign mammary fibroadenoma that justifies separate analysis of the two tumor types. The re-adjudicated data support an exposure margin of ≥24 for mammary adenocarcinoma in female rats relative to the human MRD. No exposure margin was identified for benign mammary fibroadenoma in female rats. Neither mammary tumor type was increased by lorcaserin in mice.

4.2 CRL Item 2: Mammary Tumor Aggressiveness and Mechanism

The FDA's Complete Response Letter requested that Arena address an unclear exposure response relationship between lorcaserin and mammary adenocarcinoma, which was based at least in part on the possible increased aggressiveness of mammary adenocarcinoma observed in lorcaserin treated female rats relative to vehicle control in the 2 year carcinogenicity study. Arena was asked to demonstrate that the apparent increase in aggressiveness is reasonably irrelevant to human risk assessment. Such a demonstration could include a reassessment of aggressiveness based upon the PWG findings and identifying a mechanism underlying the mammary tumors in female rats that is relatively irrelevant to human risk.

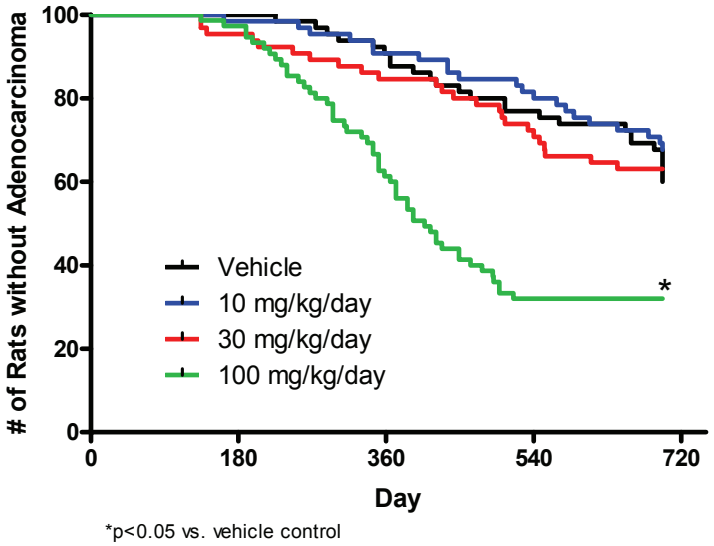
Arena's evaluation of tumor aggressiveness is summarized first, followed by an overview of the new research that supports Arena's hypothesis that lorcaserin associated mammary tumors in rats are prolactin dependent.

4.2.1 Mammary Adenocarcinoma Aggressiveness in Female Rats

Indicators of malignant tumor aggressiveness include multiplicity (the frequency with which more than 1 primary tumor occurs in an individual animal), onset latency (the time between initiation of dosing and initial detection of tumor), time to death due to the tumor of interest, and incidence of metastases. The parameters suggest that mammary adenocarcinoma in female rats was only more aggressive than spontaneous mammary adenocarcinoma in control rats in the lorcaserin high dose group, where incidence was also increased.

Multiplicity was increased over control at the lorcaserin high dose, but not at the low or mid doses (Table 50). The onset rate *trend* test was significant (Table 50); however, when each lorcaserin dose was evaluated separately, mammary adenocarcinoma time to detection differed significantly from vehicle only at the lorcaserin high dose of 100 mg/kg/day (Figure 29).

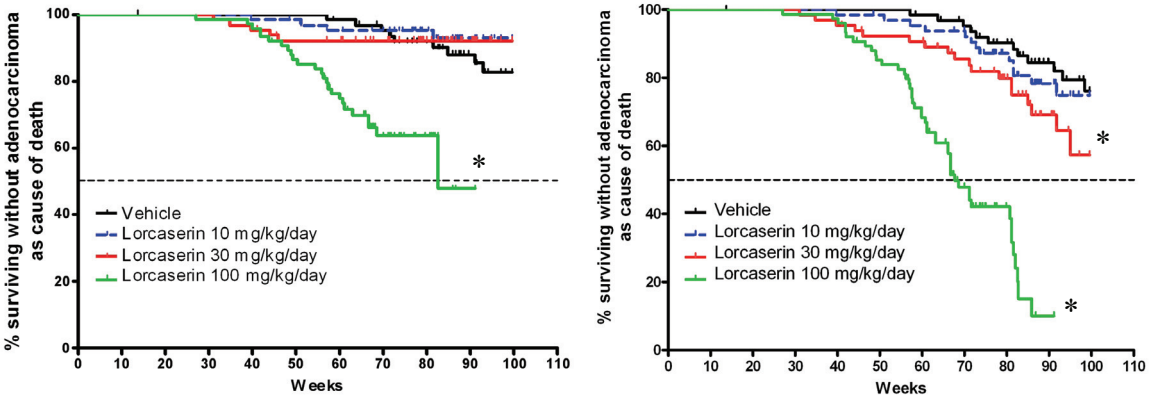
Figure 29. Time to Detection (Latency) of Mammary Gland Adenocarcinoma in Female Rats



A time to death analysis was conducted in two ways. First, only those deaths that were attributed specifically to mammary adenocarcinoma were analyzed (Figure 30A). Only the lorcaserin high dose (100 mg/kg/day) was associated with time to death that differed significantly from vehicle control. The second analysis included not only deaths attributed specifically to mammary adenocarcinoma, but also those attributed simply to "mammary tumor" in animals that had both adenocarcinoma and fibroadenoma (Figure 30B). According to this more conservative analysis, time to death differed from control in both the mid- and high-dose groups.

Figure 30. Time to Death due to Mammary Adenocarcinoma in Female Rats

A. Adenocarcinoma Specified **B. Adenocarcinoma Specified + Assumed**



*p<0.05 vs. vehicle control

Mammary adenocarcinoma in the rat can metastasize to the lung. The historical incidences of lung metastases from mammary adenocarcinoma from 40 recent studies at the contract research organization that conducted the lorcaserin study are summarized in Table 51. Among control (vehicle treated) female rats with primary mammary adenocarcinoma, an average of 3.6% had lung metastases, with a range of 1-12.5%. In the lorcaserin rat carcinogenicity study, 21% of rats in the mid-dose group and 10% in the high-dose group with mammary adenocarcinoma had lung metastases from the mammary tumor. Therefore, the rate was not dose-responsive and only the mid-dose group was outside the historical control range.

The Pathology Working Group described the incidence of lung metastases as "equivocal," ultimately concluding that mammary adenocarcinoma was lorcaserin related only at the 100 mg/kg/day dose. The preponderance of evidence does not suggest that the mammary adenocarcinoma occurring at the low and mid doses is inherently more aggressive than the spontaneous mammary adenocarcinoma in the vehicle control group.

Table 51. Historical Control Statistics for Female Sprague-Dawley Rats – Lung Metastasis

Mammary Adenocarcinoma Metastases to the Lung		
Statistic	**% of Animals in Control Group[a]**	**% of Animals with Mammary Adenocarcinomas[b]**
Mean	1.1	3.6
Standard Deviation	1.3	3.9
Median	1.3	4.2
Mode	0	0
Range	0 to 5	0 to 12.5

[a] Numerator is the number of animals with adenocarcinoma metastatic to lung, denominator is number of animals in the group. Derived from 40 control groups.

[b] Numerator is the number of animals with adenocarcinoma metastatic to lung, denominator is number of animals with mammary adenocarcinoma. Derived from 40 control groups.

Note: Historical control data derived from MPI Research database including studies of female Sprague-Dawley rats terminating in December 2006 through May 2011. Duplicate control groups were counted separately.
Source: TX11024

Benign Fibroadenoma

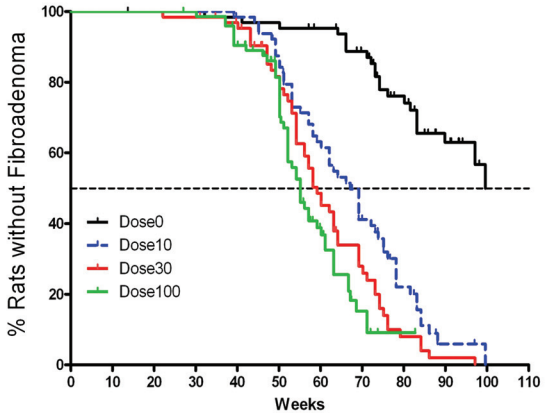
Although "aggressiveness" is not typically associated with benign neoplasms, time to onset and time to death analyses were conducted for benign mammary fibroadenomas in female rats in the 2 year carcinogenicity study. Benign fibroadenomas in rats become sufficiently large that humane sacrifice is often necessary; the animals have difficulty ambulating and feeding, and the skin over the tumors can ulcerate.

Benign mammary fibroadenoma was increased over vehicle control at all lorcaserin doses tested (Table 50). Multiplicity was also increased and time to detection differed significantly from control at each dose (Figure 31A). Time to death was also decreased by lorcaserin at each dose tested (Figure 31B). The majority of rats with mammary fibroadenoma underwent humane sacrifice in the lorcaserin 2-year carcinogenicity study. These benign tumors do not metastasize.

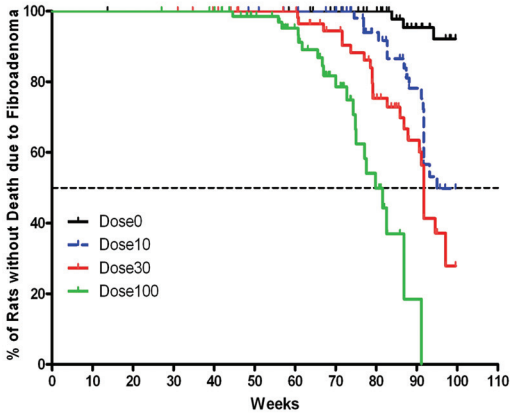
Overall, benign mammary fibroadenomas appeared to grow faster in female rats receiving lorcaserin than in the vehicle control animals. As discussed in Section 4.2.2 below, the fibroadenomas as well as the mammary adenocarcinomas appear to be prolactin dependent and are unlikely to represent a risk that is relevant to humans.

Figure 31. Mammary Fibroadenoma Time to Detection and Time to Death

A. Time to Detection



B. Time to Death due to Fibroadenoma



P<0.05 for all lorcaserin doses compared to vehicle control

4.2.2 Mechanism of Mammary Tumors in Rats

Mammary tumors occur commonly in Sprague-Dawley rats, with spontaneous incidences reported to be as high as 40-71%.[68, 69-71] The Sprague-Dawley rat is also susceptible to increases in mammary tumor incidence over the background rate in tests of pharmaceutical and other agents. The key mechanisms underlying test article-induced increases in mammary tumors in rats are hormonal changes and genotoxic carcinogenicity. Among the hormonal causes, hyperprolactinemia is by far the most common.[72] Sprague-Dawley rats are exquisitely sensitive to changes in circulating prolactin, and even short term interruption of physiological prolactin secretion in the developing female will substantially reduce the incidence of benign and malignant mammary tumors.[73] In contrast to agents that perturb hormonal regulation, an agent acting as a genotoxic mammary carcinogen in rats could pose a significant risk to humans. Lorcaserin was shown not to be genotoxic in a standard battery of preclinical tests.

Mammary neoplasms caused by drug-induced prolactin elevation in rats have not been associated with a demonstrated increase in the risk of human breast cancer. For example, anti-psychotic agents that act by antagonizing dopamine receptors increase prolactin secretion and increase mammary tumor incidence in rodents; however, current labeling for these products in the U.S. states "Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive."

Arena hypothesized that increased prolactin stimulation of the mammary gland led to mammary adenocarcinoma and benign mammary fibroadenoma formation in rats, and that the high levels of circulating prolactin achieved with dopamine blockers should not be needed for this effect. This hypothesis was based on the known sensitivity of Sprague Dawley rats to alterations in circulating prolactin and the effect of serotonergic agonism to increase pituitary prolactin

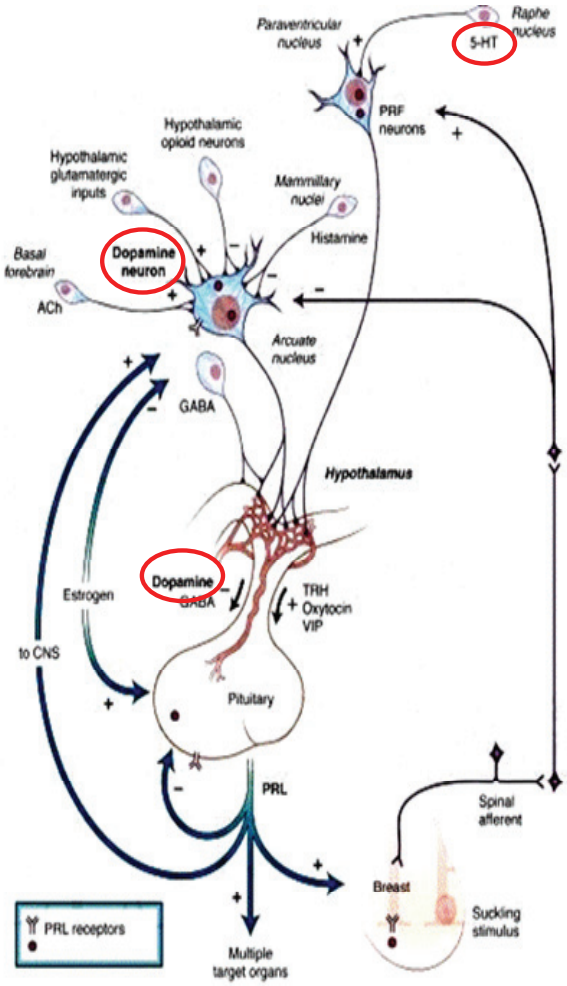
release.[4, 74, 75] Serotonin modulates prolactin release from the pituitary gland through interactions with 5-HT_{2A}, 5-HT_{2C}, and potentially other 5HT receptors in the hypothalamus and in the pituitary itself (Figure 32).[4] Other hormones and neurotransmitters also regulate pituitary prolactin secretion.[4, 76] Dopamine tonically inhibits prolactin release through the hypothalamic D2 receptor subtype. Estrogen also modulated prolactin secretion in the rat, such that prolactin concentrations and responsiveness to other modulators vary with the estrus cycle. Serotonergic regulation of prolactin release is complex and is not fully understood; while serotonergic agonists typically increase prolactin release, such agents can be inhibitory during pregnancy (or hormonal environments simulating pregnancy) in the rat.[76]

Given the multifactorial regulation of prolactin release, it is informative to consider the effects of agents with known mechanisms to help predict the effects of lorcaserin. Dopamine antagonists have been more extensively studied in this regard than have serotonergic agonists. In particular, the effects of chronic dosing are best characterized for dopamine antagonists like risperidone or olanzapine, which block the tonic inhibition of pituitary prolactin secretion. The result is profound and persistent elevation of circulating prolactin. These dopaminergic agents can increase mammary tumors in rodents through the increased prolactin effects on the mammary gland.[77-80] Importantly, while the dopamine antagonists also increase circulating prolactin in women, they have not been clearly associated with increased risk of breast cancer in humans.[3]

Several serotonergic agonists have been shown to increase circulating prolactin acutely following single administrations. However, few published reports have evaluated the effects of repeated dosing. Trazodone was evaluated in chronic dosing studies in rats. Through its major metabolite mCPP, a serotonin 2C agonist, trazodone activates the 5-HT_{2C} receptor leading to increased pituitary prolactin secretion. Trazodone also increased the incidence of mammary tumors in lifetime carcinogenicity studies, which was attributed to its effect on prolactin.[77, 81] However, the effects of trazodone/mCPP on prolactin release differ qualitatively and quantitatively from the effects of dopamine antagonists. Whereas dopamine antagonists tend to cause persistent increases in circulating prolactin, trazodone caused transient daily increases that were undetectable after repeated dosing.

Hence, the expected effect of lorcaserin on circulating prolactin in rats was transient elevation. If the lorcaserin associated mammary tumors were prolactin-dependent, then chronic lorcaserin administration should cause mammary histomorphological changes that are characteristic of prolactin hyperstimulation, and those changes should be prevented by interventions that block prolactin release or prolactin action.

Figure 32. Regulation of Prolactin Secretion by Serotonin and Dopamine



Melmed et al. (2011)[4]

To test the hypothesis that lorcaserin increases prolactin effects on the mammary gland, leading to changes that precede tumor formation, Arena conducted the following types of experiments:

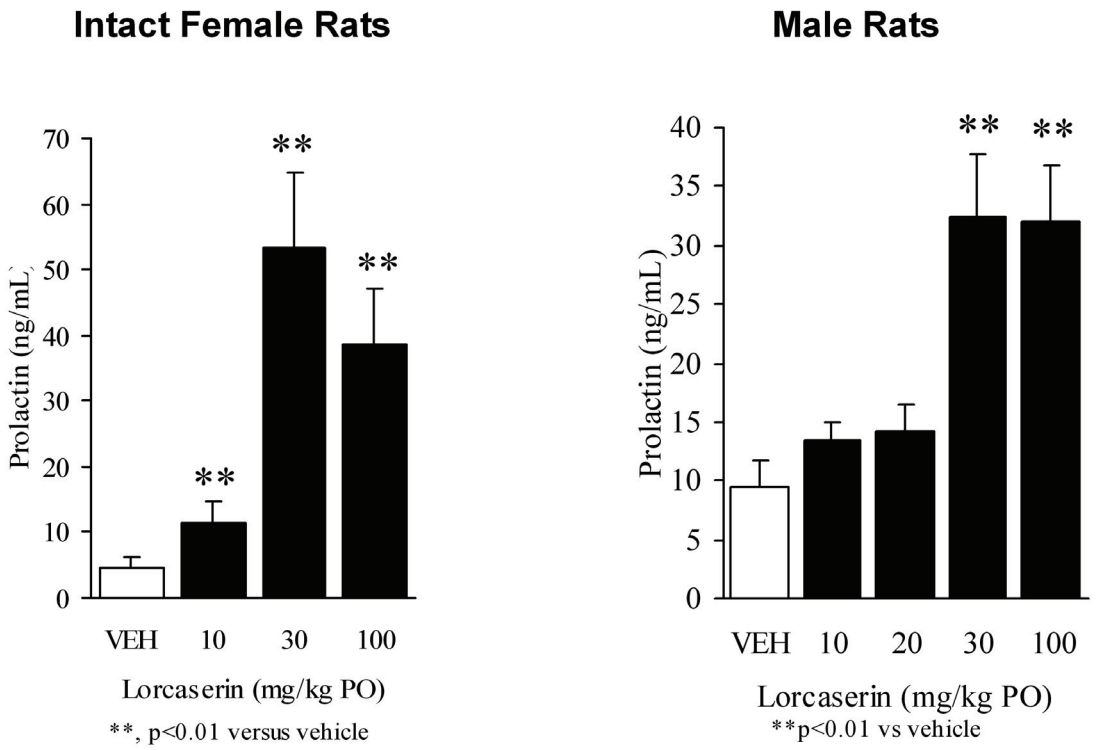
1. Preliminary experiments: to establish appropriate methods and timing
2. Definitive chronic experiments that measured lorcaserin's effects on serum prolactin, pituitary prolactin, mammary gland prolactin, mammary histomorphology, and an intracellular marker of proliferation (PCNA)
3. Pharmacological blockade experiments: to establish whether the mammary changes observed in Step 2 were prolactin dependent
    a. Effect of bromocriptine on acute lorcaserin-mediated serum prolactin elevation
    b. Effect of hypophysectomy on lorcaserin-induced mammary changes
    c. Effect of prolactin receptor antagonist on lorcaserin-induced mammary changes

Key experiments are summarized below.

Acute Effects of Lorcaserin on Serum Prolactin in Female and Male Rats

Initial experiments evaluated the effects of a single oral lorcaserin administration on serum prolactin concentrations in intact female rats and in male rats. In these experiments, lorcaserin increased circulating prolactin in both female and male rats at the three doses used in the 2-year carcinogenticity study, with maximal effect observed at the 30 mg/kg dose (Figure 33).

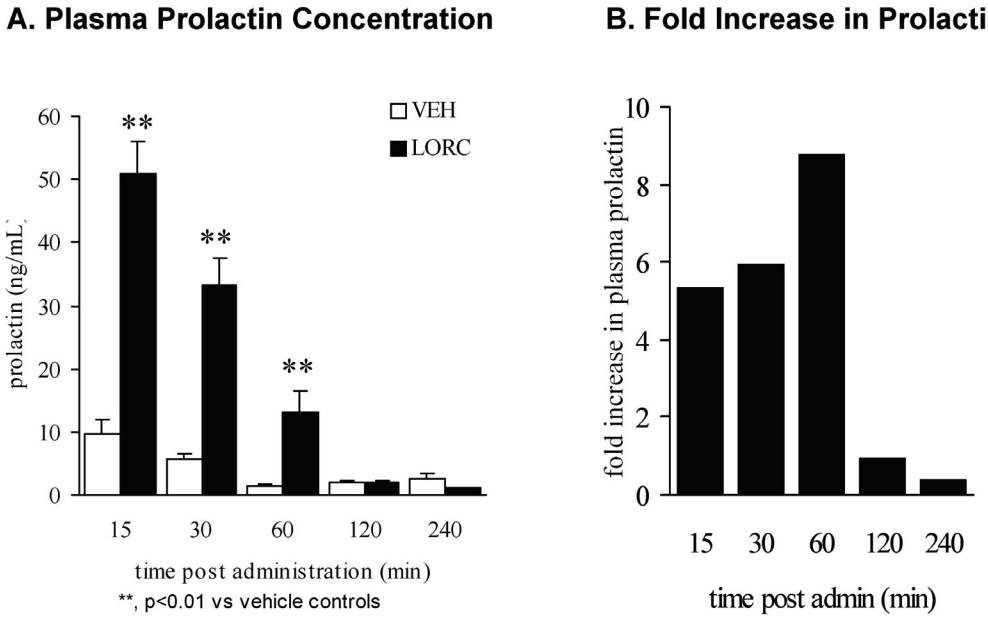
Figure 33. Serum Prolactin in Intact Female and Male Sprague-Dawley Rats 15 min Following a Single Oral Lorcaserin Administration



VEH = vehicle control; Data are mean (SEM)

The single dose effect was transient in both male and female rats, although the temporal patterns differed. In males, the maximum serum prolactin concentration was observed at 15 minutes post-dose, with a maximum incremental increase over vehicle control occurred at 60 minutes post-dose (Figure 34).

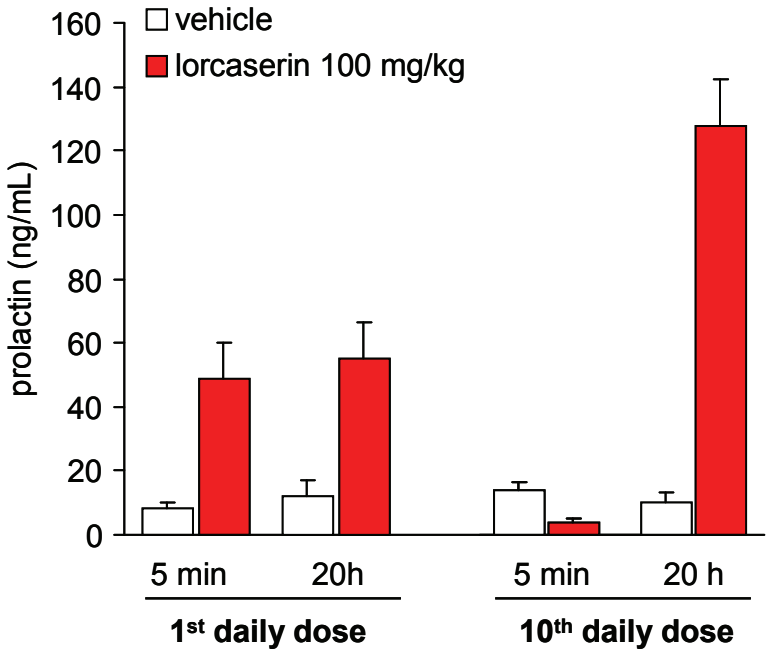
Figure 34. Time Course of Serum Prolactin Response to a Single Oral Lorcaserin Dose of 100 mg/kg in Male Sprague-Dawley Rats



Data are mean (SEM)

The time course in female rats was evaluated more extensively. Intact female S-D rats were fitted with indwelling carotid artery cannulae to permit frequent automated blood sampling without handling the animals. These animals received oral doses of lorcaserin (100 mg/kg/day) or vehicle control by mouth once daily for 10 days (Figure 35). In vehicle control rats, diurnal variation was observed on both days. In addition to these variations, lorcaserin evoked a peak at 15-30 min post-dose on Day 1, but not on Day 10. Further, lorcaserin induced a nocturnal peak 20 hours post dose on Day 1 and Day 10. This nocturnal prolactin increase at approximately 20 hours post-dose was observed consistently in female rats, and was not observed in male rats. A 20-hour post-dose blood collection was used in subsequent repeated dose experiments of female rats.

Figure 35. Time Course of Serum Prolactin at Days 1 and 10 of Daily Dosing in Intact Female Rats

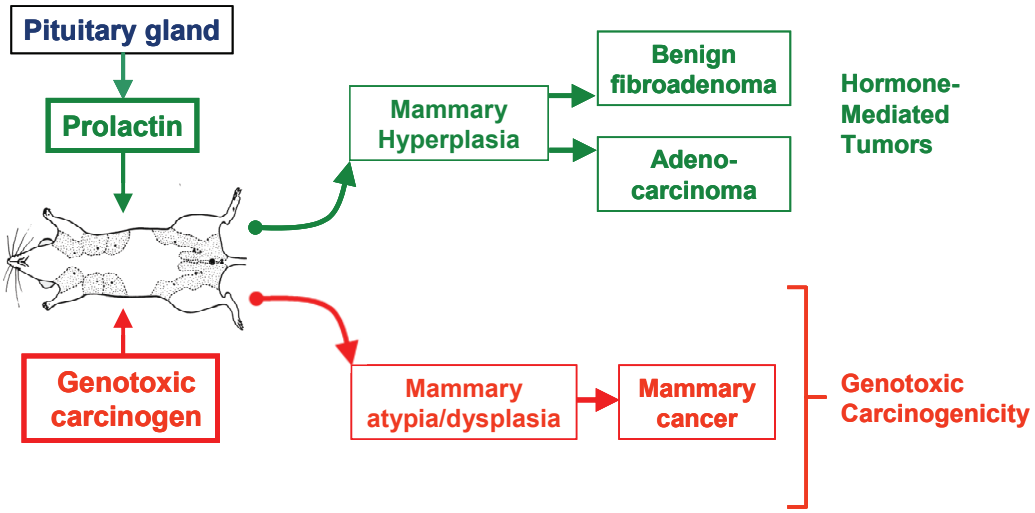


Open circles, vehicle; closed circles, lorcaserin 100 mg/kg. Shading indicates dark cycle. Mean (SEM).

Three-month Study of Lorcaserin Effects on Mammary Gland Histomorphology, Serum Prolactin and Tissue Prolactin in Female Sprague-Dawley Rats

Having demonstrated that lorcaserin increases circulating prolactin and causes increases in mammary tumors in female rats, Arena conducted experiments to evaluate the cause-effect relationship between these findings. Agents that increase mammary tumors in rats typically do so by hormonal perturbations or through genotoxic carcinogenicity (Figure 36). Although the resulting tumors from these two mechanistic classes may be histologically indistinguishable, microscopic mammary changes that occur prior to tumor formation differ for the two pathways. Hence, mammary histomorphology was examined in rats exposed for a period of time expected to precede overt tumor formation.

Figure 36. Mammary Tumors in Rats have Two Main Causes Distinguishable by Microscopic Changes that Precede Tumor Formation

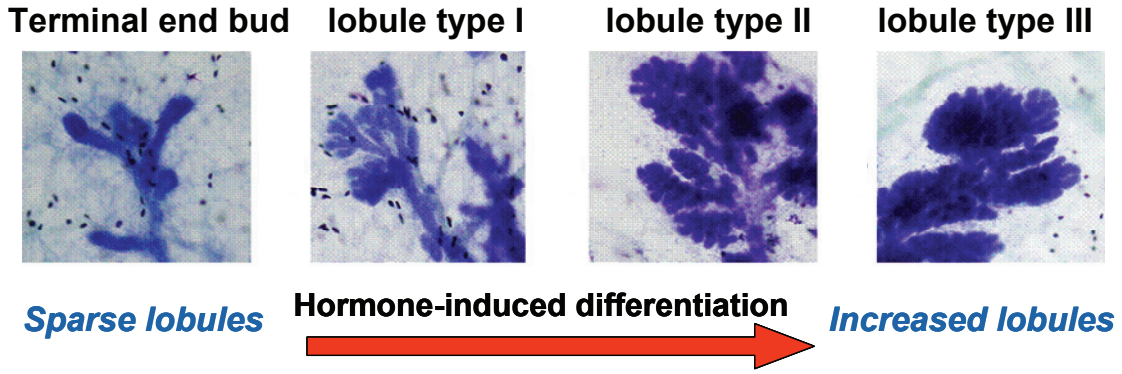


Because lorcaserin is not genotoxic in a standard panel of assays, the sponsor hypothesized that lorcaserin caused mammary tumors in rats through a prolactin-dependent mechanism. Findings that would support the hypothesis include some or all of the following: microscopic mammary changes characteristic of a hormone-mediated pathway, without changes characteristic of genotoxic carcinogenicity; increased circulating prolactin; increased tissue prolactin content (pituitary or mammary); and increased mammary tissue marker(s) of proliferation.

Female S-D rats were dosed daily for up to 3 months with vehicle control, lorcaserin (10, 30, or 100 mg/kg/day), or the positive control perphenazine (a dopamine antagonist). Cohorts were sacrificed after 7, 28, 61, and 91 days. The primary study endpoint was change in mammary morphology, which was evaluated by mammary whole mount analysis and traditional hematoxylin and eosin (H&E) staining at Days 28 and 91. All microscopic analyses were preformed using slides without information indicating treatment assignment. The whole mount preparations and the other analyses were conducted in different, independent laboratories.

In contrast to traditional H&E staining, which evaluates single transverse sections of mammary tissue, the whole mount preparation is a method to evaluate microscopic structures in the complete mammary gland, and is useful for evaluating differentiation of the gland as illustrated in Figure 37. In an immature female or non-stimulated animal, the gland contains predominantly terminal end buds and terminal ducts.[82, 83] Under hormonal stimulation, including prolactin, the primitive structures undergo proliferation, branching and lobule formation, with the terminally differentiated gland comprising type 3 lobules (as in completed pregnancy). Under some conditions (e.g., prolactin hyperstimulation), the accelerated proliferation increases the probability of abnormal proliferative responses that divert the normal differentiation process to formation of benign fibroadenoma or malignant adenocarcinoma.[84-89]

Figure 37. Schematic Illustration of Whole Mount Microscopic Changes in Rat Mammary Gland during Age and Hormone Induced Differentiation (Images not from Arena Experiment)



Source: Modified from Russo and Russo (1996)[82]

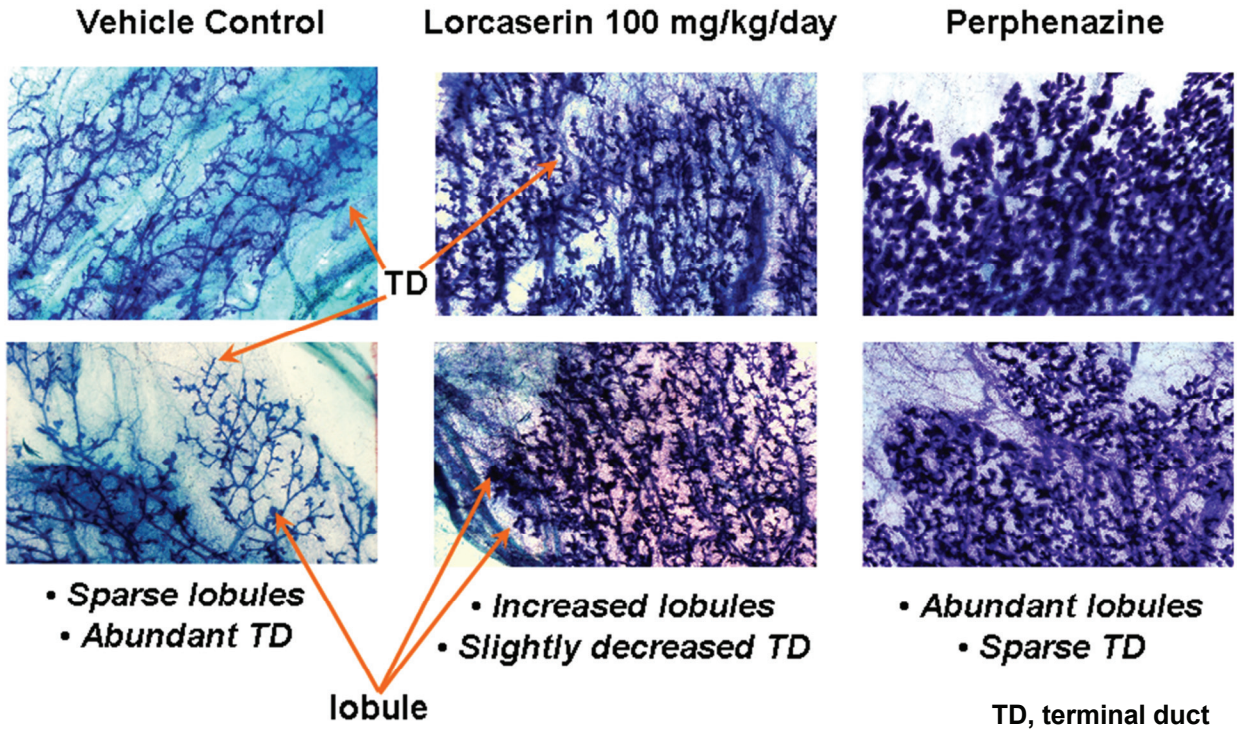
In the 3-month study of lorcaserin in female rats, the positive control perphenazine produced the expected profound hormone-mediated changes in the mammary gland, indicated by increases in lobular structures, and decreases in the more primitive terminal ducts and terminal end buds (Figure 38, Table 52). Lorcaserin had qualitatively similar, but less pronounced effects that were not strictly dose-related. Importantly, dysplasia or atypia (which could indicate a genotoxic process) were not associated with lorcaserin.

Table 52. Summary of Mammary Whole Mount Histological Data in Female Sprague-Dawley Rats

% of Structures	Vehicle	Lorcaserin Dose Group			Perphenazine
		10 mg/kg/day	30 mg/kg/day	100 mg/kg/day	
Day 28					
Terminal ducts	87.4	84.3	82.4	80.2	24.4*
Terminal end buds	4.3	4.6	3.9	4.2	1.4*
Lobules	8.4	11.1	13.7	15.7	74.2*
Day 91					
Terminal ducts	87.9	79.6*	85.1	78.2*	20.6*
Terminal end buds	1.8	1.8	1.3	0.9	0.8*
Lobules	10.4	18.6*	13.6	20.9*	78.6*

*$p < 0.05$, compared to vehicle control

Figure 38. Mammary Whole Mount Preparations: Examples from Female Sprague-Dawley Rats after 90 Days of Treatment with Lorcaserin, Vehicle, or Perphenazine



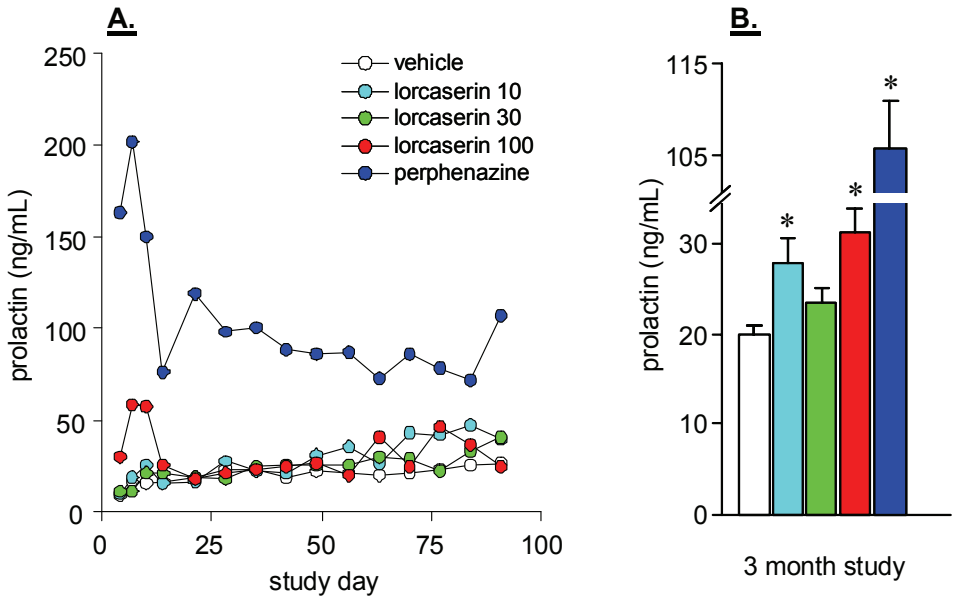
The results of H&E stained sections were generally consistent with those of the whole mount preparations, albeit of lesser magnitude (Table 53). Mammary lobular hyperplasia, which in this study was defined as increased number or size of lobular structures and increased secretory products, was increased significantly by the positive control perphenazine at both time points. Lorcaserin caused dose-related increases in secretory products at Day 28, which had diminished at the mid and high doses at Day 91. Lobular hyperplasia was minimally increased with lorcaserin, if at all. The relevance of the increased perialveolar hemorrhage is unknown. PCNA staining was increased by mid dose lorcaserin at Day 28 and by low dose lorcaserin at Day 91, and by perphenazine at both timepoints.

Table 53. Mammary Hematoxylin and Eosin Pathology Data in Female Sprague-Dawley Rats

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

Lorcaserin (100 mg/kg) significantly increased mean plasma prolactin levels at 20 hours post-dose during the first 10 days of treatment (Figure 39). Although similar elevations were not apparent in the mid dose (30 mg/kg) or the low dose (10 mg/kg) during the first two weeks of the study, intermittent increases were observed as the study progressed. These intermittent effects are more apparent when the data are analyzed as the average Hour 20 prolactin level over time per animal by treatment group (Figure 39B). Three month means per animal were increased at all 3 lorcaserin doses over vehicle control, and the increases were statistically significant at the low and high dose. As expected, more robust effects were seen with perphenazine.

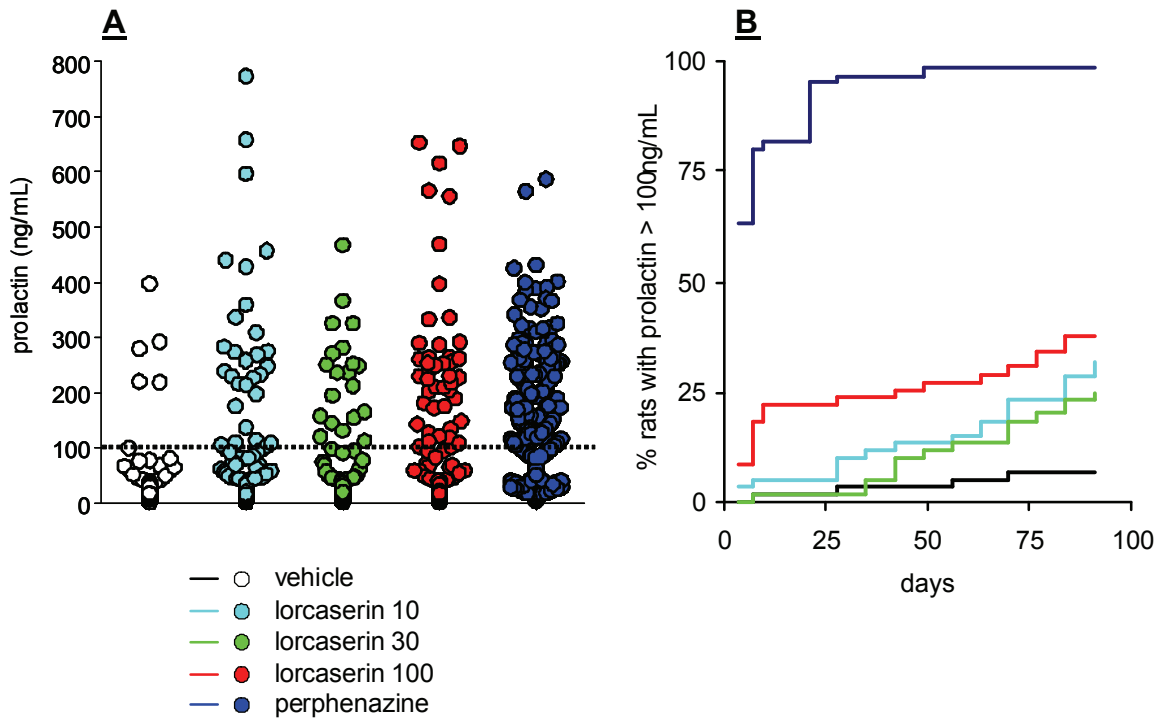
Figure 39. Mean Hour 20 Plasma Prolactin in Female Sprague Dawley Rats



Weekly Hour 20 plasma prolactin measurements from female rats dosed daily with lorcaserin (10-100 mg/kg PO) or perphenazine (5 mg/kg PO). Data are presented either as average prolactin per group at each timepoint (A, left panel), or as the mean per animal by treatment over time (B, right panel). P-value *p<0.01 versus vehicle control (rank based ANOVA).

In addition, all plasma prolactin reads taken for each animal were plotted by treatment across the three month study suggested a pattern of elevated plasma prolactin at all doses of lorcaserin tested (Figure 40A). Employing a cut-off of 100ng/mL to denote high prolactin levels, the sponsor then plotted time to first event of high prolactin (Figure 40B). This analysis shows that high prolactin was only achieved by 5% of vehicle control animals compared to a much greater number of between 25-38% of animals in the various lorcaserin groups. Not surprisingly due to its more robust mechanism, this threshold was achieved by almost all animals in the perphenazine group.

Figure 40. Plasma Prolactin in Female Sprague Dawley Rats

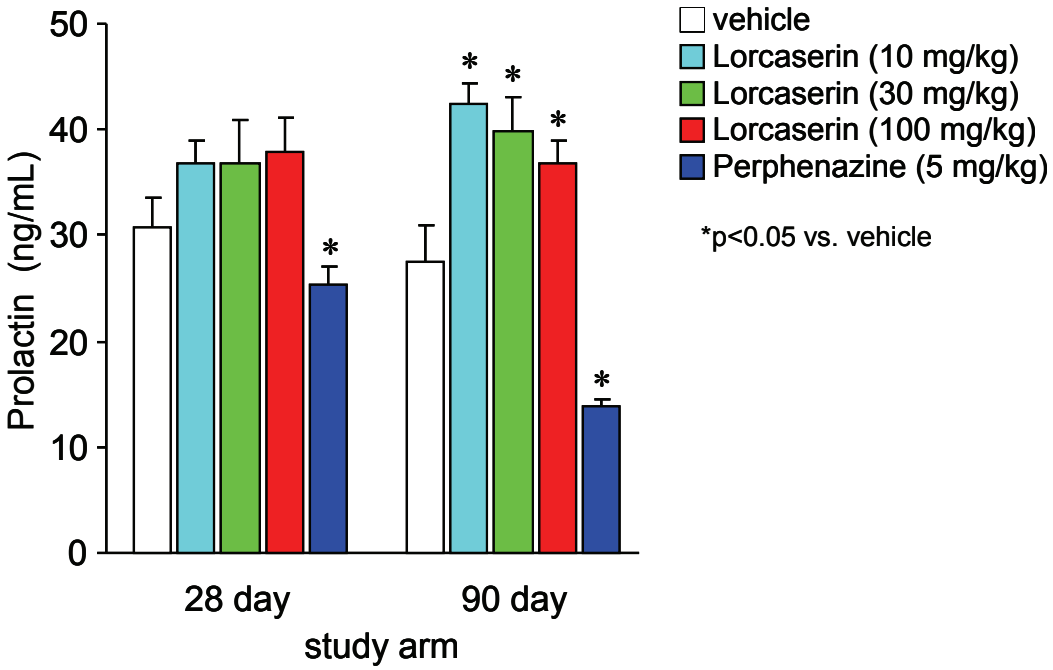


Weekly plasma prolactin measurements from female rats dosed daily with lorcaserin (10-100 mg/kg PO) or perphenazine (5 mg/kg PO). Data are presented either as a scatterplot (A, left panel), or as a Kaplan-Meier plot where time to event is defined as a prolactin read exceeding 100 ng/mL (B, right panel). P-value (Log-rank test) vs. Vehicle: Perphenazine: <.0001; Lorcaserin 10 mg/kg: 0.0006; Lorcaserin 30 mg/kg: 0.0041; Lorcaserin 100 mg/kg: <.00001

Weekly plasma prolactin measurements from female rats dosed daily with lorcaserin (10-100 mg/kg PO) or perphenazine (5 mg/kg PO) are shown. Data are presented either as a scatterplot (A, left panel), or as a Kaplan-Meier plot where time to event is defined as a prolactin read exceeding 100 ng/mL (B, right panel). P-value (Log-rank test) vs. Vehicle: Perphenazine.: <0.0001; Lorcaserin 10 mg/kg: 0.0006; Lorcaserin 30 mg/kg: 0.0041; Lorcaserin 100 mg/kg: <0.00001. Collectively, the results from these various plasma prolactin analyses demonstrate a significant increase in circulating prolactin for all 3 lorcaserin doses over time compared to vehicle treated controls which could be of biological significance in the developing female rat mammary gland.

Pituitary prolactin content was significantly increased by lorcaserin at Day 28 and persisted at Day 91 (Figure 41). Note that the number of animals at the Day 61 time point was smaller than those at Days 28 and 90. Perphenazine depleted pituitary prolactin after 28, 61, and 91 days, consistent with previous reports.[90]

Figure 41. Pituitary Prolactin Content in Female Rats during 3 Months of Lorcaserin, Vehicle, or Perphenazine Administration to Female Rats



The overall findings of the study support the hypothesis that lorcaserin affects the mammary gland through prolactin. The finding of mammary lobular changes in the whole mount preparations provided strong evidence for a lorcaserin-associated hormone effect on the mammary gland. To determine whether other hormones known to affect the mammary gland were involved, estradiol, progesterone, and luteinizing hormone were measured in the serum from the Day 1, 7, 28, 61, and 91 blood collections (Table 54). Other than a Day 1 increase in progesterone, lorcaserin did not increase these hormones. These findings reduce the possibility that a hormone other than prolactin was responsible for the observed mammary changes.

Table 54. Effect of Lorcaserin on Plasma Estradiol, Progesterone, and Luteinizing Hormone in Female Rats during a 3-Month Study

Hormone	Time Point	Vehicle	Lorcaserin 100 mg/kg/day
Estradiol (pg/mL)	Day 1	205.1 (38)	204.0 (29)
	Day 7	265.1 (65)	236.4 (39)
	Day 28	286.9 (77)	267.2 (74)
	Day 61	246.2 (50)	235.1 (53)
	Day 91	393.5 (356)	398.5 (512)
Progesterone (ng/mL)	Day 1	18.3 (9.5)	41.9 (20.4)
	Day 7	15.4 (7.2)	22.7 (17.1)
	Day 28	14.4 (9.5)	13.7 (8.8)
	Day 61	21.0 (10.9)	15.9 (15.1)
	Day 91	21.9 (13.4)	19.2 (13.6)
Luteinizing hormone (pg/mL)	Day 1	697.0 (677)	358.6 (380)
	Day 7	877.6 (387)	774.9 (535)
	Day 28	818.3 (526)	708.9 (376)
	Day 61	854.2 (536)	1087.8 (743)
	Day 91	978.2 (652)	748.3 (504)

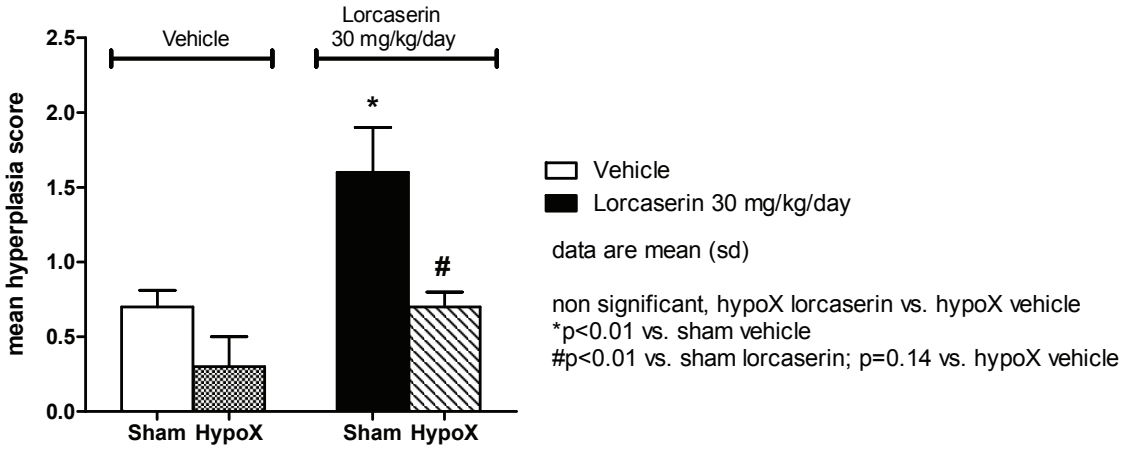
Note: Data are mean (SD).

Effect of Lorcaserin on Female Rat Mammary Gland after Hypophysectomy

To further evaluate the prolactin dependence of the lorcaserin-associated mammary morphological and proliferative changes, female rats that had undergone hypophysectomy or sham pituitary ablation were used. Because the animals lacking pituitary glands could not tolerate prolonged exposure to high dose lorcaserin, the mid dose was used and drug administration was halted after 10 days; animals were then sacrificed at Day 30. The analyses included H&E and proliferating cell nuclear antigen (PCNA), and prolactin staining of mammary tissue sections.

Mammary lobular hyperplasia scores were significantly increased by lorcaserin (30 mg/kg/day) as compared to vehicle control in the sham operated animals (Figure 42). In animals that had undergone hypophysectomy, lobular hyperplasia scores did not differ significantly in the lorcaserin and vehicle control groups. That is, in the absence of a pituitary, lorcaserin did not increase the mammary hyperplasia scores. The result indicates that the lorcaserin-mediated mammary lobular hyperplasia is dependent on the pituitary, which is the source of prolactin in the rat. Results of PCNA staining were inconsistent.

Figure 42. Effect of Hypophysectomy on Lorcaserin-Mediated Mammary Lobular Hyperplasia in Female Rats



HypoX = hypophysectomy

Effect of a Prolactin Receptor Antagonist on Lorcaserin-Mediated Mammary Gland Changes

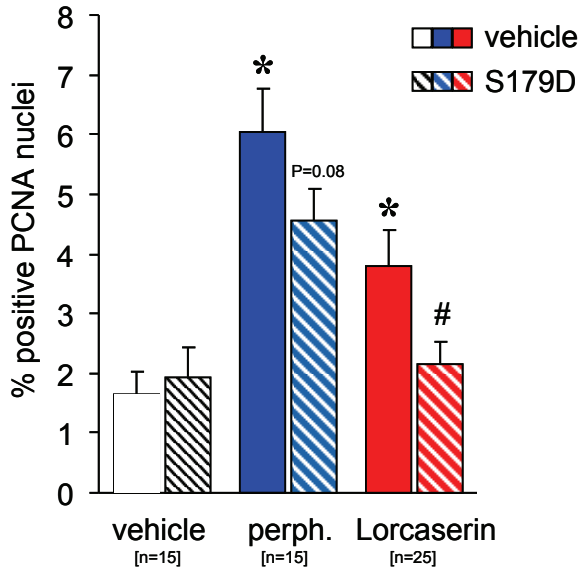
As an additional method to demonstrate prolactin dependence of the lorcaserin effects on the female rat mammary gland, a peptide antagonist of the prolactin receptor was used. The peptide, S179D, was developed by Dr. Amea Walker (University of California, Riverside, CA) and has been administered to rats for up to 1 month to block pregnancy-induced mammary changes.[91]

Female rats received S179D or vehicle via osmotic minipumps in combination with orally administered lorcaserin 100 mg/kg/day, vehicle, or perphenazine for 28 days. Mammary tissues were then examined using H&E staining, PCNA immunostaining, and prolactin immunostaining. Perphenazine and lorcaserin had minimal effects on mammary hyperplasia relative to vehicle control in this study, but the perphenazine effect was statistically significant, and the prolactin receptor antagonist had no effect on mammary hyperplasia scores with either treatment. Mammary prolactin was not increased by either treatment.

Proliferating cell nuclear antigen (PCNA) immunostaining was significantly increased by perphenazine and by lorcaserin (Figure 43). The proportion of cells with strong nuclear PCNA staining increased with perphenazine and with lorcaserin 100 mg/kg/day. The prolactin receptor antagonist significantly decreased the proportion of strongly and moderately staining cells in the lorcaserin group, and strong staining in the perphenazine group trended lower with the antagonist.

These results suggest that the proliferative effect of lorcaserin on the mammary gland of the female rat is mediated through the prolactin receptor.

Figure 43. Effects of Lorcaserin (100 mg/kg/day) and Perphenazine on Mammary PCNA Staining at Day 28 with and without Prolactin Receptor Antagonist



*p<0.05 vs. vehicle without antagonist #p<0.05 vs. lorcaserin without antagonist

Summary of Studies to Elucidate the Mechanism of Mammary Tumors in Rats

Taken together, the mechanistic experiments support the hypothesis that lorcaserin causes mammary fibroadenoma and mammary adenocarcinoma in female rats through a prolactin-dependent process. While no single experiment definitively proves the hypothesis, the weight of evidence supports this theory. Moreover, no other plausible explanation for the experimental findings is apparent. Lorcaserin was shown not to be genotoxic, and it caused changes typical of hormonal stimulation and not genotoxicity in the rat mammary gland.

Subtle alterations in circulating prolactin during mammary gland development can have substantial effects on the subsequent development of mammary tumors in rats, especially Sprague-Dawley rats.[73]

Agents that increase prolactin have not been consistently shown to increase the risk of breast cancer in women.[3, 92] For example, antipsychotic agents that have dopamine antagonist activity can markedly elevate circulating prolactin in patients; however, analyses of breast cancer risk with such agents have not consistently shown elevated risk. Azoulay et al. evaluated antipsychotic use in 106,362 patients, and found no increase in the risk of breast cancer.[3] Other studies have suggested that the relative risk of breast cancer may be as high as 1.16 in patients taking anti-psychotics; however, the interpretation of the data has been questioned given the possible ascertainment bias in the studies.[48] Current labeling for drugs that increase circulating prolactin in humans reflects the uncertainty regarding prolactin and breast cancer: *"Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed*

following chronic administration of antipsychotic drugs and are considered to be prolactin mediated. The relevance of this increased incidence of prolactin-mediated pituitary or mammary gland tumors in rodents in terms of human risk is unknown."

Even if one accepts hyperprolactinemia to be a risk factor for breast cancer, lorcaserin should not increase human breast cancer risk, since it does not elevate circulating prolactin in women taking lorcaserin at the MRD.

In addition to demonstrating a rodent-specific mechanism for mammary tumors, the applicant assembled a PWG that showed an exposure margin of ≥24 fold for mammary adenocarcinoma in the female rat relative to human at the MRD. Mammary adenocarcinoma was not increased with lorcaserin in male rats or in male or female mice in 2 year carcinogenicity studies. Importantly, mammary fibroadenoma is genetically distinct from adenocarcinoma and does not progress to adenocarcinoma in the rat or in humans.

It is the applicant's position that the exposure margin defined by the PWG re-adjudication and the demonstrated prolactin dependence of mammary tumors in female rats reasonably mitigate a risk of breast cancer in humans. With repect to mammary fibroadenoma in female rats, no margin was established, but a margin of 4, the highest female exposure, was observed in mice. In addition, data supporting the prolactin dependence of this tumor in rats should also reasonably mitigate risk in humans.

4.3 CRL Item 3. Astrocytoma in Male Rats

4.3.1 Male Rat Carcinogenicity Study Findings

The FDA's Complete Response Letter requested additional information to evaluate the potential relevance of astrocytoma in male rats to human risk. Specifically, the FDA requested that the sponsor provide additional information about the exposure to lorcaserin of the human brain relative to the rat brain at doses associated with astrocytoma.

Table 55 summarizes the incidence of astrocytoma in the 2 year male rat carcinogenicity study that was submitted with the original lorcaserin NDA. Astrocytomas were significantly increased in high-dose male rats, where plasma exposure was 55 times human plasma exposure at the MRD. For astrocytoma, brain exposure is more relevant than plasma exposure, especially given the observation that rats "concentrate" lorcaserin in the brain relative to the plasma (Table 55).

Table 55. Neoplasms Associated with Lorcaserin in Male Rats and Plasma Exposure Multiples above Human Exposure

Lorcaserin Dose (mg/kg)	**0**	**10**	**30**	**100**
Lorcaserin plasma exposure multiple over human at MRD	**NA**	**5**	**17**	**55**
Number of male rats	**65**	**65**	**65**	**75**
Brain				
Astrocytoma[a]	1	0	4	8[d]

[a] Trend is significant ($p < 0.0001$). Significantly different from control at 100 mg/kg ($p = 0.0025$).
NA = not applicable

A multi-step process was used to predict human brain exposure.

First, brain, cerebrospinal fluid (CSF), and plasma, lorcaserin exposures at steady state were measured simultaneously in rats, mice and monkeys (Table 56). All preclinical species tested "concentrated" lorcaserin in the brain relative to plasma, althouth the magnitude of the effect varied by species. More importantly, the ratio of lorcaserin exposure in the brain relative to CSF was relatively constant across species and gender, with a mean value of 101 (Table 56).

Table 56. Lorcaserin CNS to Plasma Exposure Ratios in Preclinical Species

Species	CSF/Plasma	Brain/Plasma	Brain/CSF
Mice (male, 50 mg/kg/day)	0.226	26	117
Rats (male, 10 mg/kg/day)	0.225	24	107
Rats (male, 30 mg/kg/day)	0.301	35	116
Rats (female, 10 mg/kg/day)	0.295	22	75
Monkeys (male, 10 mg/kg/day)	0.112	10	90
Mean (SD)			101 (16)

Calculated using $AUC_{last,ss}$

Second, the sponsor assumed that the relatively constant preclinical Brain to CSF exposure ratio could be applied to humans. Hence, in order to estimate brain exposure in humans, we needed to measure CSF lorcaserin exposure. CSF lorcaserin concentrations were measured serially after dosing lorcaserin to steady state in 9 healthy obese and overweight volunteers. Daily lorcaserin CSF exposure ($AUC_{last,ss}$) was calculated for CSF.

Third, the constant Brain to CSF exposure ratio derived from preclinical studies was applied to the human CSF exposure data. Using this approach, human brain lorcaserin exposure was 1.7 times plasma exposure.

Finally, the brain exposure ratio for rat relative to human was calculated. The brain exposure to plasma exposure ratio in male rats given lorcaserin at 10 mg/kg/day (the dose at which astrocytoma was not observed in the carcinogenicity study) was derived from the experiment described above and applied to measured plasma levels at this dose in male rats in the carcinogenicity study. The brain exposure to plasma exposure ratio in humans at 10 mg twice daily, predicted in the preceding step, was then applied to modeled plasma exposure at 10 mg BID from Population PK analysis of the phase 3 studies. From these ratios, a brain safety margin of approximately 70 was calculated for the 10 mg/kg/day dose. At the mid-dose of 30 mg/kg/day, where astrocytoma was numerically but not significantly increased over vehicle control using pairwise comparison, the brain exposure safety margin is even higher at approximately 360.

Astrocytoma was not increased in female rats administered lorcaserin in the 2-year carcinogenicity study, or in male or female mice in the 2-year carcinogenicity study of mice.

4.4 CRL Item 4. Weight Loss Efficacy

A detailed presentation of weight loss efficacy of lorcaserin is provided in Section 3.

4.5 CRL Item 5. Behavioral Studies in Rats

Two studies submitted with the original NDA were repeated to correct possible technical limitations. The first evaluated lorcaserin's *in vivo* selectivity, and the second was a drug discrimination study designed to assess lorcaserin's hallucinogenic potential.

4.5.1 Behavioral Study to Evaluate 5-HT_{2A} and 5-HT_{2C} activity of Lorcaserin *in vivo*

In rats, activation of the 5-HT_{2C} receptor in rats precipitates resting behavior and penile grooming. In contrast, 5-HT_{2A} activation in rats leads to characteristic behaviors described as wet dog shakes and back muscle fasciculations. Behaviors following test article administration can therefore indicate *in vivo* receptor selectivity. A study submitted with the original NDA evaluated lorcaserin relative to the 5-HT_{2A} positive control DOI, a Schedule II controlled substance.

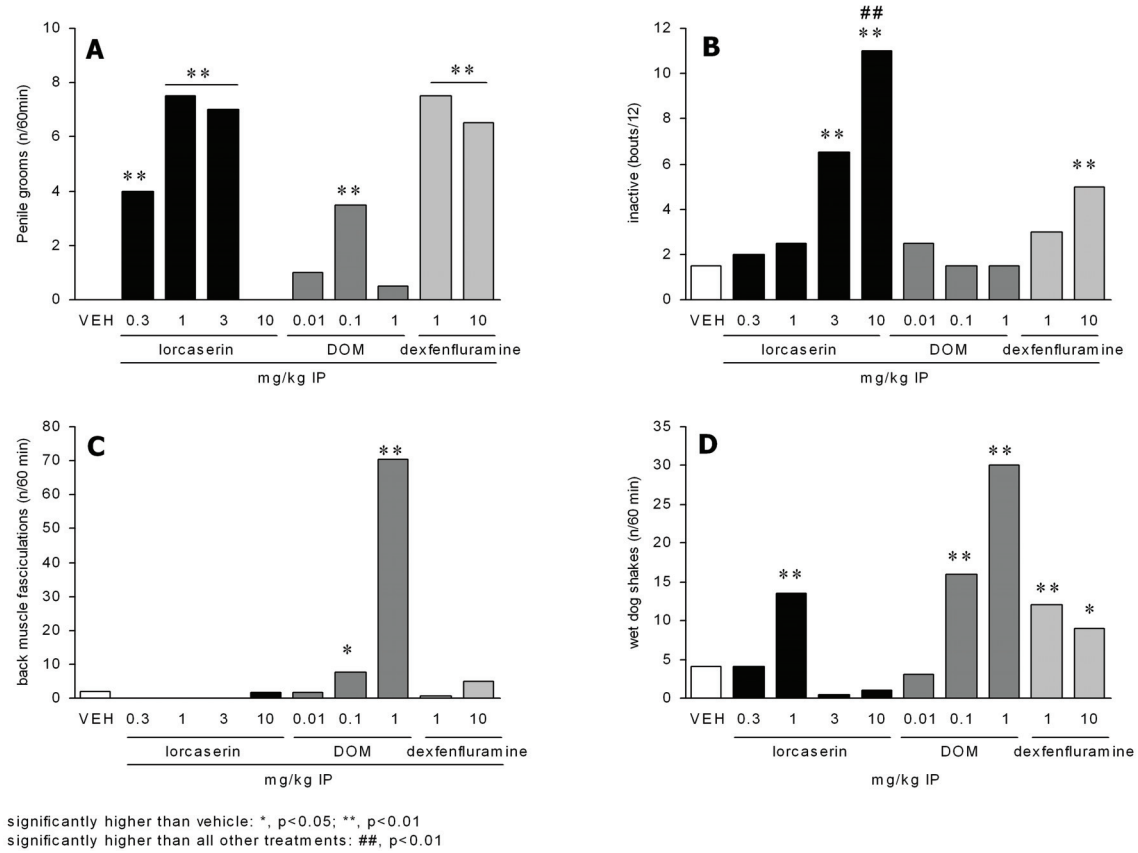
The following modifications to the earlier study were incorporated into the new experiment at the FDA's request:

1. 2,5-dimethoxy-4-methylamphetamine (DOM), a schedule I hallucinogen and relatively non-selective 5-HT_{2A} agonist, was used as the positive control for 5-HT_{2A} behaviors
2. Dexfenfluramine was included as a second positive control that should elicit both 5-HT_{2A} and 5-HT_{2C} behaviors
3. All negative and positive controls were tested concurrently with lorcaserin

The new study also broadened the range of lorcaserin doses evaluated (0.3, 1, 3, and 10 mg/kg). Lorcaserin and dexfenfluramine elicited 5-HT_{2C} behaviors; DOM had inconsistent and non-dose-related activity for 5-HT_{2C} behaviors. Lorcaserin caused no 5-HT_{2A}-mediated back muscle fasciculations at any dose, but at 1 mg/kg only, increased wet dog shakes (Figure 44). The magnitude of the wet dog shake effect was comparable to that observed with dexfenfluramine at 1 mg/kg, and with DOM at 0.1 mg/kg. Because lorcaserin's apparent 5-HT_{2A} activity was observed only at an intermediate dose, and only in one of the two assays, the predictive value for humans is unclear. It is possible that the "resting" behavior elicited by 5-HT_{2C} agonism at the higher lorcaserin doses masked or prevented the 5-HT_{2A}-mediated wet dog shakes at the higher doses.

This experiment and the similar independent experiment conducted previously show that lorcaserin is selective for the rat 5-HT_{2C} receptor relative to the 5-HT_{2A} receptor *in vivo*.

Figure 44. Behavioral Studies in Rat Demonstrate Lorcaserin Selectivity



DOM = 2,5-dimethoxy-4-methylamphetamine; VEH = vehicle

4.5.2 Drug Discrimination in Rats

A drug discrimination study submitted with the original lorcaserin NDA evaluated generalization of the subjective effects of DOM to those of lorcaserin among rats trained to press the DOM associated lever and not the saline associated lever for food when exposed to DOM. The drug discrimination study submitted with the original NDA was repeated to assure that all rats maintained at least 80% correct responses to DOM over the course of the study.

The study was performed using twelve adult male Sprague-Dawley rats. Test data are presented from the 9 rats that responded at criterion levels during test sessions with saline and DOM after the initial observations with the test substance. Drug discrimination test sessions followed single intraperitoneal (i.p.) injections of lorcaserin hemihydrate at doses of 0.1, 0.3, 1, 3 and 10 mg/kg. Rats were trained to discriminate between i.p. injections of saline and 0.56 mg/kg of DOM while responding under a fixed-ratio ten (FR 10) schedule of food presentation.

Systemic exposure in rats dosed with lorcaserin 1 mg/kg approximated exposure to humans at the recommended therapeutic dose of 10 mg BID based on C_{max}. Systemic exposure at the 10 mg/kg dose exceeded the C_{max} of the highest dose of lorcaserin tested in the humans (60 mg). Furthermore, brain partitioning in rats exceeds that in humans; hence, doses used in the drug

discrimination study produced brain exposures substantially exceeding that achieved in humans even at supratherapeutic doses.

Clear discrimination between DOM and saline vehicle was established and maintained at the throughout the study. Following administration of at least one of the 5 doses tested, lorcaserin occasioned responding predominantly on the DOM-associated lever in 7 of 9 rats (Table 57). The lorcaserin effect, however, was not clearly dose-related, was not observed in all rats and was maximal at doses (3 and 10 mg/kg) that decreased overall response rate (likely attributed to resting behavioral effects noted above).

Collectively, these data demonstrate reliable discriminative control between saline and DOM, and show that, as found with other serotonergic drugs like SSRIs and fenfluramine, lorcaserin occasioned partial generalization to the DOM-associated cue. This suggests that the subjective effects of lorcaserin are not qualitatively identical to DOM.

Table 57. Discriminative Stimulus and Rate Effects of Saline, DOM and Lorcaserin

Drug	Dose (mg/kg)	% Drug-lever Responding[a]	Rate (responses/second)[b]
DOM	0.56	97.9 ± 1.1	0.88 ± 0.10
Saline	-	1.3 ± 0.4	0.72 ± 0.09
Lorcaserin	0.1	11.6 ± 11.0	0.78 ± 0.06
	0.3	12.7 ± 10.9	0.72 ± 0.06
	1	20.4 ± 13.0	0.65 ± 0.05
	3	56.2 ± 18.9	0.24 ± 0.06
Saline	-	0.3 ± 0.2	0.90 ± 0.08
DOM	0.56	99.4 ± 0.3	0.99 ± 0.12
Lorcaserin	3 (retest)	52.3 ± 17.0	0.27 ± 0.06
	10	(100)[c]	0.03 ± 0.02
Saline	-	0.1 ± 0.1	0.97 ± 0.08
DOM	0.56	99.8 ± 0.2	0.90 ± 0.16

[a] The mean (± SEM) percentage of responses made on the DOM-associated lever for 9 rats trained to discriminate between 0.56 mg/kg DOM and saline. Discrimination data were not used in this summary for rats that failed to complete at least 1 fixed ratio (i.e., receive at least 1 food pellet in the test session)

[b] The mean response rate, expressed as responses per second (± SEM), on both levers, for 9 rats.

[c] After the administration of 10.0 mg/kg of lorcaserin only one rat made a sufficient number of responses to receive a food pellet and that rat responded exclusively on the DOM-associated lever.

4.6 CRL Item 6. Safety Update

A complete safety update is provided in Section 3.10.

5 CONCLUSIONS

5.1 Benefit-Risk Profile and Risk Management

The clinical development program for lorcaserin demonstrated clinically and statistically significant weight reduction, accompanied by significant improvements in a panel of cardiovascular risk factors. This benefit was achieved with excellent tolerability and few identifiable safety signals. Moreover, in patients who had achieved ≥5% weight loss, lorcaserin significantly improved their ability to maintain at least 5% weight reduction during a second year, as compared to patients who stopped taking lorcaserin. The overall benefit-risk profile supports approval of lorcaserin 10 mg BID for weight management.

5.2 Benefits of Treatment

Lorcaserin used in conjunction with a lifestyle modification program promoted significant weight loss in 3 pivotal trials that included nearly 8000 patients. Non-diabetic patients achieved a mean weight loss of 5.8% at one year while patients with type 2 diabetes achieved a mean weight loss of 4.8% according to MITT/LOCF analysis. Non-diabetic patients who completed the studies lost on average 8.0% of their baseline body weight; patients with type 2 diabetes lost 5.8%. Not every patient responded to lorcaserin. However, many patients achieved dramatic weight loss: the top quartile of non-diabetic patients taking lorcaserin 10 mg BID (MITT/LOCF) lost on average ~13 kg, or 29 pounds; average weight loss in the top quartile of Completers was ~16 kg, or 35 lbs. The top quartile of patients with type 2 diabetes taking lorcaserin 10 mg BID (MITT/LOCF) lost on average ~11 kg, or ~24 pounds; average weight loss in the top quartile of Completers was ~13 kg, or ~29 lbs. Furthermore, by either MITT/LOCF or Completer analyses, twice as many lorcaserin BID as placebo patients achieved at least 5% weight loss, and ~3 times as many achieved 10% or greater weight loss.

Intentional weight loss of essentially any magnitude has been shown to be beneficial, and for many outcomes, there is a continuous relationship between weight loss and improvement with no threshold effect. The Diabetes Prevention Program showed that when patients lost approximately 5% of their body weight, the risk of developing diabetes decreased by 58%; but any amount of weight loss was associated with a decrease in the risk of future diabetes.[93] In a 10-year follow-up of this study, the benefit persisted (risk reduction of 34%) despite substantial weight regain.[13] Indeed, in studies APD356-009 and APD356-011, the incidence of biochemical evidence of new onset diabetes (defined as HbA1c ≥6.5) among patients taking lorcaserin was approximately half that of patients on placebo.

The mean weight loss associated with lorcaserin use in three Phase 3 trials was sufficient to improve several cardiovascular and metabolic parameters, and to improve quality of life scores relative to placebo. Among the most clinically significant findings was the improvement in HbA1c of nearly 1% in patients with type 2 diabetes in study APD356-010. This improvement was associated with substantial decreases in the total use of antihyperglycemic medications. Moreover, lorcaserin decreased the total daily dose of antihypertensive medications used during 1 year clinical trials. Patients taking lorcaserin in each of the 3 pivotal trials also reported improved quality of life.

The effects of weight loss on cardiovascular risk markers like triglycerides, cholesterol and HDL cholesterol have been evaluated in many clinical trials. Based on a review of such trials, the NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults reported that weight loss of 2-13% improved lipid parameters.[94] Similarly, loss of only a few pounds can significantly decrease blood pressure; in a classic meta-analysis, 10 kg weight loss was associated with 7 mmHg decreases in systolic blood pressure.[95] Smaller decreases in blood pressure, like those that result from lesser degrees of weight loss, can significantly decrease the rates of MI, stroke, and cardiovascular mortality: a decrease of 2 mmHg in systolic pressure is estimated to decrease the mortality from stroke by 6%, coronary heart disease by 4%, and total mortality by 3%.[96]

Not only does modest weight loss improve biochemical markers, it has also been shown to improve various functional outcomes like those associated with urinary incontinence[97, 98] and osteoarthritis of the knee,[99] quality of life and mortality.[100]

In summary, lorcaserin has both demonstrated benefits, and benefits that can be predicted from other studies of the impact of weight loss on co-morbid conditions and risks.

5.3 Risks of Treatment

Data for over 8000 people evaluated for up to 2 years show that lorcaserin was well tolerated with few identifiable risks in the clinical trial setting. Risks that were clearly associated with lorcaserin at the MRD were limited to a group of transient, generally mild to moderate adverse events that included headache, dizziness, nausea, fatigue, dry mouth, and infrequent reports of difficulty concentrating, forgetfulness and related terms. Importantly, these events all appear to be self-limited, and to resolve with continued lorcaserin use.

Serious adverse events associated with gallbladder disorders also appeared to be increased with lorcaserin use relative to placebo, perhaps resulting from the greater weight loss with lorcaserin. Proposed labeling for the product includes this information.

Lorcaserin is a serotonergic drug, and should therefore be used carefully with other serotonergic agents since combining such agents has been associated with serotonin syndrome. While no cases meeting published criteria for serotonin syndrome were observed during development, proposed product labeling includes cautionary language.

Importantly, clinical trials monitored for some theoretical risks that were *not* observed. Adverse event surveillance and the Beck Depression Inventory-II showed no increase in depression adverse events or in depression scores. Moreover, lorcaserin did not increase the risk of suicidal ideation. Neither blood pressure nor heart rate was increased by the recommended lorcaserin dose of 10 mg BID.

A theoretical risk of 5-HT_{2B} mediated cardiac valve disease was carefully evaluated through serial echocardiographic monitoring. According to a pre-specified analysis, lorcaserin was non-inferior to placebo with respect to incidence of new FDA-defined valvulopathy. Point estimates for risk ratios or hazard ratios derived from adequately powered analyses were 1.08-1.09 with upper 95% confidence intervals <1.5. While weight loss was negatively associated with

incidence of FDA-defined valvular regurgitation, lorcaserin per se did not appear to increase the risk of valvulopathy.

Risks identified in rats, but not mice, included mammary tumors in rats and astrocytoma in male rats. Mechanistic studies suggested that mammary tumors in female rats arose from increased prolactin effects on the mammary gland, a mechanism that is more relevant to rodents than humans. Moreover, lorcaserin at the recommended dose does not elevate prolactin in humans. Mammary adenocarcinoma occurred in female rats only at plasma exposures greater than 24 times the human plasma exposure at the recommended dose. Astrocytoma occurred in male rats only at brain exposures more than 70 times the predicted brain exposure at the recommended dose. Substantial exposure margins and/or rat-specific mechanisms suggest that the observed rat tumors do not represent increased risk to humans.

Finally, the evaluation of lorcaserin's potential for recreational abuse indicated that the net effect of supratherapeutic doses was aversive rather than rewarding.

5.4 Benefit-Risk Conclusion

The phase 3 clinical evaluation of lorcaserin in 7794 patients, including patients with type 2 diabetes, demonstrates clinically meaningful efficacy and a safety profile that includes minimal and easily managed risks. In each of the individual studies and in the pooled efficacy analyses, the lorcaserin 10 mg BID dose met endpoints and the categorical efficacy benchmark stated in the *Guidance for Industry Developing Products for Weight Management* (Draft; Revision 1, February 2007):

- A significantly greater proportion of patients taking lorcaserin lost ≥ 5% of baseline body weight at 1 year as compared to placebo
- The mean weight loss at 1 year in patients taking lorcaserin was significantly greater than that in patients taking placebo
- At least 35% of patients taking lorcaserin lost ≥ 5% of baseline body weight and was approximately double the proportion in the placebo-treated group
- The weight loss efficacy was supported in each trial by favorable trends in other measures of cardiovascular risk, glycemic control and/or quality of life.

Intentional weight loss of 5-10% is associated with medical benefits that include decreased risk of type 2 diabetes, decreased blood pressure, improved lipid profile, reduced pain from osteoarthritis, and improved quality of life.[11] Average weight loss in the lorcaserin BID group for all patients (including those with diabetes) using MITT/LOCF analysis was 5.8% at one year- well within the range shown to have long-term benefit.

The MITT/LOCF analysis may underestimate lorcaserin's potential benefit for patients who experience early weight loss and who take the drug continuously. To determine how the patients most responsive to lorcaserin fared, Week 52 weight loss was determined for the upper quartile of lorcaserin BID-treated patients using both MITT/LOCF and Completer analyses in pooled phase 3 studies of non-diabetic patients (APD356-009 and APD356-011) and in patients with

type 2 diabetes (APD356-010). In the non-diabetic population, the quartile with the greatest Week 52 percent weight loss lost on average ~13 kg, or ~29 pounds, by MITT/LOCF analysis and ~16 kg, or ~35 lbs, by Completer analysis. In study APD356-010, the top quartile of lorcaserin BID patients lost on average ~ 11 kg, or ~ 24 lbs by MITT/LOCF analysis and ~13 kg, or ~29 lbs, by Completer analysis.

Data for non-diabetic patients submitted with the original NDA submission showed that lorcaserin 10 mg BI D significantly improved anthropometric parameters and cardiovascular risk factors. The new data from the APD356-010 study illustrate an additional benefit: significant improvement of glycemic control in patient with type 2 diabetes. While changes in anthropometric measures, lipids and blood pressure were in some cases small from a clinical standpoint, the lorcaserin-mediated decreases in HbA1c and fasting glucose in type 2 diabetes were substantial and clinically meaningful. More than half of patients who took lorcaserin achieved HbA1c values below 7.0%, and more patients taking lorcaserin than placebo were able to reduce doses of anti-hyperglycemic medications. The American Diabetes Association's HbA1c target of 7%[39] is based on evidence from the Diabetes Control and Complications Trial (DCCT),[101] United Kingdom Prospective Diabetes Study (UKPDS),[102-104] the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[105-107] other studies,[106] and meta-analyses[108, 109] showing reduced risk of microvascular complications (retinopathy, nephropathy) with this level of control. Even discounting specific markers of glycemic control, changes in other parameters observed in the APD356-010 study (and the studies of non-diabetic patients) predict that lorcaserin lowered cardiovascular risk. The Framingham Cardiovascular Risk Calculators for "hard" risk or "general" risk indicate that the modest changes in lipid profile and blood pressure observed with lorcaserin treatment over 1 year translate into a reduction in 10-year predicted risk relative to placebo in patients at increased risk at baseline (5% or greater 10 year risk.).

The efficacy profile of lorcaserin in phase 3 studies is supported by a safety profile that Arena proposes is acceptable to support clinical use of lorcaserin for weight management in a broad population that includes men and women age 18 and older, who are obese (BMI $\geq$30 kg/m^2), or overweight (BMI $\geq$27 kg/m^2) if 1 or more weight-related co-morbid condition is present (e.g., type 2 diabetes, hypertension, dyslipidemia, sleep apnea). The current safety database identifies no demographic subgroup in which the safety profile differs substantially from the overall study population.

The safety profile was remarkably similar for the lorcaserin once daily and twice daily groups, with only weak or no dose-response for clearly lorcaserin related adverse events. Because efficacy in the overall pooled population was dose- and exposure-related, Arena considers the 10 mg twice daily dose to have the better benefit/risk profile, and is requesting approval only for the twice daily dose.

Phase 3 echocardiographic data have addressed the theoretical risk of valvulopathy associated with potential lorcaserin agonism at the 5-HT$_{2C}$ receptor, providing point estimates of 1.08-1.16 that may be at least in part attributable solely to weight loss. Statistical modeling of the phase 3 placebo and pooled data predicts that a monitoring program extending to additional patients would demonstrate a risk ratio for lorcaserin of approximately 1.1-1.2, assuming weight loss comparable to that in clinical trials.

The data indicate that mammary adenocarcinoma observed in female rats and astrocytoma observed in male rats are unlikely to pose a risk that is relevant to humans at the proposed dose of 10 mg twice daily. Mammary adenocarcinoma in female rats is associated with an exposure margin of 24 (based on dose at which adenocarcinoma is not increased relative to proposed clinical dose), and the brain exposure margin for astrocytoma in male rats is approximately 70. Given that lorcaserin is non-genotoxic, and that each tumor type was increased by lorcaserin only in one gender of one species, Arena believes that these exposure margins indicate that these tumors are relatively irrelevant to human risk. Benign mammary fibroadenoma observed in female rats, but not observed in mice, appears to be a prolactin-mediated phenomenon; because this mechanism is believed to be peculiar to rodents and because prolactin is not elevated in humans at the intended dose, benign mammary fibroadenoma is unlikely to represent a risk to humans.

More than half of the United States population is now overweight, and one-third of adults are obese. Unfortunately, diet and exercise counseling fail for most patients. Even if "qualified" for bariatric surgery, most patients perceive invasive procedures as a last resort, preferring medical management if possible. As with any common chronic medical condition, no single agent for weight management will be efficacious for all patients and no single agent will be tolerated by all patients. Hence, patients who require medical weight management would ideally have multiple treatment options available. On an intent-to-treat basis, almost half of lorcaserin-treated patients lost 5% of their body weight at one year, and almost one-quarter lost 10%. In patients with type 2 diabetes, a substantial improvement in glycemic control was also realized. Lorcaserin's benefit/risk profile justifies making it available to obese and overweight adults who may benefit from its use.

6 REFERENCES

1. US Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Developing products for weight management. Draft Guidance. [Revision 1], 1-19. 2007.

2. Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med* 2007;356(1):29-38.

3. Azoulay L, Yin H, Renoux C, Suissa S. The use of atypical antipsychotics and the risk of breast cancer. *Breast Cancer Res Treat* 2011 September;129(2):541-8.

4. Melmed S, Polonsky KS, Larsen R, Kronenberg HM. Williams textbook of endocrinology. In: Melmed S, Polonsky KS, Larsen R, Kronenberg HM, editors. 12th ed ed. Philadelphia: Saunders/Elsevier; 2011. p. 126.

5. Singh JP, Evans JC, Levy D et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* 1999;83(6):897-902.

6. World Health Organization. Fact Sheet: Obesity and Overweight. 2003.

7. National Institutes of Health. Clinical Guidelines on Identification, Evaluation and Treatment of Overweight and Obesity in Adults. 1998 Sep.

8. Marx J. Cellular warriors at the battle of the bulge. *Science* 2003 February 7;299(5608):846-9.

9. Burton BT, Foster WR, Hirsch J, Van Itallie TB. Health implications of obesity: an NIH Consensus Development Conference. International Journal of Obesity 10[1], 155-170. 1986. ENGLAND, International journal of obesity.

10. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *JAMA* 2003 January 8;289(2):187-93.

11. Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. *Arch Intern Med* 1998 September 28;158(17):1855-67.

12. Hamman RF, Wing RR, Edelstein SL et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 2006 September;29(9):2102-7.

13. Knowler WC, Fowler SE, Hamman RF et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009 November 14;374(9702):1677-86.

14. Wassertheil-Smoller S, Blaufox MD, Oberman AS, Langford HG, Davis BR, Wylie-Rosett J. The Trial of Antihypertensive Interventions and Management (TAIM) study. Adequate weight

loss, alone and combined with drug therapy in the treatment of mild hypertension. *Arch Intern Med* 1992 January;152(1):131-6.

15. Whelton PK, Appel LJ, Espeland MA et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. *JAMA* 1998 March 18;279(11):839-46.

16. Grimm RH, Jr., Cohen JD, Smith WM, Falvo-Gerard L, Neaton JD. Hypertension management in the Multiple Risk Factor Intervention Trial (MRFIT). Six-year intervention results for men in special intervention and usual care groups. *Arch Intern Med* 1985 July;145(7):1191-9.

17. Foy CG, Lewis CE, Hairston KG et al. Intensive Lifestyle Intervention Improves Physical Function Among Obese Adults With Knee Pain: Findings From the Look AHEAD Trial. *Obesity (Silver Spring)* 2010 June 17.

18. Sjostrom L, Narbro K, Sjostrom CD et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007 August 23;357(8):741-52.

19. Baumann MH, Ayestas MA, Dersch CM, Partilla JS, Rothman RB. Serotonin transporters, serotonin release, and the mechanism of fenfluramine neurotoxicity. Ann NY Acad Sci 914, 172-186. 2000.

20. Fitzgerald LW, Burn TC, Brown BS et al. Possible role of valvular serotonin 5-HT(2B) receptors in the cardiopathy associated with fenfluramine. *Mol Pharmacol* 2000;57(1):75-81.

21. Rothman RB, Baumann MH, Savage JE et al. Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation* 2000;102(23):2836-41.

22. Roth BL. Drugs and valvular heart disease. *N Engl J Med* 2007;356(1):6-9.

23. Vickers SP, Dourish CT. Serotonin receptor ligands and the treatment of obesity. *Curr Opin Investig Drugs* 2004 April;5(4):377-88.

24. Leibowitz SF, Alexander JT. Hypothalamic serotonin in control of eating behavior, meal size, and body weight. *Biol Psychiatry* 1998 November 1;44(9):851-64.

25. Heisler LK, Jobst EE, Sutton GM et al. Serotonin reciprocally regulates melanocortin neurons to modulate food intake. *Neuron* 2006 July 20;51(2):239-49.

26. Blevins JE, Baskin DE. Hypothalamic-brainstem circuits controlling eating. In: Langhans W, Geary N, editors. *Frontiers in eating and weight regulation*. Forum of Nutrition, Volume 63 ed. Karger AG, Basel; 2010. p. 133-40.

27. Thomsen WJ, Grottick AJ, Menzaghi F et al. Lorcaserin, a novel selective human 5-hydroxytryptamine2C agonist: in vitro and in vivo pharmacological characterization. *J Pharmacol Exp Ther* 2008 May;325(2):577-87.

28. Division of Metabolic and Endocrine Drug ProductsFood and Drug Administration. Guidance for the Clinical Evaluation of Weight-control Drugs. 1-6. 1996.

29. U.S.Department of Health and Human Services Food and Drug Administration. Guidance for INdustry: Developing Products for Weight Management. Draft Guidance. [Revision 1], 1-19. 2007.

30. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346(6):399-403.

31. Mertens IL, Van Gaal LF. Overweight, obesity, and blood pressure: the effects of modest weight reduction. *Obes Res* 2000;8(3):270-8.

32. Ditschuneit HH, Frier HI, Flechtner-Mors M. Lipoprotein responses to weight loss and weight maintenance in high-risk obese subjects. *Eur J Clin Nutr* 2002;56(3):264-70.

33. Carter R 3rd, Watenpaugh DE. Obesity and obstructive sleep apnea: Or is it OSA and obesity? *Pathophysiology* 2008;15(2):71-7.

34. Hernandez TL, Ballard RD, Weil KM, et al. Effects of maintained weight loss on sleep dynamics and neck morphology in severely obese adults. *Obesity* 2009;17(1):84-91.

35. Kolotkin RL, Crosby RD. Psychometric evaluation of the impact of weight on quality of life-lite questionnaire (IWQOL-lite) in a community sample. *Qual Life Res* 2002 March;11(2):157-71.

36. Kolotkin RL, Crosby RD, Kosloski RD, Williams GR. Development of a brief measure to assess quality of life in obesity. *Obes Res* 2001;9(2):102-11.

37. Karason K, Lindroos AK, Stenlof K, Sjostrom L. Relief of cardiorespiratory symptoms and increased physical activity after surgically induced weight loss: results from the Swedish Obese Subjects study. *Arch Intern Med* 2000;160:1797-802.

38. U.S.Census Buerau. State and Country Quickfacts. *U S Census Bureau* 2010 April 22;Available at: URL: http://quickfacts.census.gov/qfd/states/00000.html.

39. American Diabetes Association. Standards of Medical Care in Diabetes 2011. *Diabetes Care* 2011 January 1;34(Supplement 1):S11-S61.

40. D'Agostino RB, Sr., Vasan RS, Pencina MJ et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008 February 12;117(6):743-53.

41. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 285[19], 2486-2497. 5-16-2001.

42. NHLBI. Framingham Heart Study Risk Score Profiles. *http://www framinghamheartstudy org/risk/index html* 2012;Available at: URL: http://www.framinghamheartstudy.org/risk/index.html.

43. Vickers SP, Dourish CT. Serotonin receptor ligands and the treatment of obesity. Curr Opin Investig Drugs 5[4], 377-388. 2004.

44. Roth BL, . Drugs and valvular heart disease. *N Engl J Med* 2007;356(1):6-9.

45. Hofmann C, Penner U, Dorow R et al. Lisuride, a dopamine receptor agonist with 5-HT2B receptor antagonist properties: absence of cardiac valvulopathy adverse drug reaction reports supports the concept of a crucial role for 5-HT2B receptor agonism in cardiac valvular fibrosis. *Clin Neuropharmacol* 2006;29(2):80-6.

46. Gray JA, Roth BL. Paradoxical trafficking and regulation of 5-HT(2A) receptors by agonists and antagonists. *Brain Res Bull* 2001;56(5):441-51.

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

48. González-Maeso J, Weisstaub NV, Zhou M et al. Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. *Neuron* 2007;53(3):439-52.

49. Fitzgerald P, Dinan TG. Prolactin and dopamine: what is the connection? A review article. *J Psychopharmacol* 2008;22(2 Suppl):12-9.

50. Emiliano AB, Fudge JL. From galactorrhea to osteopenia: rethinking serotonin-prolactin interactions. *Neuropsychopharmacology* 2004;29(5):833-46.

51. Bijl D. The Serotonin Syndrome. *The Netherlands Journal of Medicine* 2004;62(9):309-13.

52. Birmes P, Coppin D, Schmitt L, Lauque D. Serotonin Syndrome: a brief review. *Can Med Assoc J* 2003;168(11):1439-42.

53. Everhart JE. Contributions of obesity and weight loss to gallstone disease. *Ann Int Med* 1993;119(10):1029-35.

54. [No authors listed]. Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. *Arch Intern Med* 1998;158(17):1855-67.

55. Despres JP, Rimonabant in Obesity-Lipids Study Group, Golay A, Sjostrom L, Rimonabant in Obesity-Lipids Study Group. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med 353[20], 2121-2134. 2005.

56. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J, RIO-North America Study Group. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA 295[7], 761-775. 2006.

57. Van Gaal LF, Scheen AJ, Rissanen AM, Rossner S, Hanotin C, Ziegler O. Long-term effect of CB1 blockade with rimonabant on cardiometabolic risk factors: two year results from the RIO-Europe Study. *Eur Heart J* 2008 July;29(14):1761-71.

58. Gottdiener JS, Panza JA, Sutton MS, Bannon P, Kushner H, Weissman NJ. Testing the Test: The Reliability of Echocardiography in the Sequential Assessment of Valvular Regurgitation. *Am Heart J* 2002;144(1):115-21.

59. 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;144(6):1065-73.

60. Baseman DG, O'Suilleabhain PE, Reimold SC, Laskar SR, Baseman JG, Dewey RB, Jr. Pergolide use in Parkinson disease is associated with cardiac valve regurgitation. *Neurology* 2004 July 27;63(2):301-4.

61. Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007 January 4;356(1):39-46.

62. Onyike CU, Crum, RM, Lee HB, Jyketsos CG, Eaton WW. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2003;158(12):1139-47.

63. Roberts RE, Kaplan GA, Shema SJ, Strawbridge WJ. Are the obese at greater risk for depression? *Am J Epidemiol* 2000;152(2):163-70.

64. Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA. Prospective association between obesity and depression: evidence from the Alameda County Study. *Int J Obes* 2003;27:514-21.

65. Kalow W. Ethnic differences in drug metabolism. *Clin Pharmacokinet* 1982 September;7(5):373-400.

66. Capon DA, Bochner F, Kerry N, Mikus G, Danz C, Somogyi AA. The influence of CYP2D6 polymorphism and quinidine on the disposition and antitussive effect of dextromethorphan in humans. *Clin Pharmacol Ther* 1996 September;60(3):295-307.

67. McConnell EE, Solleveld HA, Swenberg JA, Boorman GA. Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *J Natl Cancer Inst* 1986 February;76(2):283-9.

68. Williams GM, Iatropoulos MJ, Enzmann HG. Principles of testing for carcinogenic activity. In: Wallace Hayes A, editor. *Principles and Methods of Toxicology*.Philadelphia, PA: Taylor and Francis; 2008. p. 1265-316.

69. Dinse GE, Peddada SD, Harris SF, Elmore SA. Comparison of NTP historical control tumor incidence rates in female Harlan Sprague Dawley and Fischer 344/N Rats. *Toxicol Pathol* 2010;38(5):765-75.

70. Brix AE, Nyska A, Haseman JK, Sells DM, Jokinen MP, Walker NJ. Incidences of selected lesions in control female Harlan Sprague-Dawley rats from two-year studies performed by the National Toxicology Program. *Toxicol Pathol* 2005;33(4):477-83.

71. McMartin DN, Sahota PS, Gunson DE, Hsu HH, Spaet RH. Neoplasms and related proliferative lesions in control Sprague-Dawley rats from carcinogenicity studies. Historical data and diagnostic considerations. *Toxicol Pathol* 1992;20(2):212-25.

72. Greaves P. Mammary gland. *Histopathology of Preclinical Toxicity Studies: Interpretation and Relevance in Drug Safety Evaluation*. 4th ed. Amsterdam: Elsevier; 2012. p. 69-97.

73. Nagasawa H, Morii S. Inhibition by early treatment with bromocriptine of spontaneous mammary tumour development in rats with no side-effects. *Acta Endocrinol (Copenh)* 1982 September;101(1):51-5.

74. Mazzola-Pomietto P, Aulakh CS, Wozniak KM, Murphy DL. Evidence that m-chlorophenylpiperazine-induced hyperthermia in rats is mediated by stimulation of 5-HT2C receptors. *Psychopharmacology (Berl)* 1996 February;123(4):333-9.

75. Van de Kar LD, Rittenhouse PA, Li Q, Levy AD. Serotonergic regulation of renin and prolactin secretion. *Behav Brain Res* 1996;73(1-2):203-8.

76. Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: Structure, Function, and Regulation of Secretion. *Physiol Rev* 2000 January 10;80(4):1523-631.

77. Bristol-Myers Squibb Canada. Desyrel (trazodone hydrochloride) Product Monograph. [Control No. 094864]. 10-29-2004.

78. AstraZeneca Pharmaceuticals. Seroquel (quetiapine fumarate) Prescribing Information. 2011.

79. Ortho-McNeil Pharmaceuticals I. Haldol (haloperidol) Prescribing Information. 2005.

80. Ben-David M. Mechanism of induction of mammary differentiation is Sprague-Dawley female rats by perphenazine. *Endocrinology* 1968 December;83(6):1217-23.

81. Fernstrom JD, Van Itallie CM, Fernstrom MH. Effects of acute and chronic trazodone administration on serum prolactin levels in adult female rats. *Life Sci* 1983 December 19;33(25):2559-65.

82. Russo IH, Russo J. Mammary gland neoplasia in long-term rodent studies. *Environ Health Perspect* 1996 September;104(9):938-67.

83. Stringer BM, Rowson J, Williams ED. Effect of raised serum prolactin on breast development. *J Anat* 1989 February;162:249-61.

84. Blankenstein MA, Broerse JJ, van Zwieten MJ, van der Molen HJ. Prolactin concentration in plasma and susceptibility to mammary tumors in female rats from different strains treated chronically with estradiol-17 beta. *Breast Cancer Res Treat* 1984;4(2):137-41.

85. Briand P. Hormone-dependent mammary tumors in mice and rats as a model for human breast cancer (review). *Anticancer Res* 1983 July;3(4):273-81.

86. Meites J. Relation of the neuroendocrine system to the development and growth of experimental mammary tumors. *J Neural Transm* 1980;48(1):25-42.

87. Noble RL, Cutts JH. Mammary Tumors of the Rat: A Review. *Cancer Res* 1959;19:1125-39.

88. Welsch CW. Hormonal regulation of experimental mammary tumors. In: Leung BS, editor. *Hormones and murine mammary tumorigenesis: an historical perspective*. Eden Press; 1983. p. 1-29.

89. Welsch CW, Nagasawa H. Prolactin and Murine Mammary Tumorigenesis: A Review. *Cancer Res* 1977 April 1;37(4):951-63.

90. Clinton SK, Li PH, Visek WJ. The combined effects of dietary protein and fat on prolactin in female rats. *J Nutr* 1985 March;115(3):311-8.

91. Kuo CB, Wu W, Xu X et al. Pseudophosphorylated prolactin (S179D PRL) inhibits growth and promotes beta-casein gene expression in the rat mammary gland. *Cell Tissue Res* 2002 September;309(3):429-37.

92. Wang PS, Walker AM, Tsuang MT et al. Dopamine antagonists and the development of breast cancer. *Arch Gen Psychiatry* 2002 December;59(12):1147-54.

93. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346(6):399-403.

94. The National Heart, Lung, and Blood Institute. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. 1998. Report No.: NIH Publication No. 98-4083.

95. The National Heart, Lung, and Blood Institute. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. 1998. Report No.: NIH Publication No. 98-4083.

96. Whelton PK, He J, Appel LJ et al. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA* 2002 October 16;288(15):1882-8.

97. Phelan S, Kanaya AM, Subak LL et al. Weight Loss Prevents Urinary Incontinence in Women With Type 2 Diabetes: Results From the Look AHEAD Trial. *J Urol* 2012 March;187(3):939-44.

98. Subak LL, Wing R, West DS et al. Weight loss to treat urinary incontinence in overweight and obese women. *N Engl J Med* 2009 January 29;360(5):481-90.

99. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2007 April;66(4):433-9.

100. Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C. Prospective Study of Intentional Weight Loss and Mortality in Overweight White Men Aged 40ΓÇô64 Years. *Am J Epidemiol* 1999 March 15;149(6):491-503.

101. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *N Engl J Med* 1993 September 30;329(14):977-86.

102. Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000 August 12;321(7258):405-12.

103. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998 September 12;352(9131):854-65.

104. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998 September 12;352(9131):837-53.

105. Ismail-Beigi F, Craven T, Banerji MA et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010 August 7;376(9739):419-30.

106. Chew EY, Ambrosius WT, Davis MD et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010 July 15;363(3):233-44.

107. Gerstein HC, Miller ME, Byington RP et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008 June 12;358(24):2545-59.

108. Selvin E, Marinopoulos S, Berkenblit G et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004 September 21;141(6):421-31.

109. Stettler C, Allemann S, Juni P et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials. *Am Heart J* 2006 July;152(1):27-38.

110. Droogmans S, Franken PR, Garbar C et al. In vivo model of drug-induced valvular heart disease in rats: pergolide-induced valvular heart disease demonstrated with echocardiography and correlation with pathology. *Eur Heart J* 2007 September;28(17):2156-62.

111. Elangbam CS, Job LE, Zadrozny LM et al. 5-hydroxytryptamine (5HT)-induced valvulopathy: compositional valvular alterations are associated with 5HT2B receptor and 5HT transporter transcript changes in Sprague-Dawley rats. *Exp Toxicol Pathol* 2008 August;60(4-5):253-62.

112. Hauso O, Gustafsson BI, Loennechen JP, Stunes AK, Nordrum I, Waldum HL. Long-term serotonin effects in the rat are prevented by terguride. *Regul Pept* 2007 October 4;143(1-3):39-46.

113. MPI Research, Inc. Study Report [900-009, Arena Study No. TX03015]: Amendment to the Final Report, APD356: 28-Day Oral Toxicity Study in Rats.

114. ChanTest, Inc. Study Report [030318.BSF, Arena Study No. TX03020]: GLP Study: Effects of APD356 on Cloned hERG Channels Expressed in Mammalian Cells.

115. MPI Research, Inc. Study Report [900-012, Arena Study No. TX03017]: APD356: Cardiovascular Effects in the Cynomolgus Monkey After Single Oral Dose.

116. MPI Research, Inc. Study Report [900-008, Arena Study No. TX03016]: APD356: 28-Day Oral Toxicity Study in Cynomolgus Monkeys.

117. MPI Research, Inc. Study Report [900-013, Arena Study No. TX03018]: APD356: Pulmonary Effects in Rats After Single Oral Dose.

118. MPI Research, Inc. Study Report [900-047, Arena Study No. TX05004]: APD356: 13-Week Oral Toxicity Study in Mice with a 4-Week Recovery Period.

119. Console GM, Gomez Dumm CL, Brown OA, Ferese C, Goya RG. Sexual dimorphism in the age changes of the pituitary lactotrophs in rats. *Mech Ageing Dev* 1997 May;95(3):157-66.

120. Kohama T, Terada S, Suzuki N, Inoue M. Effects of dehydroepiandrosterone and other sex steroid hormones on mammary carcinogenesis by direct injection of 7,12-dimethylbenz(a) anthracene (DMBA) in hyperprolactinemic female rats. *Breast Cancer Res Treat* 1997 April;43(2):105-15.

121. Whysner J, Ross PM, Williams GM. Phenobarbital mechanistic data and risk assessment: enzyme induction, enhanced cell proliferation, and tumor promotion. *Pharmacol Ther* 1996;71(1-2):153-91.

122. Olsen JH, Wallin H, Boice JD, Jr., Rask K, Schulgen G, Fraumeni JF, Jr. Phenobarbital, drug metabolism, and human cancer. *Cancer Epidemiol Biomarkers Prev* 1993 September;2(5):449-52.

123. Saghir SA, Charles GD, Bartels MJ et al. Mechanism of trifluralin-induced thyroid tumors in rats. *Toxicol Lett* 2008 July 30;180(1):38-45.

124. Klaassen CD, Hood AM. Effects of microsomal enzyme inducers on thyroid follicular cell proliferation and thyroid hormone metabolism. *Toxicol Pathol* 2001 January;29(1):34-40.

125. Curran PG, DeGroot LJ. The effect of hepatic enzyme-inducing drugs on thyroid hormones and the thyroid gland. *Endocr Rev* 1991 May;12(2):135-50.

126. Holsapple MP, Pitot HC, Cohen SM et al. Mode of action in relevance of rodent liver tumors to human cancer risk. *Toxicol Sci* 2006 January;89(1):51-6.

127. Capen CC. Overview of structural and functional lesions in endocrine organs of animals. *Toxicol Pathol* 2001 January;29(1):8-33.

128. Cardesa A, Ribalta T, Vogeley KT, Reifenerger G, Wechsles W, Turusov VS. Tumours of the peripheral nervous system. In: Turusov VS, Mojica W, editors. *Pathology of Tumours in Laboratory Animals Vol 1 – Tumours of the Rat*. 2 ed. Lyon, France: IARC; 1990. p. 699-724.

129. Greaves P. Nervous system and special sense organs. *Histopathology of Preclinical Toxicity Studies*. 3rd ed. London, England: Academic Press; 2007. p. 38.

130. Zwicker GM, Eyster RD, Sells DM, Gass JH. Comparative incidences of skin neoplasms in Sprague-Dawley, F344 and Wistar rats. In: Mohr U, Dungworth DL, Capen CC, editors. *Pathobiology of the Aging Rat.*Washington DC: ILSI Press; 1994. p. 391-421.

131. Grasso P, Golberg L. Subcutaneous sarcoma as an index of carcinogenic potency. *Food Cosmet Toxicol* 1966 June;4(3):297-320.

132. Enzmann H, Bomhard E, Iatropoulos M, Ahr HJ, Schlueter G, Williams GM. Short- and intermediate-term carcinogenicity testing--a review. Part 1: the prototypes mouse skin tumour assay and rat liver focus assay. *Food Chem Toxicol* 1998 November;36(11):979-95.

133. Penn I. Depressed immunity and skin cancer. Immunology Today 5, 291-293. 1984.

134. Fisher MS, Kripke ML. Suppressor T lymphocytes control the development of primary skin cancers in ultraviolet-irradiated mice. *Science* 1982 June 4;216(4550):1133-4.

135. Comer SD, Ashworth JB, Foltin RW, Johanson CE, Zacny JP, Walsh SL. The role of human drug self-administration procedures in the development of medications. *Drug Alcohol Depend* 2008 July 1;96(1-2):1-15.

7 APPENDICES

Appendix 1 Product Description

The lorcaserin drug substance is a single enantiomer, hemihydrate form of the hydrochloride salt of lorcaserin. Lorcaserin HCl hemihydrate is a highly soluble and highly permeable white to off-white powder that meets the criteria for a Biopharmaceutics Classification System (BCS) Class-1 drug.

The drug product, lorcaserin HCl 10-mg tablet, is an immediate-release tablet dosage form for oral administration. It is a round, biconvex, film-coated, blue-colored tablet with a debossed "A" on one side and a "10" on the other.

Nonproprietary name:	Lorcaserin hydrochloride
Company name:	Arena Pharmaceuticals, Inc.
Dosage form:	Tablet
Strength:	10 mg
Route of administration:	Oral
Proposed indication:	Weight management

Appendix 2 Nonclinical Pharmacology and Toxicology

7.1 Summary of Nonclinical Pharmacology and Toxicology

Lorcaserin is a potent and selective 5-HT_{2C} agonist which has been characterized in a panel of *in vitro* and *in vivo* pharmacologic studies and pharmacokinetic, toxicity, and carcinogenicity studies. The animals chosen for toxicity studies were appropriate based upon pharmacologic and metabolic profiles.

Lorcaserin *in vitro* pharmacologic activity is restricted to the subtype 2 serotonin receptors, with approximately 14-fold and 61-fold greater potency for human 5-HT_{2C} than 5-HT_{2A} and 5-HT_{2B} receptors, respectively. Lorcaserin is a partial agonist of the 5-HT_{2A} receptor, exerting maximal activity that is only ~25% the activity of serotonin itself. The two major metabolites of lorcaserin in animals and humans (lorcaserin sulfamate [M1] and *N*-carbamoyl glucuronide of lorcaserin [M5]) are inactive at a panel of 82 serotonin and other G-protein coupled receptors, ion channels, and transporters. Lorcaserin activates 5-HT_{2C} receptors *in vivo* (indicated by decreased food intake, decreased weight gain), but does not consistently induce behaviors that are characteristic of 5-HT_{2A} receptor activation (wet dog shakes, back muscle fasciculations, dopamine release in the nucleus accumbens) or effects that are associated with the 5-HT_{2B} receptor (cardiac valvulopathy).

In animals, lorcaserin is rapidly absorbed, with bioavailability ranging from 38-94%, dose-proportional exposure at relevant pharmacological and toxicological doses, and half-life consistent with projections of once or twice daily dosing in humans. Accumulation in plasma and brain is modest, with brain levels exceeding plasma levels by ~25-fold in rodents and 10-fold in primates. Lorcaserin undergoes extensive hepatic metabolism by multiple enzyme systems, with similar profiles in animals and humans. Excretion of lorcaserin and its metabolites is almost exclusively through urine.

Lorcaserin was evaluated in a standard battery of genotoxicity, reproductive toxicity, general toxicity, and carcinogenicity studies. Lorcaserin showed no reproductive toxicity or genotoxicity. In general toxicity studies in mice, rats, and cynomolgus monkeys, demonstrated that lorcaserin was generally well tolerated at doses below the maximum tolerated dose (MTD) and there appeared to be no adverse findings of direct relevance to humans at therapeutic doses. Maximum tolerated doses were defined by mortality in mice and rats and by emesis in monkeys. The most consistent findings in rodents at doses below the MTD were evidence of increased red blood cell (RBC) turnover at doses $\geq$ 50 mg/kg in mice and rats: low-grade anemia, reticulocytosis, extramedullary hematopoiesis, and increased pigmented splenic macrophages.

In monkeys that received doses below the MTD, findings were limited to emesis, penile extension, sporadic and mild elevations in ALT, focal renal tubular regeneration (and degeneration at the highest dose of 125 mg/kg), hepatic lipidosis, and cystic ovarian follicles, primarily at doses $\geq$ 50 mg/kg. The liver changes were not dose related and the renal findings were focal, mild and may not have been treatment related.

Extensive histopathological analysis in general toxicity and carcinogenicity studies showed that lorcaserin had no effects on heart valves, other cardiac tissues, or the pulmonary vasculature in studies up to 2 years in rats and mice and up to 1 year in monkeys.

Two-year carcinogenicity studies were conducted in mice and rats. There was no evidence of carcinogenicity in mice. In rats, benign and malignant mammary tumors were increased in females. Male rats in the highest lorcaserin dose group had increases in thyroid, subcutis, skin, brain, and benign mammary tumors. Each tumor type found in rats occurred at an exposure well above that at the human dose, and/or was attributable to a rodent-specific mechanism. In female rats, the incidence of mammary adenocarcinoma was increased at the highest lorcaserin dose, and benign mammary fibroadenomas were increased over control at all doses tested. The mammary tumors are attributable to increased prolactin, a mechanism that is relevant to the rat, but of questionable relevance to humans. Moreover, circulating prolactin was not elevated in humans taking lorcaserin at the maximum recommended dose. In male rats, the high dose of lorcaserin (100 mg/kg/day) was toxic, as indicated by weight loss, high mortality, and histopathologic changes. Brain lorcaserin exposure at the low dose, where astrocytoma was not observed, was approximately 70 times human brain exposure at the MRD.

7.2 Nonclinical Pharmacology

7.2.1 *In Vitro* Receptor Binding and Activity of Lorcaserin and Its Major Metabolites

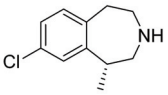
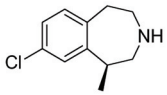
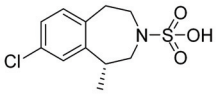
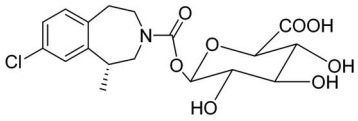
Lorcaserin is a selective 5-HT_{2C} receptor agonist, with greater potency at the human 5-HT_{2C} receptor than the closely related 5-HT_{2A} and 5-HT_{2B} receptors. Lorcaserin's *in vitro* functional EC_{50} in an inisitol phosphate accumulation assay was 39 nM, with 14-fold and 61-fold greater potency for human 2C than 2A and 2B receptors, respectively (Table 58). Binding affinities for the 5-HT_2 receptors were similar in human and rat, but functional selectivity for the rat receptors differed from that for the human receptors. Lorcaserin is a full agonist at the 2C and 2B receptors, and is a partial agonist (maximal activity 25% of serotonin) at the 2A receptor in rat and human. Lorcaserin tested at 1-10 µM *in vitro* had little or no activity at serotonin, dopamine, and norepinephrine transporters or in a screen of 82 receptors, ion channels, and transporters. Activity was limited to 5-HT subtype 2 receptors.

Table 58. Lorcaserin Selectivity for Humans and Rat 5-HT_2 Receptors

Values expressed as mean (95% CI)	**Human 5-HT_{2C}**	**Human 5-HT_{2A}**	**Human 5-HT_{2B}**
Binding Affinity K_i (nM)	13 (11-15)	92 (81-104)	147 (123-177)
Functional Activity EC_{50} (nM)	39 (28-55)	553 (450-680)	2380 (2050-2770)
Values expressed as mean (95% CI)	**Rat 5-HT_{2C}**	**Rat 5-HT_{2A}**	**Rat 5-HT_{2B}**
Binding Affinity K_i (nM)	16 (11-23)	81 (59-110)	114 (95-137)
Functional Activity EC_{50} (nM)	545 (404-736)	1110 (690-1800)	195 (134-284)

A similar *in vitro* testing paradigm was applied to the lorcaserin enantiomer and the two major metabolites, lorcaserin sulfamate (M1) and *N*-carbamoyl glucuronide of lorcaserin (M5) (Table 59).

Table 59. Molecular Structures and Alternative Nomenclature for Lorcaserin, Lorcaserin Enantiomer, and Metabolites M1 and M5

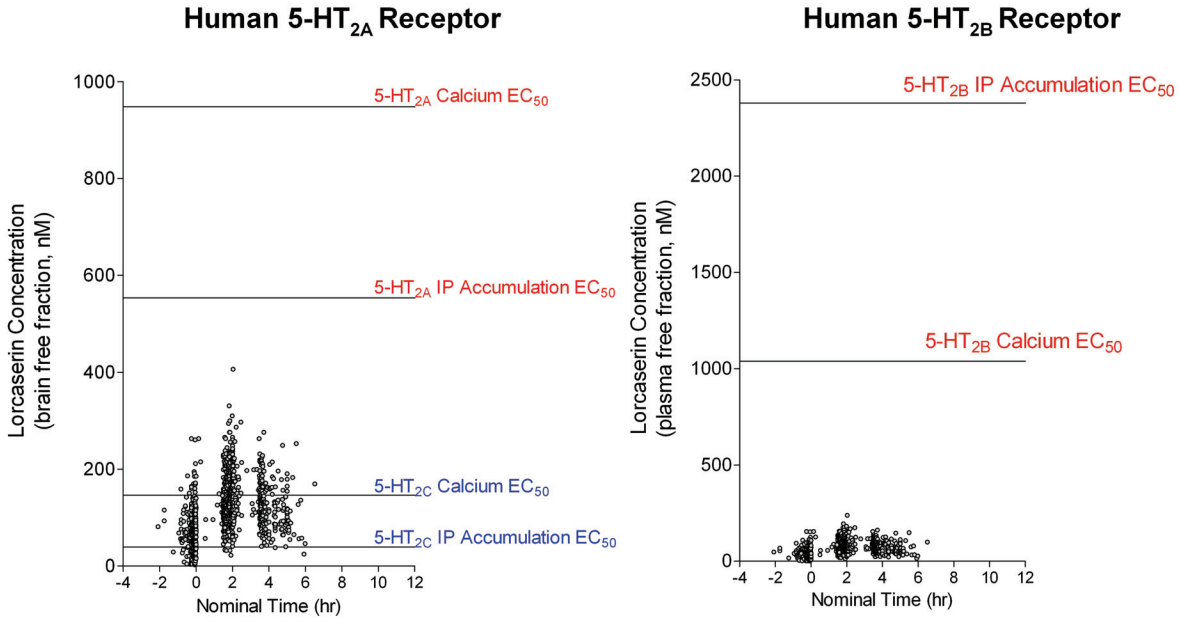
	Lorcaserin	Lorcaserin Enantiomer	M1	M5
Molecular structure				
Nomenclature	APD356, AR226173	AR226175	Lorcaserin sulfamate, HSO_3-APD356, AR244208	*N*-Carbamoyl glucuronide of lorcaserin, AR306388

Lorcaserin enantiomer is a low-level impurity (< 1%) in the lorcaserin active pharmaceutical ingredient (API), and lorcaserin does not undergo chiral conversion *in vivo*. M1 is the major circulating metabolite in rats, mice, monkeys, and humans. M5 is observed in all of these species, and is the major metabolite in monkey and human urine. Neither metabolite had significant binding affinity or activity at a panel of receptors and ion channels when tested at 1-10 µM.

RELEVANCE OF RECEPTOR POTENCY TO HUMAN SAFETY

The receptor potency data may be helpful in predicting human safety. Receptor EC_{50} values for lorcaserin were compared to the measured or predicted human free drug exposures at the maximum recommended dose of 10 mg BID (Figure 45). The 5-HT_{2C} receptor EC_{50} values from two different *in vitro* assays (inositol phosphate accumulation, intracellular calcium) were within the predicted human brain free drug exposure concentration range. Hence, lorcaserin at 10 mg BID is expected to activate the target receptor and reduce food intake. In contrast, lorcaserin is not expected to activate the 5-HT_{2A} or 5-HT_{2B} receptors at the recommended dose. To evaluate the 5-HT_{2A} receptor, brain exposure is most relevant. The predicted human brain concentration at various times after lorcaserin administration (see Section 4.3) is well below the concentration needed to half-maximally activate the 5-HT_{2A} receptor. Similarly, lorcaserin free drug plasma concentrations are well below the levels required to activate the 5-HT_{2B} receptor (Figure 45).

Figure 45. Receptor Potency Values Relative to Human Exposure Based on Lorcaserin Free Fraction



Note: Each symbol is a patient receiving lorcaserin 10 mg BID at steady state. Blood samples from each patient were collected nominally at 15 minutes before the morning dose, 2 hours post-dose, and 4 hours post-dose.

7.2.2 *In Vivo* Pharmacodynamic Effects and Selectivity

The pharmacodynamic activity of lorcaserin was evaluated in adult male Sprague-Dawley (S-D) rats and in the Levin rat model of human obesity by monitoring food intake and/or body weight changes.

In addition, standard rat behavioral paradigms were used to evaluate the *in vivo* selectivity of lorcaserin for 5-HT_{2C} receptors relative to 5-HT_{2A} and 5-HT_{2B} receptors. Activation of central 5-HT_{2A} receptors has been linked to perceptual or mood changes that could be relevant to abuse potential in humans. Activation of 5-HT_{2B} receptors in the heart has been implicated in the pathogenesis of serotonin-associated valvulopathy that is characterized by valvular thickening, fibrosis and valvular regurgitation.

7.2.2.1 Pharmacodynamic Activity at 5-HT_{2C} Receptors

Lorcaserin reduced food intake and decreased body weight gain in a dose-dependent manner in male and female S-D and Levin diet-induced obese (DIO) rats. These effects were reversed by selective antagonists of the 5-HT_{2C} receptor, but not by selective antagonists of the 5-HT_{2A} receptor. Daily lorcaserin ingestion was associated with significant decreases in total body fat mass. Doses of 4.5 mg/kg twice daily to 36 mg/kg twice daily were efficacious, with maximal weight effects observed at 18 mg/kg (males) and 36 mg/kg (females) twice daily. The estimated maximum plasma and brain lorcaserin concentrations at the minimum efficacious dose (4.5 mg/kg BID) are 900 nM and 20,000 nM, respectively.

7.2.2.2 *In Vivo* Selectivity: Potential Activation of 5-HT_{2A} Receptors

In rats, activation of the 5-HT_{2C} receptor in rats precipitates resting behavior and penile grooming. In contrast, 5-HT_{2A} activation in rats leads to characteristic behaviors described as wet dog shakes and back muscle fasciculations. Observations of behaviors following test article administration can therefore indicate *in vivo* receptor selectivity. Male S-D rats received lorcaserin, vehicle, the positive 2A control 2,5-dimethoxy-4-methylamphetamine (DOM), or the positive control for 2A and 2C, dexfenfluramine.

Administration of lorcaserin to male rats induced a pattern of behavior that was qualitatively and quantitatively closer to that of dexfenfluramine than of DOM (Figure 44). Regarding signs of 5-HT_{2C} activation, penile grooming was increased by both dexfenfluramine and lorcaserin at all doses, whereas it was increased by DOM only at an intermediate dose, and to approximately half the level of that achieved by the other two compounds. Inactivity also was increased by both dexfenfluramine and lorcaserin, but not by DOM. In contrast, 5-HT_{2A} signs showed the opposite pattern of effect: back muscle fasciculations were increased by DOM, whereas both dexfenfluramine and lorcaserin were without effect, and whereas DOM dose-dependently increased wet dog shakes, they were significantly increased by lorcaserin only at a single, intermediate dose. Wet dog shakes were increased by dexfenfluramine at both doses tested. The increase in wet dog shakes affected by dexfenfluramine and lorcaserin were approximately half the magnitude of the increase seen after treatment with DOM.

This experiment and a similar independent experiment show that lorcaserin is selective for the rat 5-HT_{2C} receptor relative to the 5-HT_{2A} receptor *in vivo*.

7.2.2.3 Potential Activation of 5-HT_{2B} Receptors

Activation of 5-HT_{2B} receptors in the rat can cause heart valve thickening with consequent valvular regurgitation. When serotonin or the non-selective 5-HT_{2B} agonist pergolide is given to rats, heart valve thickening is observed as early as 10 weeks at the aortic valve and by 20 weeks at the mitral valve.[110, 110-112]

In preclinical evaluations of lorcaserin at high doses (55-82 times human exposure at MRD) up to 2 years, no lorcaserin-related heart valve thickening or fibrosis was observed in any rat; nor were any lorcaserin-related effects on myocardium, endocardium, *chordae tendineae*, or pulmonary vasculature observed. The duration of exposure greatly exceeded that required for the development of serotonergic valvular toxicity in rats,[110] suggesting that lorcaserin does not induce the 5-HT_{2B}-mediated valvular abnormalities in rats that are associated with serotonin and pergolide. In addition, lorcaserin at exposures of up to 50 times human for one year did not induce changes in cardiac valves or pulmonary vasculature in monkeys.

7.3 Pharmacokinetics and Absorption, Distribution, Metabolism, and Excretion

7.3.1 Absorption, Distribution, Metabolism, and Elimination

Lorcaserin was rapidly absorbed after oral dosing ($t_{max} \leq 0.5$ h in rodents; ≤ 3.5 h in monkeys, ≤ 2.0 h in humans), and bioavailability was high (rats [94%], dogs [38%], and monkeys [49%]). Systemic accumulation of lorcaserin at steady-state was two-fold or less across species, gender, and dose. In rats, female exposure was higher than male.

Target organ CNS exposure after oral lorcaserin administration occurred rapidly. At steady-state, brain-to-plasma ratios were 26 (male mice at 50 mg/kg), 24 (male rats at 10 mg/kg), 22 (female rats at 20 mg/kg), and 10 (monkeys at 10 mg/kg). Lorcaserin CNS accumulation at steady-state was proportional to lorcaserin plasma accumulation. Following administration of [^{14}C]-lorcaserin to rats, [^{14}C]-labeled material was detected in all tissues examined, with the highest levels in gastrointestinal contents, stomach, small intestine, bladder, and lungs. Lorcaserin was moderately bound to plasma proteins (61% to 76%) across all species examined.

Lorcaserin metabolism was extensive and qualitatively similar in all species, including humans. Lorcaserin sulfamate (M1) was the major circulating metabolite in rats, mice, monkeys, and humans. The *N*-carbamoyl glucuronide of lorcaserin (M5) was observed in all species, and was the major excreted metabolite in monkeys and humans. M1 and M5 were inactive in a panel of *in vitro* binding and activity assays. M1 and M5 plasma exposure in toxicology species exceeded human exposure. No unique human metabolites were observed; all major and minor metabolites formed in humans were formed in rats, mice, or monkeys.

Lorcaserin is metabolized by multiple human cytochrome P450 (CYP) enzymes and FMO1. Multiple sulfotransferases (SULTs) and UDP-glucuronosyltransferases (UGTs) are responsible for the formation of M1 and M5, respectively. Lorcaserin is not an inhibitor of human liver microsomal CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 enzymes ($IC_{50} > 200$ µM), but is a competitive inhibitor of human microsomal CYP2D6 ($IC_{50} = 3.99$ µM). Lorcaserin shows low potential for CYP induction in human hepatocytes. It is neither a substrate nor an inhibitor of P-glycoprotein. These results suggest that lorcaserin has a low probability of drug-drug interactions with concomitant medication.

Lorcaserin is eliminated primarily in urine (> 90%) with minor amounts (< 5%) excreted in feces of rodents and primates, including humans.

7.3.2 Comparative Exposures in Humans and Animals

Table 60 summarizes the exposure multiples in toxicology species at the No Adverse Effect Levels (NOAEL), relative to human exposure at 10 mg twice daily, for toxicology and carcinogenicity studies. Human exposure was calculated in two different ways. First, the human 24-hour AUC value of 1.02 µg·h/mL was determined from simulated mixed gender human exposures based on detailed 10 mg QD plasma concentration-time profiles from a Phase 1 study. The first method was used in the original NDA submission. Second, the median steady-state AUC value of 0.964 µg·h/mL was derived from a formal population pharmacokinetic analysis of

the Phase 3 study data. For consistency with the original NDA, exposure margins in this document are based on the first value (1.02 µg·h/mL).

Table 60. Lorcaserin Exposures (AUC_{last}) and Exposure Margins in Nonclinical Species Relative to Human Exposure at 10 mg BID

Species	Duration	NOAEL (mg/kg/day)		Exposure Margin over Human at the MRD	
				Male	Female
General Toxicology Studies					
Mouse	13 weeks	50		7.6	2.3
Rat	28 days	10		2.9	4.4
	13 weeks	5		0.75	1.7
	6 months	5		1.2	2.9
Monkey	28 days	10		7.6	7.3
	13 weeks	2		1.1	0.5
	52 weeks	2		1.0	0.6
Carcinogenicity Studies	**Duration**	**AUC_{last} (µg·h/mL)**		**Exposure Margin**	
		Male	**Female**	**Male**	**Female**
Margins Calculated Using Human Exposure of 1.02 µg·h/mL[a, c]					
Mouse carcinogenicity[a]	2 years				
5 mg/kg/day		0.5	0.3	0.5	0.3
25 mg/kg/day		3.9	1.6	4	2
50 mg/kg/day		7.5	3.7	7	4
Rat carcinogenicity[a]	2 years				
10 mg/kg/day		4.8	6.9	5	7
30 mg/kg/day		16.9	24.1	17	24
100 mg/kg/day		55.9	83.8	55	82
Margins Calculated Using Human Exposure of 0.964 µg·h/mL[b, d]					
Mouse carcinogenicity[b]	2 years				
5 mg/kg/day		--	--	0.5	0.3
25 mg/kg/day		--	--	4	2
50 mg/kg/day		--	--	8	4
Rat carcinogenicity[b]	2 years				
10 mg/kg/day		--	--	5	7
30 mg/kg/day		--	--	17	25
100 mg/kg/day		--	--	58	87

Exposure margins estimated as in original NDA, using AUC of 1.02 µg·h/mL (MRD of 10 mg bid).

[a] Exposure margins estimated using AUC at steady state of 0.964 µg·h/mL (MRD of 10 mg bid, nominal Week 12 data) derived from updated Population PK Analysis.

[b] Human exposure at MRD of 10 mg BID determined from simulated mixed gender human exposures based on 10 mg QD plasma concentration-time profiles

[c] Based upon the average weight of Phase 3 patients of ~100 kg and 10 mg BID dose.

-- = no data

7.4 Nonclinical Safety Pharmacology and Toxicology

The toxicity of lorcaserin was evaluated in single-dose and repeat-dose toxicity studies in the mouse, rat, and monkey. Genotoxicity was evaluated in two *in vitro* assays and one *in vivo* assay. Two-year carcinogenicity studies were conducted in the mouse and rat. The reproductive and developmental effects of lorcaserin in rat and rabbit were also evaluated. Good laboratory practice (GLP) studies included: 1) 13-week repeat dose and 2-year carcinogenicity studies in mice; 2) 28-day, 13-week, and 6-month repeat-dose and 2-year carcinogenicity studies in rats; 3) 28-day, 13-week and 12-month repeat dose studies in monkeys.

7.4.1 CNS Safety Pharmacology

Functional observation battery (FOB) evaluations were conducted during the 28-day repeat-dose toxicity study in rats in order to assess the CNS safety profile.[113] Treatment groups of 10 S-D rats/sex were administered 0, 2, 10, and 50 mg/kg lorcaserin. Lorcaserin did not affect any variables assessed in the FOB evaluation and, therefore, a no observed effect level (NOEL) of 50 mg/kg was established. Lorcaserin plasma exposure at the NOEL in male and female rats, respectively, was 18- and 32-times greater than that in humans at the maximum recommended dose of 10 mg BID.

7.4.2 Cardiovascular Safety Pharmacology

The *in vitro* effects of lorcaserin on the hERG channel current were measured at 3, 10, 30, and 100 μM concentrations.[114] Lorcaserin produced statistically significant concentration dependent inhibition of hERG current with an estimated IC_{50} of 14 μM.

In a canine Purkinje fiber assay, lorcaserin at ≥ 30 μM induced significant prolongation of the action potential duration at 90% depolarization (APD_{90}) at all of the tested stimulus intervals ($p < 0.05$). Lorcaserin did not induce significant changes in the action potential duration at 60% repolarization (APD_{60}), resting membrane potential, action potential amplitude, or action potential maximum rate of rise at any stimulus interval or at any concentration tested, except that at 0.3 μM and 3 μM lorcaserin at a 2-second basic cycle length, the resting membrane potential was significantly reduced. None of the observed effects of lorcaserin were frequency-dependent.

Effects of lorcaserin on cardiovascular function were evaluated in monkeys.[115] Four male and three female cynomolgus monkeys were administered vehicle or lorcaserin at doses of 2, 10, or 100 mg/kg p.o. Systolic, diastolic, and mean arterial blood pressures; heart rate; body temperature; and electrocardiographic parameters were obtained. Lorcaserin doses up to 100 mg/kg did not affect any cardiovascular endpoint, and thus an NOEL of 100 mg/kg was established. At this dose in the 28-day monkey toxicology study, exposure margins over human at the MRD were 69-72 in both genders.[116]

7.4.3 Respiratory Safety Pharmacology

The effects on pulmonary function of single doses of lorcaserin (0, 2, 10, and 50 mg/kg) were studied in rats.[117] Lorcaserin had no effect on respiratory rate, tidal volume, or minute volume. An NOEL of 50 mg/kg was established.

7.4.4 Toxicology Studies

The safety of lorcaserin was evaluated in toxicity studies in the mouse, rat, and monkey. Doses and corresponding plasma exposure values are provided in Table 60.

7.4.4.1 Summary of General Toxicology Findings

In the mouse, dose-limiting toxicity was mortality, which occurred immediately after a single oral dose of 1000 mg/kg. Clonic convulsions were noted at doses of 100 mg/kg and 300 mg/kg. In repeat-dose GLP studies of 14 days and 13 weeks, mortality occurred at doses ≥ 200 mg/kg. At 350 mg/kg, treatment-related mortality occurred in 70% of males. At 250 mg/kg, in addition to mortality, mice exhibited decreased red cell mass and increased reticulocytosis, increased liver weight, centrilobular hepatocellular hypertrophy, increased extramedullary hematopoiesis and thymic necrosis. At this dose, exposure multiples in male and female mice were 35 times and 9 times that, respectively, of human exposure at the MRD of 10 mg BID. In the 13-week study, the no observed adverse effect level (NOAEL) was 50 mg/kg, at which dose a single isolated incidence of mortality, and centrilobular hepatocellular hypertrophy and pigmented splenic macrophages were observed. There was no evidence of a lorcaserin effect on heart valves or pulmonary vasculature in any of these mouse studies. The NOAEL in the 13-week study, 50 mg/kg/day, produced exposure multiples of 7.6 and 2.3 in males and females, respectively, relative to the human MRD.[118]

In the rat, the dose-limiting toxicity in the single-dose study was mortality, which occurred within 15 minutes of a 1000-mg/kg oral dose. In 10-day repeat-dose studies, no mortality was observed at doses ≤ 150 mg/kg/day. The highest dose tested in 28-day studies, 50 mg/kg/day, was associated with increased serum lipids, centrilobular hepatocellular hypertrophy, splenic extramedullary hematopoiesis, increased pigmented macrophages, and reticulocytosis, and increased kidney weights, with mild renal tubular epithelial hyperplasia in males only. A 13-week study and a 6-month study gave similar findings except there were no renal tubular epithelial changes, and increases in kidney weights were limited to the 6-month study; the NOAEL was 5 mg/kg/day, which produced exposure multiples of 1.2 and 2.9 (males and females) relative to human exposure at a dose of 10 mg BID. At the highest dose given for 6 months, 50 mg/kg/day, some mortality was observed in addition to the previously observed findings, except there were no increases in kidney weights or other renal findings; exposure multiples were 22 and 34 (males and females) times human exposure at a dose of 10 mg BID.

In cynomolgus monkeys, dose-limiting emesis occurred at 300 mg/kg single dose. In repeat-dose studies, the maximum tolerated dose was 100-125 mg/kg/day, and was associated with emesis, decreased activity, and penile extension. In a 28-day repeat-dose study, one male given 100 mg/kg/day experienced a seizure on Day 1 only and not with subsequent dosing. In the 12-month study, one male at 125 mg/kg also experienced a seizure, again on Day 1 only.

Exposure multiples of 74 and 68 (males and females) relative to human exposure at 10 mg BID were reached at a dose of 100 mg/kg/day. Reduced weight gain and food consumption occurred in 28-day, 13-week, and 12-month studies at doses ≥ 10 mg/kg/day. Cholesterol, LDL, and HDL decreased at ≥ 10 mg/kg/day in the 12-month study. Focal tubular epithelial cell regeneration was observed in the kidneys in 0/8, 1/8, 2/8, 3/8, and 6/8 animals given 0, 2, 10, 50, and 125 mg/kg lorcaserin, respectively, and focal renal tubular epithelial degeneration was observed in 1/8 monkeys at 125 mg/kg. Cystic ovarian follicles were observed in the ovaries of 0/4, 0/4, 1/4, 1/4, and 3/4 females given 0, 2, 10, 50, or 125 mg/kg lorcaserin, respectively; the finding was reversible. Based upon the equivocal finding of renal tubular epithelial regeneration, the NOAEL was considered to be 2 mg/kg/day.

7.4.4.2 Reproductive Toxicity

In a standard battery of studies in rats and rabbits, lorcaserin showed no evidence of reproductive toxicity, based on fertility, early embryonic development, and pre- and post-natal development. No adverse effect on the F_1 generation was observed.

7.4.4.3 Male Rat Carcinogenicity Study Findings

In male rats, treatment related increases in neoplasms occurred in some tissues (Table 55) that are often sites of spontaneous neoplasms (MPI historical control data). Malignant tumor increases occurred only in the high dose group (100 mg/kg).

Shown in Table 55 are plasma exposure multiples for rats, relative to human, for lorcaserin and the M1 metabolite. At the high dose, these values were 55 and 136, respectively (Table 55). For astrocytoma, brain exposure is more relevant than plasma exposure; as discussed in Section 4.3 the rat brain lorcaserin exposure at 10 mg/kg/day was ~70 times the human brain exposure at 10 mg twice daily.

Distinct mechanisms can account for the increases in the majority of neoplasms observed in male rats. These include hormone perturbation (mammary gland), metabolic overload (liver, thyroid), and toxicity/irritant effects (skin). Each of the tumor types is discussed below.

Table 61. Neoplasms Associated with Lorcaserin in Male Rats and Plasma Exposure Multiples above Human Exposure

Lorcaserin Dose (mg/kg)	0	10	30	100
Lorcaserin plasma exposure multiple over human at MRD	**NA**	**5**	**17**	**55**
M1 plasma exposure multiple over human at MRD	**NA**	**36**	**68**	**136**
Number of male rats	**65**	**65**	**65**	**75**
Mammary gland				
Adenocarcinoma	0	0	2	2
Benign fibroadenoma[a]	0	1	4	6[a]
Thyroid gland				
Follicular cell adenoma	0	5[b]	4	8[b]
Skin				
Squamous cell carcinoma[c]	0	0	4	5[c]
Brain				
Astrocytoma[d]	1	0	4	8[d]
Subcutis				
Benign fibroma[e]	3	7	11[e]	17[e]
Malignant schwannomas[f]	0	0	1	5[f]

[a] Trend is significant (p = 0.0001). Significantly different from control at 100 mg/kg (p = 0.002).
[b] Significantly different from control at 10 mg/kg (p = 0.0423) and 100 mg/kg (p = 0.0139).
[c] Trend is significant (p = 0.0008). Significantly different from control at 100 mg/kg (p = 0.0245).
[d] Trend is significant (p < 0.0001). Significantly different from control at 100 mg/kg (p = 0.0025).
[e] Trend is significant (p < 0.0001). Significantly different from control at 30 mg/kg (p = 0.0091) and 100 mg/kg (p < 0.0001).
[f] Trend is significant (p = 0.003). Significantly different from control (p = 0.0478).
NA = not applicable

Male Mammary Gland Tumors

Mammary gland adenocarcinoma was not significantly increased in male rats; benign fibroadenoma was increased at the high dose. The lorcaserin exposure margin at the mid dose, where mammary fibroadenoma was not increased over vehicle, was 17 relative to human exposure. As in females, mechanistic studies suggest that mammary tumors result from increased prolactin effects on the mammary gland, which is induced by lorcaserin (Section 4.2.2).[119, 120] As discussed below, prolactin is not typically associated with increased risk of mammary cancer in women. Moreover, serum prolactin was not increased in humans at the recommended dose of lorcaserin. Hence, even if relevant to humans, this mechanism would not be operative at therapeutic doses.

Thyroid Follicular Cell Adenoma

Thyroid adenomas were significantly increased in low- and high-dose males. The increase is attributable to induction of UGT liver enzymes, a rat-specific mechanism. UGT enzymes are responsible for T4 (thyroxine) and T3 (triiodo-thyronine) metabolism, and thyroid tumors are associated with UGT inducers such as phenobarbital when administered to rats.[121-126] UGT induction similar to that caused by phenobarbital was observed in rats following repeated oral doses of 10, 30, and 100 mg/kg lorcaserin.[123]

In rats, T4 and T3 have shorter half lives than in humans because rats lack thyroxine-binding globulin (TBG).[127] Thyroxine in rats is therefore subjected to increased metabolism by UGTs and renal elimination. The resultant chronic increase in TSH causes glandular hypertrophy. UGT induction exacerbates this effect, increasing thyroid neoplasia in rodents. The UGT induction mechanism is not considered relevant to humans.[123] Phenobarbital, a potent UGT (and CYP) inducer in both humans and rats, is only associated with thyroid tumors in rats.

Subcutaneous Fibroma and Schwannoma

In the subcutis, benign fibromas were significantly increased at the mid and high dose, and malignant schwannomas, tumors of nerve sheaths also known as neurinomas,[128] were significantly increased at the high dose. The increases occurred at 17× and 55× the human exposure at the MRD, respectively. Neither tumor type was increased in mice, which are susceptible to development of subcutaneous neoplasms.[129] Rat subcutaneous neoplasms increase with age[130] and can result from irritant effects[131] including subcutaneously injected iron dextran.[45] It is possible that these tumors were increased in male rats due to their poor general condition, as indicated by a marked reduction in body weight.

Squamous Cell Carcinoma of the Skin

Squamous cell carcinoma of the skin was increased at the high dose, where plasma drug exposure was 55x human exposure at the MRD. This tumor type was not observed in female rats, or in mice, which are susceptible to development of epidermal neoplasms.[129, 132] As with the increased subcutaneous neoplasms, squamous cell carcinoma of the skin may be related to the poor general condition of the high-dose male animals, which was indicated by marked body weight loss. Immunosuppression, which can occur with debilitation like that observed in the high dose males, may have enhanced skin tumor development.[133, 134]

7.4.4.4 Female Rat Carcinogenicity Study Findings

Increases in tumor incidences in female rats were restricted to the mammary gland, benign fibroadenoma and malignant adenocarcinoma. These results are extensively discussed in sections 5 (CRL response #1) and 6 (CRL response #2) in the main body of this document. Briefly, mammary adenocarcinoma was found by an independent Pathology Working Group to be related to lorcaserin only at the high dose (100 mg/kg/day), providing a safety margin of 24 fold over human exposure at the recommended dose. Benign fibroadenoma was increased at all 3 lorcaserin doses, with exposure at the low dose being 7 fold over human. Evidence of a prolactin mechanism, reasonably irrelevant to human risk, was developed for both of these mammary tumor types.

Appendix 3 Clinical Pharmacology

7.5 Overview of Clinical Pharmacology Trials

Lorcaserin had consistent and highly predictable pharmacokinetic properties in clinical studies, both in healthy subjects and in the target patient population of overweight and obese adults. The pharmacokinetic properties of lorcaserin were evaluated in individual clinical studies and by using a population approach. No significant effects of gender, race, or age were observed. Body weight had a minor effect on lorcaserin exposure in repeated dose studies. Exposure of lorcaserin metabolites M1 (lorcaserin sulfamate) and M5 (*N*-carbamoyl glucuronide of lorcaserin), but not lorcaserin, was increased in subjects with severe renal impairment or with end stage renal disease requiring hemodialysis. Mild or moderate hepatic impairment slightly increased lorcaserin exposure; however, the magnitude should not necessitate dose adjustment. The only drug-drug interaction identified was minimal to moderate inhibition of CYP2D6; the magnitude of the effect was substantially less than that reported for poor metabolizers, and should not warrant lorcaserin dose adjustment.

7.6 Pharmacokinetics

The clinical evaluation of lorcaserin's pharmacokinetic properties included single- and multiple-dose studies in healthy subjects (APD356-001 and APD356-002), assessments of renal or hepatic impairment and elderly age (APD356-016, APD356-017, and APD356-018, respectively), drug-drug interaction with a CYP2D6 substrate (APD356-008 and APD356-012), food effects (APD356-015), and sampling during Phase 2 and Phase 3 efficacy studies (APD356-003, APD356-004, APD356-009, and APD356-011).

7.6.1 Absorption, Distribution, Metabolism, and Excretion

Lorcaserin is rapidly absorbed, reaching peak concentrations at a median 1.5-2 hours following a dose. Greater than 90% of the administered dose is absorbed. Lorcaserin is moderately bound to human plasma proteins (~70%). Red blood cell partitioning is minimal. The estimated volume of distribution (V/F) is 252 L in a 92.5-kg subject. Preclinical studies of rats and cynomolgus monkeys showed that lorcaserin had higher exposure in the brain relative to plasma, with steady state brain-to-plasma ratio of 10 and 24 in the monkey and rat, respectively. Accumulation in the brain paralleled that in plasma with repeat dosing.

Lorcaserin is eliminated primarily by metabolism. The majority of a single radioactively labeled dose of lorcaserin is recovered in urine (92.3%) and feces (2.2%). Less than 1% of the dose was recovered from the urine as intact parent drug; the remainder comprised metabolites formed by glucuronidation, sulfate conjugation, and oxidation. The major circulating metabolite is the sulfamate of lorcaserin (M1); the major urinary metabolite is the *N*-carbamoyl glucuronide of lorcaserin (M5). Neither M1 nor M5 had significant binding activity at a large panel of receptors, transporters, and ion channels. All circulating lorcaserin metabolites identified in humans were also present in at least one species evaluated in toxicology studies. Multiple pathways were identified for lorcaserin metabolism; in addition, multiple enzymes are involved in each of the major metabolic pathways. These observations suggest that there is a low probability that the

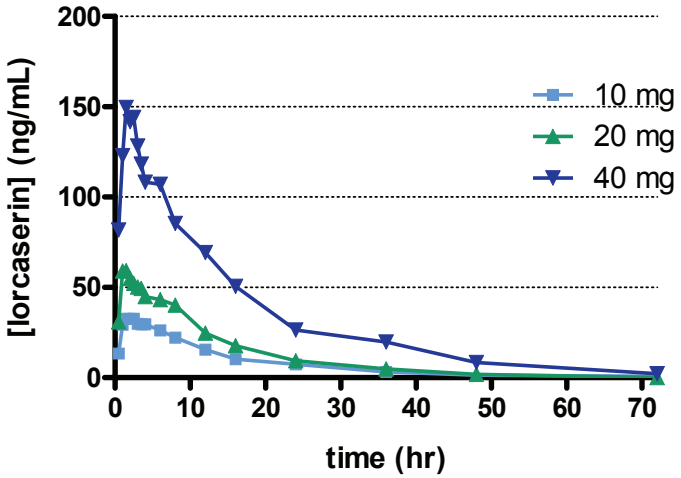
overall pharmacokinetic profile of lorcaserin will be affected due to drug-drug interactions by concomitant medications.

7.6.2 Single Dose and Repeat Dose Pharmacokinetics

7.6.2.1 Plasma Exposure

In single dose studies, lorcaserin C_{max} and AUC increased proportionally with dose, with no change in t_{max} (Figure 46). In multiple-dose studies, exposure also increased proportionally with dose.

Figure 46. Concentration versus Time Plot for Single Dose Lorcaserin in Healthy Subjects



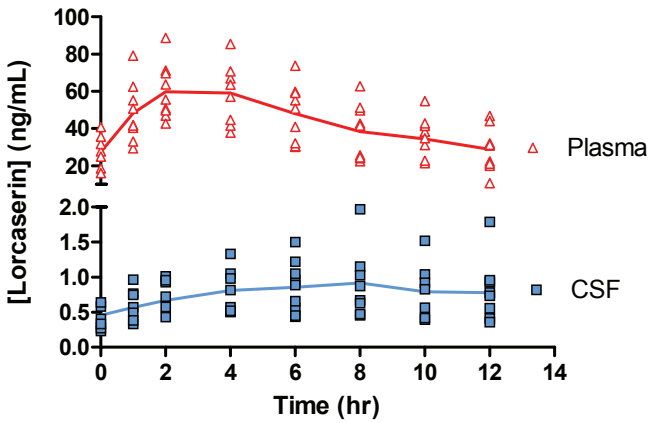
After repeat once-daily dosing, lorcaserin accumulated modestly, as reflected by small increases in C_{max} and AUC. CLl/F, V/F, and $t_{1/2}$ were independent of dose and time.

In healthy subjects, the predicted steady-state AUC_{24h} value after 10 mg BID dosing was 1020 h·ng/mL. The predicted plasma lorcaserin exposure after 10 mg BID dosing was 2-fold higher compared to actual QD exposures. In a formal population PK analysis, the median steady-state lorcaserin AUC_{24h} after 10 mg BID dosing is 964 h·ng/mL.

7.6.2.2 Cerebrospinal Fluid Exposure

Lorcaserin 10 mg BID was administered orally once daily to 11 healthy obese or overweight volunteers. After 6.5 days (steady state), cerebrospinal fluid and plasma were collected at pre-specified time after the morning dose (Figure 47). The average CSF-to-plasma ratio was 0.017. Brain exposure was estimated using the mean (SD) measured CSF:brain ratio (from mice, rats and cynomolgus monkeys) of 101 (18). Using this approach, brain exposure is estimated to be 1.7 times plasma exposure when lorcaserin 10 mg BID is dosed to steady state.

Figure 47. Post-dose Lorcaserin Concentrations in Plasma and CSF after Dosing 10 mg BID to Steady State



7.6.3 Effect of Intrinsic Factors on Pharmacokinetics

Formal clinical studies evaluated the effects of age, gender, renal function, and hepatic function on the pharmacokinetic properties of lorcaserin. These factors and race were also evaluated using a population PK approach, incorporating data from the single and multiple dose studies of healthy subjects and the two Phase 3 studies. Gender and race did not affect apparent lorcaserin clearance or volume of distribution in population PK modeling.

7.6.3.1 Effects of Age

In the APD356-018 study, which compared lorcaserin PK in overweight or obese adults 18 - 65 years old to overweight or obese elderly adults > 65 years old, C_{max} values were slightly lower in the elderly group compared to the adult group (geometric mean ratio of 0.83). The population PK modeling showed a small, clinically insignificant effect of age on CL/F. Simulations within the population PK analysis showed that an increase of < 10% in lorcaserin concentrations is predicted with a doubling of age from 30 to 60 years. The minimal reduction in C_{max} from the APD356-018 study and the results from the population pharmacokinetic analysis suggest that overall difference in exposure (AUC and C_{max}) between young and elderly is minimal and not clinically significant.

7.6.3.2 Body Weight

Body weight slightly, but significantly, affected predicted lorcaserin exposure in population PK models. Patients with lower body weights are predicted to have slightly higher lorcaserin exposure as compared to patients with higher body weight (Table 63). This prediction is correlated with slightly greater efficacy for weight loss among patients with the lowest baseline body weight in the pooled Phase 3 studies as compared to those with the highest baseline body weights.

7.6.3.3 Renal Impairment

Single 10 mg doses of lorcaserin were administered to subjects with normal renal function, or renal impairment ranging from mild to end stage (based on Cockcroft-Gault creatinine clearance) in study APD356-016. C_{max} values were moderately lower for the mild, moderate, and severe renal impairment subjects. AUC values were higher for the mild renal impairment group, slightly higher for the moderate renal impairment group and lower for the severe renal impairment group relative to the normal renal function group. Although lorcaserin exposure was not substantially correlated with renal function, the exposure of metabolite M1 and, to a lesser extent, M5 was markedly increased in subjects with severe renal impairment or end stage renal impairment requiring hemodialysis. Lorcaserin and M1 were not cleared by hemodialysis; M5 was partially cleared by hemodialysis.

Although substantial margins exist for exposures of metabolites M1 and M5 in nonclinical toxicology studies over those measured in this single-dose human renal impairment study, experience at these higher levels in humans is limited to this study. Based on the increased exposures of the M1 and M5 metabolites, lorcaserin should not be used in patients with severe renal impairment or end-stage renal disease unless further studies are conducted to explore appropriate dosing and demonstrate chronic safety in this population.

7.6.3.4 Hepatic Impairment

Single 10 mg doses of lorcaserin were administered to subjects with normal hepatic function, mild hepatic impairment or moderate hepatic impairment as defined by the Child-Pugh classification scheme in study APD356-017. In subjects with mild and moderate hepatic impairment, C_{max} following a single 10 mg dose was slightly decreased by 8% and 14%, respectively; AUC was slightly increased by 25% and 30%, respectively. These increases are not considered large enough to recommend dose adjustments for hepatic impairment of moderate or lesser severity.

Formal population pharmacokinetic analysis showed that serum alanine transaminase and bilirubin, as measures of liver function, were not correlated with lorcaserin pharmacokinetic parameters.

7.6.4 Effect of Extrinsic Factors on Pharmacokinetics

7.6.4.1 Effects of Diet

The effect of a high fat meal on the pharmacokinetic properties of lorcaserin was evaluated using an early development formulation (Study APD356-001B) and again using the market-image formulation (Study APD356-015). Overall lorcaserin exposure was unaffected by a high fat meal as compared to the fasting state. However, t_{max} was slightly delayed from a median value of 1.5-2 hours to a value of ~3 hours. This small effect will not necessitate special dosing instructions related to meals.

7.6.4.2 Drug-drug Interactions

EFFECTS OF LORCASERIN ON CONCOMITANT MEDICATIONS

Extensive *in vitro* characterization of lorcaserin identified only weak inhibition of CYP2D6 (IC_{50} = 3.99 μM) as a potential concern for drug-drug interactions. Accordingly, two clinical studies were conducted to evaluate the effect of lorcaserin on the metabolism of the CYP2D6 substrate dextromethorphan. Lorcaserin increased the exposure of dextromethorphan after 20 mg QD or 10 mg BID dosing under steady-state conditions. The increase in exposure after the 10 mg BID dose, the maximum dose used in the Phase 3 clinical studies, was approximately 2-fold, suggesting that lorcaserin minimally to moderately inhibits metabolism of the sensitive CYP2D6 probe substrate dextromethorphan.

EFFECTS OF CONCOMITANT MEDICATIONS ON LORCASERIN

No formal analyses of the effect of other agents on lorcaserin were performed. Because lorcaserin is metabolized by multiple pathways and multiple enzymes, single concomitant agents are predicted to have minimal impact on lorcaserin exposure. A wide spectrum of concomitant medications were permitted in the Phase 3 trials, and the coefficient of variation (CV) for lorcaserin exposure was very small (~34%) in the population PK analysis.

7.7 Population Pharmacokinetics

Population pharmacokinetic (PK) and pharmacodynamic (PD) analyses were performed for lorcaserin. Five clinical trials were included in the analyses: Phase 1 studies in healthy volunteers (n = 59) with well defined lorcaserin plasma concentration-time profiles, APD356-001A (single dose) and APD356-002 (multiple dose); and pivotal Phase 3 studies in obese/overweight patients (n = 1004) with sparse PK sampling, APD356-009, APD356-010, and APD356-011.

A one-compartment model best described the lorcaserin plasma concentration-time profile. Statistical analyses showed no significant differences in lorcaserin PK parameters across the four multiple dose studies, establishing a lack of difference in pharmacokinetic behavior between healthy volunteers and obese/overweight patients. Modeled exposures were similar in the Phase 3 studies of non-diabetic patients (Table 62). Lorcaserin clearance was slightly higher in patients with Type 2 diabetes; exposures were somewhat lower than in non-diabetics (Table 62).

Table 62. Observed Lorcaserin Plasma Concentrations and Modeled Exposure at Steady-State in Phase 3 Studies

PK Parameters Mean (SE)	APD356-009	APD356-011		APD356-010	
	10 mg BID (n=248)	10 mg QD (n=105)	10 mg BID (n=238)	10 mg QD (n=75)	10 mg BID (n=217)
C_{min} (ng/mL)	27.2 (0.99)	11.6 (1.2)	25.8 (1.1)	7.1 (6.3)	19.3 (12.4)
C_{max} (ng/mL)	56.8 (1.39)	39.7 (1.8)	56.1 (1.6)	32.9 (14.0)[a]	42.8 (16.3)[a]
C_{ss} (ng/mL)	44.0 (0.95)	23.8 (0.85)	43.1 (0.92)	nd	nd
$AUC_{ss,24h}$ (μg·h/mL)	1.05 (0.02)	0.57 (0.02)	1.04 (0.02)	nd	nd

nd, not determined

[a] C_{min}, pre-dose; C_{max} approximated by 2 h post-dose sample

The covariates tested were age, body weight, BMI, ALT, bilirubin, creatinine clearance, ideal body weight, sex, and formulation). The final model incorporated the following as covariates: body weight, CL/F, diabetic status (effect on CL/F), and formulation effect on bioavailability. The exposure of lorcaserin is predicted to be higher in patients with lower body weight. However, the overall significance is modest, as exemplified by the difference in the simulated lorcaserin exposure (AUC_{ss} and C_{ss}) based on the final population pharmacokinetic model for a 75-kg, 92.5-kg (median body weight of the population pharmacokinetic data set), and a 125-kg subject. The predicted percent change in lorcaserin exposure was approximately 20% relative to median body weight (92.5 kg) and thus, the clinical difference is predicted to be modest. Actual Phase 3 exposure data are summarized in Table 63.

A question of particular relevance is how lorcaserin exposure might be affected by weight loss during treatment. To investigate this question, a simulation was performed for a hypothetical single subject receiving 10 mg lorcaserin BID weighing 125 kg who then lost 10% of his body weight. The steady-state lorcaserin concentration-time profiles indicate that following a 10% loss of body weight in a subject receiving 10 mg BID lorcaserin there will be less than a 10% increase in lorcaserin exposure. These data imply that lorcaserin dose and dosing regimen will not require adjustment following reduction in body weight.

7.7.1 Population Pharmacokinetics/Pharmacodynamics

For the population PK/PD analysis, overweight and obese patients from Phase 3 clinical studies APD356-009, APD356-010, and APD356-011 were used to evaluate the exposure response relationship of lorcaserin. For the analysis, a continuous population PK/PD model was created to predict the percent body weight loss for patients receiving a placebo dose or a 10 mg QD or BID dose of lorcaserin. Individual estimates for the exposure of lorcaserin over 24 hours ($AUC_{ss,24hr}$) were calculated from the population PK model. Based on the population PK/PD analysis, the time to reach 50% of maximal weight loss was approximately 8 weeks. The predicted time to reach maximal effects was approximately 32 weeks, which is in good agreement with the observed weight loss results. The predicted maximal weight loss for a 92.5-kg patient receiving a 10 mg QD or BID dose of lorcaserin was approximately 6% and 8%, respectively. Patients with diabetes were predicted to lose less weight than non-diabetics. No other covariates (i.e., age, ALT, bilirubin, baseline body weight, creatinine clearance, race, and sex) significantly affected the time to reach maximal effect or maximal weight loss.

In addition to the continuous PK/PD model, a logistic regression analysis for $\geq 5\%$ and $\geq 10\%$ body weight loss versus lorcaserin exposure ($AUC_{ss,24hr}$) was performed. Based on the logistic regression analysis, there was a higher probability of achieving $\geq 5\%$ and $\geq 10\%$ body weight loss with increasing exposure of lorcaserin. The results of the continuous and logistic regression analysis demonstrate a pharmacodynamic relationship between lorcaserin exposure and weight loss.

7.7.2 Genetic Differences in Response

Because the metabolism of lorcaserin is mediated through multiple pathways and enzymes, no single genetic difference is predicted to significantly affect lorcaserin pharmacokinetic parameters. No formal analysis was performed within clinical trials.

7.7.3 Observed Lorcaserin Exposures in Phase 3 Clinical Trials

The actual lorcaserin concentrations measured at Week 52 in patients in Phase 3 trials are summarized in Table 63. The summary illustrates that exposure was dose-related, and the lorcaserin concentrations were consistently slightly greater in patients with lower body weights than in those with higher body weights, as predicted by population PK modeling.

Table 63. Observed Lorcaserin Plasma Concentrations at Week 52: Studies APD356-009 and APD356-011

	Lorcaserin 10 mg QD			Lorcaserin 10 mg BID		
Mean (SE)	n	Change from Baseline Weight (kg)	Concentration (ng/mL)	n	Change from Baseline Weight (kg)	Concentration (ng/mL)
All Patients						
Pre-Dose	73	-7.4 (0.7)	11.6 (1.2)	186	-8.4 (0.5)	25.8 (1.1)
2 hours Post-Dose	84	-6.4 (0.7)	39.7 (1.8)	191	-8.2 (0.5)	56.1 (1.6)
Body Weight Quartiles						
Pre-Dose						
Q1 (< 88.3 kg)	21	-8.0 (1.3)	13.4 (3.5)	41	-7.9 (1.0)	29.3 (2.4)
Q2 (88.3 - 98.7 kg)	17	-7.4 (1.3)	13.7 (2.4)	62	-8.1 (0.9)	29.2 (2.1)
Q3 (> 98.7 - 110.5 kg)	18	-7.7 (1.8)	10.6 (1.3)	41	-7.8 (1.1)	22.9 (1.8)
Q4 (> 110.5 kg)	17	-6.2 (1.4)	8.3 (0.8)	42	-10.0 (1.3)	20.3 (1.5)
2 hours Post-Dose						
Q1 (< 88.3 kg)	22	-6.3 (1.7)	48.5 (3.8)	41	-7.9 (1.0)	65.1 (4.0)
Q2 (88.3 - 98.7 kg)	24	-5.5 (1.3)	42.8 (3.1)	62	-7.9 (0.9)	61.8 (2.9)
Q3 (> 98.7 - 110.5 kg)	19	-7.8 (1.7)	35.0 (3.5)	44	-7.6 (1.0)	49.4 (3.0)
Q4 (> 110.5 kg)	19	-6.1 (1.4)	30.4 (2.1)	44	-9.6 (1.2)	46.3 (2.4)

Note: Only Subjects with non-missing plasma concentration and change from baseline weight values are included. Plasma concentration values of <LLOQ are set to missing.

7.8 Pharmacodynamics

Lorcaserin is a selective agonist of the 5-HT_{2C} receptor. In extensive *in vitro* evaluations, lorcaserin exerted no activity at a panel of other receptors, transporters or ion channels when tested at concentrations of 1 or 10 μM. These *in vitro* concentrations are well above the 230 nM (~45 ng/mL) steady state plasma concentrations observed at the recommended clinical dose of 10 mg BID. Lorcaserin activates the 5-HT_{2A} and 5-HT_{2B} receptors *in vitro* with potencies approximately $1/14^{th}$ and $1/61^{th}$ the potency at the 5-HT_{2C} receptor. Its major pharmacological effect is therefore predicted to be decreased food intake, with consequent weight loss. The EC_{50} of lorcaserin at the 5-HT_{2C} receptor in *in vitro* functional assays is ~39 nM.

7.8.1 Concentration-effect Relationships

The Phase 1 APD356-001C study evaluated the effects of lorcaserin at 3 doses on caloric consumption during a standard meal. A single dose of 10 mg, but not 0.1 mg or 1 mg, decreased food consumption by healthy non-obese subjects. The plasma lorcaserin concentrations

measured at around the time of the predicted C_{max} were 31.5 ng/mL (~161 nM) after a 10 mg dose, 2.82 ng/mL (~14 nM) after 1 mg, and below the limit of detection at 0.1 mg.

In Phase 1 studies, doses of lorcaserin ≥ 20 mg were less well tolerated than lower doses, due primarily to increased incidences of transient headache, dizziness, and nausea. Doses less that 20 mg were therefore chosen for Phase 2 exploration.

Phase 2 studies APD356-003 and APD356-004 made preliminary assessments of lorcaserin's efficacy for weight reduction, and established dose-response relationships. In the 4-week APD356-003 study, daily oral doses of 1 mg, 5 mg, and 15 mg were administered; 15 mg QD caused significant weight loss, while 1 mg and 5 mg did not. Trough lorcaserin concentration measured pre-dose at steady state (Day 8) was 0.86 ng/mL (~4.4 nM), 4.62 ng/mL (~23.6 nM) and 14.37 ng/mL (~73.4 nM) in the 1, 5, and 15 mg QD groups, respectively. In the 12-week APD356-004 study, lorcaserin doses of 10 mg QD, 15 mg QD, and 10 mg BID produced significant dose-related efficacy. Corresponding pre-dose exposures at steady state (Day 15) were 12.98 ng/mL (~66.3 nM), 16.97 ng/mL (~86.7 nM) and 25.72 ng/mL (~131.4 nM). These data indicated that efficacy was related to dose and exposure, and doses of at least 10 mg QD were required to achieve significant weight reduction.

In Phase 3 studies of efficacy and safety, doses of 10 mg QD and 10 mg BID produced significant weight loss at 1 year; the 10 mg BID dose also achieved significant maintenance of weight loss at 2 years (10 mg QD dose not tested in Year 2). As discussed in 7.7.1, population PK/PD modeling demonstrated a significant positive correlation between lorcaserin exposure and weight loss. Consistent with the model, the 10 mg BID dose had significantly greater efficacy for weight loss than did the 10 mg QD dose in the APD356-011 study and in the pooled analysis of APD356-009 and APD356-011. However, observed efficacy for weight loss in the APD356-010 study was essentially equivalent with the once daily and twice daily doses. The reason underlying the lack of dose-response for weight loss in the APD356-010 study is not known.

There was no relationship between lorcaserin exposure and FDA-defined valvulopathy.

7.8.2 Pharmacodynamic Drug-Drug Interactions

No formal evaluation was performed to detect the effects of concomitant medications on the efficacy of lorcaserin. Based on the diverse pathways involved in lorcaserin metabolism, no single concomitant agent is predicted to significantly impact lorcaserin exposure, and therefore, lorcaserin efficacy. Population PK modeling identified only body weight as a potential factor predicted to influence lorcaserin efficacy. As discussed above, the magnitude of the body weight effect is too small to justify dose adjustments.

7.9 Conclusions

Lorcaserin is a selective 5-HT_{2C} agonist that has been developed as a 10 mg tablet formulation with predictable, dose-proportional exposure. Exposure was slightly negatively correlated with baseline body weight; no other demographic, intrinsic or extrinsic factors that significantly affect lorcaserin exposure were identified. Severe or end stage renal impairment significantly increased M1 and M5 exposure, leading to the recommendation that lorcaserin not be administered to patients with creatinine clearance $\leq$ 30 mL/min unless further studies are conducted in this population. No other factors requiring dose adjustments were identified. The relationship between exposure and weight loss response was consistent across clinical trials. There was no relationship between exposure and FDA-defined valvulopathy.

Appendix 4 Clinical Efficacy Additional Analyses

Table 64. Patient Demographics in Non-diabetic Phase 3 Studies APD356-009 and APD356-011: Safety Population

Parameter [a]	APD356-009 (Year 1)		APD356-011		
	Lorcaserin 10 mg BID N = 1593	Placebo N = 1584	Lorcaserin 10 mg QD N = 801	Lorcaserin 10 mg BID N = 1602	Placebo N = 1601
Age (years)					
Mean ± SD	43.8 ± 11.32	44.4 ± 11.11	43.8 ± 11.66	43.8 ± 11.81	43.7 ± 11.76
Range	18 – 66	18 – 66	18 – 65	18 – 65	18 – 65
Groups, n (%)					
18 – 24	75 (4.7)	76 (4.8)	51 (6.4)	110 (6.9)	91 (5.7)
25 – 34	288 (18.1)	253 (16.0)	143 (17.9)	267 (16.7)	311 (19.4)
35 – 44	438 (27.5)	450 (28.4)	211 (26.3)	433 (27.0)	419 (26.2)
45 – 54	484 (30.4)	470 (29.7)	224 (28.0)	451 (28.2)	440 (27.5)
55 – 65	307 (19.3)	334 (21.1)	172 (21.5)	341 (21.3)	340 (21.2)
>65	1 (0.1)	1 (0.1)	0	0	0
Sex Female	1321 (82.9)	1331 (84.0)	656 (81.9)	1289 (80.5)	1249 (78.0)
Male	272 (17.1)	253 (16.0)	145 (18.1)	313 (19.5)	352 (22.0)
Race[b], n (%)					
Asian	12 (0.8)	9 (0.6)	3 (0.4)	12 (0.7)	10 (0.6)
Black	298 (18.7)	298 (18.8)	160 (20.0)	306 (19.1)	319 (19.9)
White	1081 (67.9)	1046 (66.0)	538 (67.2)	1080 (67.4)	1064 (66.5)
Hispanic	181 (11.4)	213 (13.4)	86 (10.7)	174 (10.9)	181 (11.3)
NAI/AN	11 (0.7)	4 (0.3)	7 (0.9)	7 (0.4)	10 (0.6)
NH/PI	1 (0.1)	3 (0.2)	4 (0.5)	10 (0.6)	6 (0.4)
Other	9 (0.6)	11 (0.7)	3 (0.4)	13 (0.8)	11 (0.7)
Mean (± SD) BMI (kg/m^2)	36.20 ± 4.260	36.15 ± 4.271	35.76 ± 4.253	35.97 ± 4.249	35.89 ± 4.140
BMI Range (kg/m^2)	26.8 – 46.2	26.7 – 46.5	27.1 – 45.0	27.0 – 53.0	27.0 – 45.0
BMI groups, n (%)					
< 30 kg/m^2	87 (5.5)	76 (4.8)	32 (4.0)	75 (4.7)	55 (3.4)
30 ≤ 35 kg/m^2	602 (37.8)	640 (40.4)	364 (45.4)	655 (40.9)	685 (42.8)
35 ≤ 40 kg/m^2	569 (35.7)	536 (33.8)	248 (31.0)	542 (33.8)	538 (33.6)
>40 kg/m^2	335 (21.0)	332 (21.0)	157 (19.6)	330 (20.6)	323 (20.2)
Weight (kg)					
Mean ± SD	100.43 ± 15.721	99.70 ± 15.564	99.76 ± 16.595	100.12 ± 15.547	100.47 ± 16.185
Range	62.6 – 156.9	62.7 – 156.0	67.1 – 183.3	64.1 – 158.0	64.0 – 165.2

[a] APD356-009 and Pooled demographic data were based on baseline visit, APD356-011 demographics were based on screening visit

[b] NAI/AN: North American Indian/Alaska Native, NH/PI: Native Hawaiian/Pacific Islander

7.10 Sensitivity Analyses of the Year 1 Primary Endpoints in Additional Patient Populations and with Additional Imputation Methods

Analyses of the proportion of patients achieving ≥ 5% weight loss using the Per Protocol/ Completer and "Returning Dropout" (RDP/Wk52) populations also showed lorcaserin to be superior to placebo (Table 6). As expected, greater efficacy was observed in all treatment groups in the Completer population as compared with the MITT population.

Analyses of the Per Protocol/Completer and RDP/Wk52 populations for mean weight loss also showed lorcaserin to be superior to placebo (Table 7). Efficacy was greater in the Completer populations than in the MITT population in all treatment groups.

Analyses of the proportion of patients achieving ≥ 10% weight loss using the Per Protocol/ Completer and RDP/Wk52 populations also showed lorcaserin to be superior to placebo (Table 8).

Mean weight change in responders, defined as those who lost at least 5% of their starting body weight at Week 52, was also determined. Weight loss in responders without diabetes (APD356-009 + APD356-011) was 11.2% in the lorcaserin BID group, 0.8% greater than in placebo responders. In patients with type 2 diabetes (APD356-010), weight loss was 10.4% in the lorcaserin BID group, 1.9% greater than in the placebo group. Although weight loss was only slightly greater in lorcaserin than in placebo responders, twice as many lorcaserin treated as compared to placebo treated patients achieved this degree of weight loss.

Additional sensitivity analyses were conducted using the data from individual studies and pooled studies APD356-009 and APD356-011 (lorcaserin 10 mg BID vs. placebo). Categorical and mean weight loss endpoints were analyzed using a repeated measures analysis and multiple imputation with the MITT population. The true ITT population (all randomized patients, even if no study medication was taken) was analyzed using baseline observation carried forward (BOCF) imputation for missing values. Each of the analyses confirmed the results of the primary analysis using the MITT population with LOCF imputation (Table 65, Table 66, and Table 67).

Table 65. Summary of Sensitivity Analyses of Mean Weight Change in Phase 3 Studies: MITT/Repeated Measures and ITT/BOCF

		MITT/Repeated Measures			ITT/BOCF			Responders[a]	
Study	**Parameter**	**Placebo**	**Lorcaserin 10 mg BID**	**p-Value**	**Placebo**	**Lorcaserin 10 mg BID**	**p-Value**	**Placebo**	**Lorcaserin 10 mg BID**
APD356-009									
	N	1498	1537		1587	1595		304	732
	Baseline (mean)	--	--		99.67	100.40		98.8	99.1
	Change from Baseline, kg[b]	-2.57	-6.68		-1.48	-4.33		-10.0	-10.9
	Diff in LS Means (95% CI)		-4.11 (-4.48, -3.74)	< 0.001		-2.85 (-3.25, -2.46)	< 0.001	--	--
	Change from Baseline, %[a]	-2.57	-6.67	< 0.001	-1.48	-4.38	< 0.001	-10.1	-11.1
APD356-011									
	N	1539	1560		1603	1603		383	728
	Baseline (mean)	--	--		100.8	100.47		99.9	98.8
	Change from Baseline, kg[b]	-3.24	-6.58		-2.04	-4.46		-10.5	-11.1
	Diff in LS Means (95% CI)		-3.34 (-3.72, -2.96)	< 0.001		-1.71 (-2.24, -1.18)	< 0.001	--	--
	Change from Baseline, %[a]	-3.24	-6.68	< 0.001	-2.04	-4.53	< 0.001	-10.5	-11.3
Pooled Studies APD356-009 and -011									
	N	3037	3097		3190	3198		687	1460
	Baseline (mean)	--	--		100.2	100.4		99.4	99.0
	Change from Baseline, kg[b]	-2.92	-6.63		-1.8	-4.4		-10.3	-11.0
	Diff in LS Means (95% CI)		3.71 (-3.98, -3.44)	< 0.001		-2.64 (-2.93, -2.35)	< 0.001	--	--
	Change from Baseline, %[a]	-2.91	-6.72	< 0.001	-1.76	-4.40	< 0.001	-10.3	-11.2
APD356-010									
	N	248	251		253	256		40	94
	Baseline (mean)				102.3	103.5		101.7	102.0
	Change from Baseline, kg[b]	-2.1	-5.1		-1.35	-3.91	< 0.001	-8.72	-10.6
	Diff in LS Means (95% CI)		-2.99 (-3.74, -2.23)			-2.53 (-3.42, -1.65)		--	--
	Change from Baseline, %[a]	-2.1	-5.1	< 0.001	-1.29	-3.80	< 0.001	-8.52	-10.4

Note: Responders column presents summary statistics only.

[a] Responders population: all patients who achieved at least 5% weight loss from baseline at Week 52 using the MITT population with LOCF imputation, derived from pooled dataset (APD356-009 and APD356-011)

[b] Change from baseline in LS mean body weight.

-- not calculated

Table 66. Summary of Sensitivity Analyses of Categorical Weight Loss Endpoints for Patients achieving ≥5% Weight Loss: ITT/BOCF

	ITT/BOCF			Responders[a]	
Study Parameter	**Placebo**	**Lorcaserin 10 mg BID**	**p-Value**	**Placebo**	**Lorcaserin 10 mg BID**
% of Patients Achieving ≥ 5% Weight Loss at Week 52					
APD356-009					
N	1587	1595		304	732
n (%)	225 (14.2)	567 (35.6)		304 (100.0)	732 (100.0)
Diff in % (95% CI)		21.4 (18.5, 24.3)	< 0.001		--
Odds Ratio (95% CI)		3.4 (2.8, 4.0)			--
APD356-011					
N	1603	1603		383	728
n (%)	293 (18.3)	581 (36.2)		383 (100.0)	728 (100.0)
Diff in % (95% CI)		18.0 (15.0, 21.0)	< 0.001		--
Odds Ratio (95% CI)		2.5 (2.2, 3.0)			--
Pooled APD356-009 and APD356-011					
N	3190	3198		687	1460
n (%)	516 (16.2)	1143 (35.7)		687 (100.0)	1460 (100.0)
Diff in % (95% CI)		19.6 (17.5, 21.7)	< 0.001		--
Odds Ratio (95% CI)		2.9 (2.6, 3.3)			--
APD356-010					
N	253	256		40	94
n (%)	29 (11.5)	78 (30.5)	< 0.001	40 (100.0)	94 (100.0)
Diff in % (95% CI)		19.0 (12.2, 25.9)			--
Odds Ratio (95% CI)		3.41 (2.1, 5.5)			--

Note: Responders column presents summary statistics only.

[a] Responders population: all patients who achieved at least 5% weight loss from baseline at Week 52 using the MITT population with LOCF imputation, derived from pooled dataset (APD356-009 and APD356-011).

-- not calculated

Table 66. Summary of Sensitivity Analyses of Categorical Weight Loss Endpoints for Patients achieving ≥10% Weight Loss: ITT/BOCF and Week 52 Populations (cont.)

Study Parameter				Responders[a]	
	Placebo	Lorcaserin 10 mg BID	p-Value	Placebo	Lorcaserin 10 mg BID
% of Patients Achieving ≥ 10% Weight Loss at Week 52					
APD356-009					
N	1587	1595		304	732
n (%)	94 (5.9)	303 (19.0)		116 (38.2)	34.7 (47.4)
Diff in % (95% CI)		13.1 (10.8, 15.3)	< 0.001		--
Odds Ratio (95% CI)		3.8 (2.9, 4.8)			--
APD356-011					
N	1603	1603		383	728
n (%)	131 (8.2)	319 (19.9)		148 (38.6)	348 (47.8)
Diff in % (95% CI)		11.7 (9.4, 14.1)	< 0.001		--
Odds Ratio (95% CI)		2.8 (2.3, 3.5)			--
Pooled APD356-009 and APD356-011					
N	3190	3198		687	1460
n (%)	225 (7.1)	617 (19.3)		264 (38.4)	695 (47.6)
Diff in % (95% CI)		12.2 (10.6, 13.9)	< 0.001		--
Odds Ratio (95% CI)		3.2 (2.7, 3.7)			--
APD356-010					
ITT/BOCF					
N	253	256		40	94
n (%)	10 (4.0)	36 (14.1)	< 0.001	11 (27.5)	41 (43.6)
Diff in % (95% CI)		10.1 (5.2, 15.0)	< 0.001		--
Odds Ratio (95% CI)		4.0 (2.0, 8.3)			--

Note: Responders column presents summary statistics only.

[a] Responders population: all patients who achieved at least 5% weight loss from baseline at Week 52 using the MITT population with LOCF imputation, derived from pooled dataset (APD356-009 and APD356-011).

-- not calculated

Table 67. Sensitivity Analysis of Primary Endpoints in Phase 3 Studies using Multiple Imputation: MITT Population

	Placebo N=3190	Lorcaserin 10 mg BID N=3198	Between Treatment Comparison		
Pooled Studies APD356-009 and -011					
CATEGORICAL ENDPOINTS			**Diff in Proportion (95% CI)[a]**	**Odds Ratio (95% CI)[b]**	**p-Value[b]**
% achieving ≥ 5% weight loss					
n(%)	947 (29.7)	1719 (53.7)	24.1 (21.0, 27.1)	2.78 (2.40, 3.15)	< 0.001
% achieving ≥ 10% weight loss					
n(%)	367 (11.5)	866 (27.1)	15.6 (13.3, 17.8)	2.89 (2.41, 3.37)	< 0.001
CONTINUOUS ENDPOINTS			**Diff in LS Means (95% CI)**		**p-Value**
Change from baseline in weight (kg)					
LS mean (SEM)	-2.43 (0.15)	-6.04 (0.16)	-3.60 (-4.02, -3.19)	--	< 0.001
% Change from baseline weight (%)					
LS mean (SEM)	-2.43 (0.15)	-6.12 (0.16)	-3.69 (-4.10, -3.28)	--	< 0.001
	Placebo N=256	**Lorcaserin 10 mg BID N=253**	**Between Treatment Comparison**		
Study APD356-010					
CATEGORICAL ENDPOINTS			**Diff in Proportion (95% CI)[a]**	**Odds Ratio (95% CI)[b]**	**p-Value[b]**
% achieving ≥ 5% weight loss					
n(%)	46 (18.2)	112 (43.9)	25.7 (17.5, 34.0)	3.6 (2.0, 5.2)	0.0012
% achieving ≥ 10% weight loss					
n(%)	11 (4.5)	47 (18.4)	13.9 (8.2, 19.7)	4.9 (1.4, 8.4)	0.0287
CONTINUOUS ENDPOINTS			**Diff in LS Means (95% CI)**		**p-Value**
Change from baseline in weight (kg)					
LS mean (SEM)	-1.85 (0.36)	-5.23 (0.38)	-3.39 (-4.41, -2.37)	--	< 0.001
% Change from baseline weight (%)					
LS mean (SEM)	-1.76 (0.36)	-5.15 (0.37)	-3.40 (-4.39, -2.40)	--	< 0.001

[a] Computed using Cochran-Mantel-Haenszel weighted normal approximation method with stratification by protocol.
[b] From the logistic regression model, adjusting for baseline body weight and protocol.
-- not calculated

Appendix 5 Clinical Safety Additional Analyses

7.11 Withdrawal, Dependence and Abuse Potential

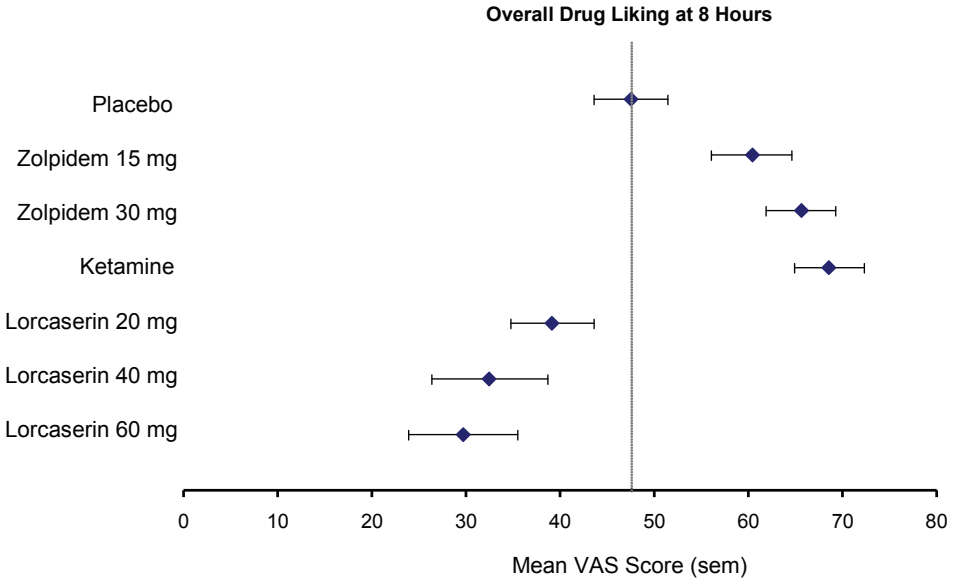
Potential withdrawal effects were specifically evaluated in two Phase 2 studies, APD356-003 and APD356-004. In APD356-003, patients were assigned to receive 1, 5 or 15 mg lorcaserin once daily for 4 weeks. In APD356-004, patients were assigned to receive 10 or 15 mg lorcaserin once daily or 10 mg lorcaserin twice daily for 12 weeks. For both studies, study drug was taken at home except on scheduled study visit days. Once the dosing portion of the study was complete and treatment was abruptly stopped (i.e., no tapering), each patient was asked to return to the clinic for 3 additional follow-up visits to assess any psychological, behavioral, or mood changes using the Bond and Lader Mood visual analogue scale (VAS), Subjective Sensation Questionnaire (SSQ) Hunger/Appetite VAS (Study APD356-003 only) and assessment of any AEs. The absence of changes in Bond and Lader Mood VAS composite and individual scores during the follow-up period supports a lack of withdrawal effect. Scores on the SSQ VAS also did not show changes during the follow-up period.

Psychological dependence on lorcaserin was not assessed directly; however, there were no reports of Aes indicative of dependence (e.g., craving or anxiety-related events) in these or other studies of lorcaserin. Indirect measures of reinforcement used in the human abuse potential study (APD356-013), i.e., Take Drug Again VAS and subjective drug value (SDV), showed that subjects are not willing to take the drug again and that lorcaserin does not have reinforcing effects.[135]

7.11.1 Abuse Potential

A formal abuse potential study was conducted in recreational drug users. Lorcaserin (20 mg, 40 mg, 60 mg) was compared to placebo, zolpidem (15 mg and 30 mg) and ketamine (100 mg) in a blinded fashion. Various aspects of the experience were evaluated using questionnaires and visual analog scales. Overall, lorcaserin at 20 mg was not distinguishable from placebo. The 40 and 60 mg doses were generally liked less than zolpidem or ketamine, and disliked more than any of the comparators. Subjects rated the overall lorcaserin experiences as negative, and indicated that they would not take the drug again for recreational purposes. As an example, the results of the "overall drug liking" VAS are presented in Figure 48. The potential for abuse based on these study results is considered to be very low.

Figure 48. "Overall Drug Liking" VAS Responses in Abuse Potential Study



Visual Analog Scale range: 0-100, with higher score indicating greater drug liking

7.12 Effects of Lorcaserin on ECG and QTc Interval

ECG and QTC effects were evaluated in a formal thorough ECG/QT study and in all other studies of lorcaserin. Lorcaserin had no effect on QTc, whether calculated using individual correction, QTcB or QTcF. Small, clinically insignificant increases in population mean PR interval were observed in some clinical studies. These increases did not lead to an excess of adverse events related to the PR interval.

7.12.1 Thorough ECG/QT Study APD356-007

APD356-007 was as a double-blind, randomized, parallel design thorough ECG/QT study in healthy male and female subjects. Continuous electrocardiograms were collected using Holter monitors for the statistical analyses of ECG parameters. Moxifloxacin was administered as a positive control. Lorcaserin was tested at doses of 15 mg QD and 40 mg QD. The primary QT analysis used individually corrected QT intervals (QtcI).

The results of this thorough ECG trial showed no effect on heart rate, AV conduction, depolarization, or cardiac repolarization, as measured by the PR, QRS, or QTc interval durations (Table 68). Moxifloxacin induced the expected increase in QTc, with an increase in mean individually corrected QtcI of 2.9 msec (Table 69). Lorcaserin at 15 mg QD or at the supratherapeutic dose of 40 mg QD did not increase mean QtcI over placebo, nor did it increase the number of patients with QtcI greater than 480 msec or 500 msec.

Though this trial was not powered to detect outliers, no clinically relevant outliers for any ECG interval were observed.

Table 68. Mean Changes in ECG Parameters in the APD356-007 Thorough ECG/QT Study

ECG Parameter	Placebo N=60	Moxifloxacin 400 mg N=60	Lorcaserin 15 mg N=60	Lorcaserin 40 mg N=59
Heart Rate (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

Table 69. Time-averaged Qtcl Results for APD356-007 Thorough ECG/QT Study

Dose Group	Placebo	Moxifloxacin 400 mg	APD356 15 mg	APD356 40 mg
QtcI in ms[a]	-2.8	2.9	-5.0	-9.6
QtcI Max Mean Change	13.0	18.8	13.2	8.7
QtcI new >500 ms: N (%)	0	0	0	0
QtcI new >480 ms: N (%)	0	0	0	0
QtcI 30-60 ms inc: N (%)	2 (3%)	6 (10%)	3 (5%)	1 (2%)
QtcI >60 ms inc: N (%)	0	0	0	0

Abbreviations: ms=milliseconds; QtcI=Individual correction

[a] Mean change from baseline;

7.12.2 ECG Parameters in Phase 3 Trials

ECGs were performed at baseline and at least one time point thereafter in Phase 3 trials. Changes in individual ECG parameters are summarized in Table 70. PR intervals increased slightly more in the lorcaserin BID group than in the placebo group; the effects were not dose-dependent. A larger proportion of the lorcaserin BID group compared with placebo experienced PR intervals >200 msec (Table 71). No other effects were consistently associated with lorcaserin.

Table 70. ECG Interval Mean Values and Change from Baseline to Week 52 in Pooled Phase 3 Studies (APD356-009 and -011) and Study APD356-010: Safety Population

Parameter	Pooled Studies APD356-009 and -011: Non-diabetic Patients			Study APD356-010: Patients with Type 2 Diabetes		
	Placebo N=3185	Lorcaserin 10 mg BID N=3195	Lorcaserin 10 mg QD N=801	Placebo N=252	Lorcaserin 10 mg BID N=256	Lorcaserin 10 mg QD N=95
QT (msec)	N=1824	N=2033	N=599	N=217	N=215	N=86
Baseline, mean (sd)	398.8 (27.3)	397.7 (27.0)	399.6 (26.4)	391.6 (27.4)	391.6 (27.2)	389.0 (28.9)
Change from Baseline						
Mean (sem)	-0.16 (0.529)	1.69 (0.493)	2.56 (0.894)	0.5 (1.6)	4.9 (1.6)	3.1 (2.3)
Median	0.00	1.00	3.00	0.0	5.0	7.0
Inter-quartile range	-16.00 to 15.00	-12.00 to 15.00	-12.00 to 16.00	-92 to 61	-82 to 98	-65 to 48
QTc Bazett (msec)						
Baseline	414.0 (22.7)	413.0 (22.7)	414.3 (20.1)	419.6 (21.1)	420.8 (21.5)	419.2 (20.2)
Change from Baseline						
Mean	-1.04 (0.468)	-4.50 (0.463)	1.44 (0.799)	-0.8 (1.5)	-1.6 (1.5)	-2.7 (2.2)
Median	-1.00	-5.00	0.00	-2.0	-3.0	-6.5
Inter-quartile range	-14.00 to 12.00	-19.00 to 9.00	-12.00 to 15.00	-75 to 53	-56 to 65	-44 to 68
QTc Fridericia (msec)						
Baseline	408.8 (20.1)	407.7 (20.0)	409.1 (17.8)	409.8 (17.7)	410.6 (18.8)	408.6 (18.6)
Change from Baseline						
Mean	-0.72 (0.388)	-2.41 (0.382)	1.82 (0.647)	-0.4 (1.2)	0.6 (1.2)	-0.7 (1.8)
Median	-0.11	-2.09	2.00	0.0	0.0	-0.5
Inter-quartile range	-12.00 to 10.00	-13.56 to 9.00	-9.00 to 12.00	-71 to 44	-44 to 57	-33 to 50
PR (msec)	N=1823	N=598	N=2031	N=216	N=215	N=86
Baseline	160.7 (20.7)	161.5 (21.9)	161.6 (20.8)	162.2 (19.3)	165.8 (23.3)	169.4 (22.7)
Change from Baseline						
Mean	2.08 (0.300)	2.98 (0.290)	1.87 (0.530)	1.3 (0.9)	2.5 (0.9)	4.0 (1.7)
Median	2.00	3.00	2.00	1.0	2.0	3.0
Inter-quartile range	-6 to 10	-6 to 10	-5 to 10	-68 to 50	-32 to 68	-27 to 52

Table 71. Categorical ECG Values at Any Time in Pooled Phase 3 Studies (APD356-009 and -011) and Study APD356-010: Safety Population

Parameter n[a](%) of patients	Pooled Studies APD356-009 and -011: Non-diabetic Patients Placebo N=3185	 Lorcaserin 10 mg BID N=3195	 Lorcaserin 10 mg QD N=801	Study APD356-010: Patients with Type 2 Diabetes Placebo N=252	 Lorcaserin 10 mg BID N=256	 Lorcaserin 10 mg QD N=95
Heart Rate (bpm)						
<45	22 (0.9)	50 (1.9)	6 (1.0)	1 (0.5)	3 (1.4)	0
45-49	105 (4.1)	192 (7.2)	20 (3.3)	3 (1.4)	5 (2.3)	3 (3.5)
50-54	317 (12.5)	445 (16.8)	59 (9.8)	18 (8.3)	16 (7.4)	4 (4.7)
101-115	3 (0.1)	2 (<0.1)	1 (0.2)	1 (0.5)	0	0
116-130	0 (0.0)	1 (<0.1)	0 (0.0)	0	0	0
>130	0 (0.0)	0 (0.0)	1 (0.2)	0	0	0
QT (msec)						
450-480	106 (4.2)	140 (5.3)	25 (4.2)	5 (2.3)	5 (2.3)	4 (4.7)
481-500	12 (0.5)	24 (0.9)	6 (1.0)	1 (0.5)	1 (0.5)	0
≥501 on 2 or more ECGs	2 (<0.1)	1 (<0.1)	0	0	0	0
≥501 and CFB>60	25 (1.0)	47 (1.8)	5 (0.8)	2 (0.9)	2 (0.9)	0
QTcF (msec)						
450-480	83 (3.3)	81 (3.1)	25 (4.2)	4 (1.8)	7 (3.3)	0
481-500	5 (0.2)	3 (0.1)	(0.2)	0	0	0
≥501 on 2 or more ECGs	0	0	0	0	0	0
≥501 and CFB>60	11 (0.4)	7 (0.3)	0	0	0	0
QTcB (msec)						
450-480	165 (6.5)	149 (5.6)	35 (5.8)	19 (8.8)	20 (9.3)	5 (5.8)
481-500	15 (0.6)	10 (0.4)	2 (0.3)	1 (0.5)	1 (0.5)	0
≥501 on 2 or more ECGs	0	0	0	0	0	0
≥501 and CFB>60	15 (0.6)	11 (0.4)	1 (0.2)	0	2 (0.9)	1 (1.2)
PR (msec)						
>200	137 (5.4)	188 (7.1)	21 (3.5)	12 (5.6)	21 (9.8)	10 (11.6)
<120	31 (1.2)	28 (1.1)	2 (0.3)	1 (0.5)	0	0

[a] Number of patients with non-missing baseline test, and at least one non-missing post-baseline test. Used as denominator for percentages in a category.

A more detailed analysis of PR interval lengthening was conducted (Table 72). Among the subgroup of patients with PR >200 msec at Week 52, more lorcaserin-treated patients had experienced PR interval increases of 20-40 msec as compared to placebo; no dose-related effect was apparent for increases of >40 msec. Hence, most patients with PR >200 msec at Week 52 reached that threshold with an increase of <20 msec from baseline.

Table 72. Summary of Maximum PR Changes Meeting Specified Criteria during 52 Weeks of Study in Pooled Phase 3 Studies (APD356-009 and -011) and Study APD356-010: Safety Population

Category	Studies APD356-009 and -011: Non-diabetic Patients			Study APD356-010: Patients with Type 2 Diabetes		
	Placebo N=3185	Lorcaserin 10 mg BID N=3195	Lorcaserin 10 mg QD N=801	Placebo N=252	Lorcaserin 10 mg BID N=256	Lorcaserin 10 mg QD N=95
Patients with PR Data (N)	2545	2650	598	216	215	86
n (%) of patients						
PR change >20 to ≤30 & PR > 200 msec at Week 52	23 (0.9)	32 (1.2)	2 (0.3)	3 (1.2)	4 (1.6)	5 (5.8)
PR change >30 to ≤40 & PR > 200 msec at Week 52	8 (0.3)	18 (0.7)	3 (0.5)	2 (0.8)	3 (1.2)	1 (1.2)
PR change >40 & PR > 200 msec at Week 52	10 (0.4)	5 (0.2)	0	1 (0.4)	1 (0.4)	1 (1.2)
PR change >20 to ≤30 msec	157 (6.2)	195 (7.4)	36 (6.0)	nd	nd	nd
PR change >30 to ≤40 msec	32 (1.3)	59 (2.2)	9 (1.5)	nd	nd	nd
PR change >40 msec	22 (0.9)	16 (0.6)	1 (0.2)	nd	nd	nd
PR >200 and Baseline PR >200 msec	60 (2.4)	84 (3.2)	7 (1.2)	nd	nd	nd
PR >200 and Baseline PR ≤200 msec	77 (3.0)	104 (3.9)	14 (2.3)	nd	nd	nd

nd, not determined

The number of adverse events of PR interval prolongation or electrocardiographic first degree A-V block was small (3 events during Year 1 in placebo group, 4 events in lorcaserin BID group), and did not differ meaningfully among treatment groups.

Table 73. Summary by Sex of Common Lorcaserin-associated Adverse Events and Adverse Events of Special Interest in Pooled Phase 3 Studies (APD356-009 and -011) and Study APD356-010: Safety Population

Preferred Term or Category	Pooled APD356-009 and -011: Non-Diabetic Patients						APD356-010: Patients with Type 2 Diabetes					
	WOMEN			MEN			WOMEN			MEN		
	PBO N=2580	Lorcaserin 10 mg BID N=2610	Lorcaserin 10 mg QD N=656	PBO N=605	Lorcaserin 10 mg BID N=585	Lorcaserin 10 mg QD N=145	PBO N=137	Lorcaserin 10 mg BID N=137	Lorcaserin 10 mg QD N=53	PBO N=115	Lorcaserin 10 mg BID N=119	Lorcaserin 10 mg QD N=42
Headache	286 (11.1)	484 (18.5)	121 (18.4)	51 (8.4)	84 (14.4)	13 (9.0)	13 (9.5)	27 (19.7)	9 (17.0)	6 (5.2)	13 (10.9)	7 (16.7)
Nausea	149 (5.8)	232 (8.9)	57 (8.7)	21 (3.5)	32 (5.5)	4 (2.8)	14 (10.2)	17 (12.4)	4 (7.5)	6 (5.2)	7 (5.9)	4 (9.5)
Dizziness	94 (3.6)	243 (9.3)	44 (6.7)	29 (4.8)	30 (5.1)	6 (4.1)	10 (7.3)	10 (7.3)	7 (13.2)	6 (5.2)	8 (6.7)	4 (9.5)
Paraesthesia	13 (0.5)	31 (1.2)	8 (1.2)	2 (0.3)	7 (1.2)	4 (2.8)	0	4 (2.9)	0	2 (1.7)	0	2 (4.8)
Hypoglycaemia	1 (<0.1)[a]	2 (0.1)	0	0	0	0	28 (20.4)	40 (29.2)	20 (37.7)	25 (21.7)	35 (29.4)	12 (28.6)
Related to Prolactin	2 (0.1)	3 (0.1)	0	0	0	0	0	1 (0.7)	0	0	0	0
Depression, Narrow SMQ	62 (2.4)	73 (2.8)	16 (2.4)	16 (2.6)	8 (1.4)	1 (0.7)	2 (1.5)	6 (4.4)	4 (7.5)	4 (3.5)	3 (2.5)	1 (2.4)
Depression, Broad SMQ	38 (1.5)	77 (3.0)	13 (2.0)	6 (1.0)	9 (1.5)	2 (1.4)	1 (0.7)	2 (1.5)	0	0	1 (0.8)	1 (2.4)
Suicide/Self Injury SMQ	9 (0.3)	15 (0.6)	6 (0.9)	5 (0.8)	4 (0.7)	0	0	1 (0.7)	0	1 (0.9)	2 (1.7)	2 (4.8)
Psychosis, Narrow SMQ	1 (< 0.1)	0	0	0	2 (0.3)	0	0	0	0	1 (0.9)	0	0
Psychosis, Broad SMQ	8 (0.3)	10 (0.4)	1 (0.2)	0	3 (0.5)	1 (0.7)	0	0	1 (1.9)	0	1 (0.8)	0
Gallbladder SMQ	16 (0.6)	24 (0.9)	5 (0.8)	0	2 (0.3)	0	0	1 (0.7)	0	1 (0.9)	1 (0.8)	0
Serotonin Syndrome terms	14 (0.5)	47 (1.8)	12 (1.8)	4 (0.7)	9 (1.5)	1 (0.7)	4 (2.9)	4 (2.9)	1 (1.9)	0	0	0
NMS, Broad SMQ	130 (5.0)	157 (6.0)	37 (5.6)	44 (7.3)	37 (6.3)	10 (6.9)	14 (10.2)	15 (10.9)	4 (7.5)	9 (7.8)	11 (9.2)	6 (14.3)
Dystonia, Narrow SMQ	0	1 (< 0.1)	0	0	0	0	0	0	0	0	0	0
Dystonia, Broad SMQ	60 (2.3)	53 (2.0)	13 (2.0)	10 (1.7)	14 (2.4)	3 (2.1)	7 (5.1)	4 (2.9)	2 (3.8)	4 (3.5)	8 (6.7)	1 (2.4)

Abbreviations: LOR, lorcaserin; PBO, placebo; SMQ, Standard MedDRA Query; BID, twice daily; QD, once daily; NMS, Neuroleptic Malignant Syndrome
Note: At each level of summarization, patients reporting more than one event were only counted once.
[a] Includes event of "hypoglycaemic unconsciousness"

Table 74. Summary by Race of Common Lorcaserin-associated Adverse Events and Adverse Events of Special Interest in Pooled Phase 3 Studies (APD356-009 and -011) and Study APD356-010: Safety Population

Preferred Term or Category	Pooled APD356-009 and -011: Non-Diabetic Patients									APD356-010: Patients with Type 2 Diabetes								
	Caucasian			African American			Hispanic/Latino			Caucasian			African American			Hispanic/Latino		
	PBO	LOR BID	LOR QD	PBO	LOR BID	LOR QD	PBO	LOR BID	LOR QD	PBO	LOR BID	LOR QD	PBO	LOR BID	LOR QD	PBO	LOR BID	LOR QD
N=	2110	2161	538	617	604	160	394	355	86	166	150	49	45	55	26	27	39	17
Headache	193 (9.1)	356 (16.5)	90 (16.7)	73 (11.8)	118 (19.5)	27 (16.9)	65 (16.5)	76 (21.4)	14 (16.3)	9 (5.4)	18 (12.0)	8 (16.3)	5 (11.1)	10 (18.2)	5 (19.2)	3 (11.1)	10 (25.6)	2 (11.8)
Nausea	118 (5.6)	176 (8.1)	40 (7.4)	32 (5.2)	50 (8.3)	11 (6.9)	16 (4.1)	33 (9.3)	8 (9.3)	9 (5.4)	19 (12.7)	5 (10.2)	6 (13.3)	4 (7.3)	1 (3.8)	3 (11.1)	1 (2.6)	2 (11.8)
Dizziness	78 (3.7)	183 (8.5)	32 (5.9)	24 (3.9)	42 (7.0)	10 (6.3)	16 (4.1)	37 (10.4)	7 (8.1)	8 (4.8)	8 (5.3)	4 (8.2)	2 (4.4)	5 (9.1)	4 (15.4)	5 (18.5)	2 (5.1)	2 (11.8)
Paraesthesia	8 (0.4)	23 (1.1)	6 (1.1)	4 (0.6)	6 (1.0)	3 (1.9)	2 (0.5)	8 (2.3)	3 (3.5)	2 (1.2)	4 (2.7)	0	0	0	2 (7.7)	0	0	0
Hypoglycaemia	0	0	0	0	0	0	0	0	0	31 (18.7)	38 (25.3)	14 (28.6)	10 (22.2)	24 (43.6)	11 (42.3)	7 (25.9)	10 (25.6)	6 (35.3)
Related to Prolactin	1 (<0.1)	3 (0.1)	0	1 (0.2)	0	0	1 (0.3)	0	0	0	0	0	0	1 (1.8)	0	0	0	0
Depression, Narrow SMQ	51 (2.4)	55 (2.5)	12 (2.2)	20 (3.2)	15 (2.5)	4 (2.5)	7 (1.8)	10 (2.8)	1 (1.2)	3 (1.8)	4 (2.7)	2 (4.1)	0	2 (3.6)	2 (7.7)	3 (11.1)	0	0
Depression, Broad SMQ	35 (1.7)	64 (3.0)	11 (2.0)	7 (1.1)	10 (1.7)	4 (2.5)	2 (0.5)	9 (2.5)	0	1 (0.6)	2 (1.3)	0	0	1 (1.8)	0	0	0	1 (5.9)
Suicide/Self Injury SMQ	12 (0.6)	15 (0.7)	5 (0.9)	1 (0.2)	2 (0.3)	1 (0.6)	1 (0.3)	2 (0.6)	0	1 (0.6)	3 (2.0)	1 (2.0)	0	0	1 (3.8)	0	0	0
Psychosis, Narrow SMQ	1 (<0.1)	2 (0.1)	0	0	0	0	0	0	0	1 (0.6)	0	0	0	0	0	0	0	0
Psychosis, Broad SMQ	5 (0.2)	9 (0.4)	1 (0.2)	2 (0.3)	1 (0.2)	1 (0.6)	1 (0.3)	3 (0.8)	0	0	0	0	0	0	0	0	0	1 (5.9)
Gallbladder SMQ	15 (0.7)	17 (0.8)	3 (0.6)	0	3 (0.5)	0	1 (0.3)	6 (1.7)	1 (1.2)	1 (0.6)	2 (1.3)	0	0	0	0	0	0	0

Table 74. Summary by Race of Common Lorcaserin-associated Adverse Events and Adverse Events of Special Interest in Pooled Phase 3 Studies (APD356-009 and -011) and Study APD356-010: Safety Population (cont.)

Preferred Term or Category	Pooled APD356-009 and -011: Non-Diabetic Patients									APD356-010: Patients with Type 2 Diabetes								
	Caucasian			African American			Hispanic/Latino			Caucasian			African American			Hispanic/Latino		
	PBO	LOR BID	LOR QD	PBO	LOR BID	LOR QD	PBO	LOR BID	LOR QD	PBO	LOR BID	LOR QD	PBO	LOR BID	LOR QD	PBO	LOR BID	LOR QD
N=	2110	2161	538	617	604	160	394	355	86	166	150	49	45	55	26	27	39	17
Serotonin Syndrome terms	10 (0.5)	40 (1.9)	8 (1.5)	5 (0.8)	5 (0.8)	3 (1.9)	3 (0.8)	9 (2.5)	1 (1.2)	3 (1.8)	1 (0.7)	0	0	1 (1.8)	0	0	2 (5.1)	1 (5.9)
NMS, Broad SMQ[a]	119 (5.6)	138 (6.4)	33 (6.1)	40 (6.5)	39 (6.5)	11 (6.9)	14 (3.6)	14 (3.9)	2 (2.3)	19 (11.4)	16 (10.7)	5 (10.2)	2 (4.4)	8 (14.5)	3 (11.5)	1 (3.7)	2 (5.1)	2 (11.8)
Dystonia, Narrow SMQ	0	0	0	0	1 (0.2)	0	0	0	0	0	0	0	0	0	0	0	0	0
Dystonia, Broad SMQ	54 (2.6)	49 (2.3)	14 (2.6)	10 (1.6)	9 (1.5)	1 (0.6)	6 (1.5)	8 (2.3)	1 (1.2)	7 (4.2)	9 (6.0)	1 (2.0)	4 (8.9)	2 (3.6)	1 (3.8)	0	0	1 (5.9)

Abbreviations: LOR, lorcaserin; PBO, placebo; BID, twice daily; QD, once daily; SMQ, Standard MedDRA Query; NMS, Neuroleptic Malignant Syndrome

Note: At each level of summarization, patients reporting more than one event were only counted once.

Table 75. Summary by Age of Common Lorcaserin-associated Adverse Events and Adverse Events of Special Interest in Pooled Phase 3 Studies (APD356-009 and -011) and Study APD356-010: Safety Population

	Pooled APD356-009 and -011: Non-Diabetic Patients						APD356-010: Patients with Type 2 Diabetes					
	Age <Median (44)			Age ≥Median (44)			Age <Median (54)			Age ≥Median (54)		
Preferred Term or Category	PBO N=1502	LOR 10 mg BID N=1500	LOR 10 mg QD N=380	PBO N=1683	LOR 10 mg BID N=1695	LOR 10 mg QD N=421	PBO N=130	LOR 10 mg BID N=113	LOR 10 mg QD N=46	PBO N=122	LOR 10 mg BID N=143	LOR 10 mgQD N=49
Headache	176 (11.7)	294 (19.6)	66 (17.4)	161 (9.6)	274 (16.2)	68 (16.2)	12 (9.2)	23 (20.4)	9 (19.6)	7 (5.7)	17 (11.9)	7 (14.3)
Nausea	88 (5.9)	126 (8.4)	35 (9.2)	82 (4.9)	138 (8.1)	26 (6.2)	12 (9.2)	8 (7.1)	4 (8.7)	8 (6.6)	16 (11.2)	4 (8.2)
Dizziness	54 (3.6)	116 (7.7)	21 (5.5)	69 (4.1)	157 (9.3)	29 (6.9)	5 (3.8)	9 (8.0)	3 (6.5)	11 (9.0)	9 (6.3)	8 (16.3)
Paraesthesia	4 (0.3)	15 (1.0)	8 (2.1)	11 (0.7)	23 (1.4)	4 (1.0)	1 (0.8)	0	2 (4.3)	1 (0.8)	4 (2.8)	0
Hypoglycaemia	0	0	0	0	0	0	21 (16.2)	34 (30.1)	13 (28.3)	32 (26.2)	41 (28.7)	19 (38.8)
Related to Prolactin	2 (0.1)	3 (0.2)	0	1 (0.1)	1 (0.1)	0	0	1 (0.9)	0	0	0	0
Depression, Narrow SMQ	30 (2.0)	40 (2.7)	8 (2.1)	48 (2.9)	41 (2.4)	9 (2.1)	3 (2.3)	5 (4.4)	2 (4.3)	3 (2.5)	4 (2.8)	3 (6.1)
Depression, Broad SMQ	15 (1.0)	37 (2.5)	7 (1.8)	29 (1.7)	49 (2.9)	8 (1.9)	1 (0.8)	1 (0.9)	0	0	2 (1.4)	1 (2.0)
Suicide/Self Injury SMQ	9 (0.6)	12 (0.8)	1 (0.3)	5 (0.3)	7 (0.4)	5 (1.2)	1 (0.8)	2 (1.8)	1 (2.2)	0	1 (0.7)	1 (2.0)
Psychosis, Narrow SMQ	1 (0.1)	0	0	0	2 (0.1)	0	1 (0.8)	0	0	0	0	0
Psychosis, Broad SMQ	3 (0.2)	3 (0.2)	1 (0.3)	5 (0.3)	10 (0.6)	1 (0.2)	0	1 (0.9)	0	0	0	1 (2.0)
Gallbladder SMQ	11 (0.7)	14 (0.9)	4 (1.1)	5 (0.3)	12 (0.7)	1 (0.2)	0	1 (0.9)	0	1 (0.8)	1 (0.7)	0
Serotonin Syndrome terms	5 (0.3)	23 (1.5)	6 (1.6)	13 (0.8)	33 (1.9)	7 (1.7)	3 (2.3)	1 (0.9)	0	1 (0.8)	3 (2.1)	1 (2.0)
NMS, Broad SMQ	54 (3.6)	81 (5.4)	20 (5.3)	120 (7.1)	113 (6.7)	27 (6.4)	14 (10.8)	11 (9.7)	5 (10.9)	9 (7.4)	15 (10.5)	5 (10.2)
Dystonia, Narrow SMQ	0	1 (0.1)	0	0	0	0	0	0	0	0	0	0
Dystonia, Broad SMQ	20 (1.3)	25 (1.7)	4 (1.1)	50 (3.0)	42 (2.5)	12 (2.9)	5 (3.8)	6 (5.3)	1 (2.2)	6 (4.9)	6 (4.2)	2 (4.1)

Abbreviations: LOR, lorcaserin; PBO, placebo; BID, twice daily; QD, once daily; SMQ, Standard MedDRA Query; NMS, Neuroleptic Malignant Syndrome

Note: At each level of summarization, patients reporting more than one event were only counted once.

Table 76. Common Adverse Events and AEs of Interest by Starting BMI Subgroup in Pooled Phase 3 Studies APD356-009 and -011: Safety Population

AE Category Preferred Term	BMI<30 kg/m^2			BMI 30 to ≤35 kg/m^2			BMI 35 to <40 kg/m^2			BMI ≥40 kg/m^2		
Starting BMI Subgroup	PBO N=149	LOR 10 mg BID N=169	LOR 10 mg QD N=37	PBO N=1297	LOR 10 mg BID N=1244	LOR 10 mg QD N=355	PBO N=1092	LOR 10 mg BID N=1118	LOR 10 mg QD N=243	PBO N=647	LOR 10 mg BID N=664	LOR 10 mg QD N=166
Headache	8 (5.4)	24 (14.2)	7 (18.9)	124 (9.6)	239 (19.2)	66 (18.6)	133 (12.2)	199 (17.8)	34 (14.0)	72 (11.1)	106 (16.0)	27 (16.3)
Nausea	7 (4.7)	13 (7.7)	3 (8.1)	65 (5.0)	111 (8.9)	30 (8.5)	57 (5.2)	92 (8.2)	20 (8.2)	41 (6.3)	48 (7.2)	8 (4.8)
Dizziness	2 (1.3)	13 (7.7)	4 (10.8)	45 (3.5)	120 (9.6)	30 (8.5)	48 (4.4)	98 (8.8)	11 (4.5)	28 (4.3)	42 (6.3)	5 (3.0)
Paraesthesia	2 (1.3)	2 (1.2)	0	3 (0.2)	14 (1.1)	7 (2.0)	5 (0.5)	12 (1.1)	5 (2.1)	5 (0.8)	10 (1.5)	0
Hypoglycaemia	0	0	0	1 (0.1)	1 (0.1)	0	0	1 (0.1)	0	0	0	0
Related to Prolactin	0	0	0	1 (0.1)	0	0	2 (0.2)	2 (0.2)	0	0	2 (0.3)	0
Depression, Narrow SMQ	4 (2.7)	7 (4.1)	1 (2.7)	33 (2.5)	27 (2.2)	6 (1.7)	21 (1.9)	31 (2.8)	3 (1.2)	20 (3.1)	16 (2.4)	7 (4.2)
Depression, Broad SMQ	1 (0.7)	4 (2.4)	1 (2.7)	23 (1.8)	30 (2.4)	4 (1.1)	12 (1.1)	34 (3.0)	5 (2.1)	8 (1.2)	18 (2.7)	5 (3.0)
Suicide/Self Injury SMQ	0	0	0	6 (0.5)	8 (0.6)	4 (1.1)	5 (0.5)	5 (0.4)	2 (0.8)	3 (0.5)	6 (0.9)	0
Psychosis, Narrow SMQ	0	0	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)	0	0	0	0
Psychosis, Broad SMQ	0	1 (0.6)	0	4 (0.3)	7 (0.6)	1 (0.3)	4 (0.4)	4 (0.4)	1 (0.4)	0	1 (0.2)	0
Gallbladder SMQ	0	1 (0.6)	0	7 (0.5)	6 (0.5)	1 (0.3)	6 (0.5)	14 (1.3)	2 (0.8)	3 (0.5)	5 (0.8)	2 (1.2)
Serotonin Syndrome terms	1 (0.7)	3 (1.8)	1 (2.7)	7 (0.5)	24 (1.9)	6 (1.7)	6 (0.5)	19 (1.7)	3 (1.2)	4 (0.6)	10 (1.5)	3 (1.8)
NMS, Broad SMQ	13 (8.7)	9 (5.3)	4 (10.8)	62 (4.8)	68 (5.5)	23 (6.5)	53 (4.9)	69 (6.2)	12 (4.9)	46 (7.1)	48 (7.2)	8 (4.8)
Dystonia, Narrow SMQ	0	0	0	0	0	0	0	1 (0.1)	0	0	0	0
Dystonia, Broad SMQ	4 (2.7)	2 (1.2)	0	34 (2.6)	26 (2.1)	8 (2.3)	20 (1.8)	26 (2.3)	6 (2.5)	12 (1.9)	13 (2.0)	2 (1.2)

Abbreviations: LOR, lorcaserin; PBO, placebo; BID, twice daily; QD, once daily; SMQ, Standard MedDRA Query; NMS, Neuroleptic Malignant Syndrome

Note: At each level of summarization, patients reporting more than one event were only counted once. AEs were coded with MedDRA version 12.0 for preferred terms.

Table 77. Common Adverse Events and AEs of Interest by Starting BMI Subgroup in APD356-010, Patients with Type 2 Diabetes: Safety Population

AE Category Preferred Term	BMI<30 kg/m^2			BMI 30 to ≤35 kg/m^2			BMI 35 to <40 kg/m^2			BMI ≥40 kg/m^2		
Starting BMI Subgroup	PBO N=24	LOR 10 mg BID N=21	LOR 10 mg QD N=12	PBO N=88	LOR 10 mg BID N=82	LOR 10 mg QD N=28	PBO N=86	LOR 10 mg BID N=91	LOR 10 mg QD N=33	PBO N=54	LOR 10 mg BID N=62	LOR 10 mg QD N=22
Headache	1 (4.2)	5 (23.8)	3 (25.0)	5 (5.7)	9 (11.0)	4 (14.3)	10 (11.6)	15 (16.5)	7 (21.2)	3 (5.6)	11 (17.7)	2 (9.1)
Nausea	2 (8.3)	2 (9.5)	0	4 (4.5)	6 (7.3)	4 (14.3)	7 (8.1)	12 (13.2)	2 (6.1)	7 (13.0)	4 (6.5)	2 (9.1)
Dizziness	1 (4.2)	3 (14.3)	0	3 (3.4)	6 (7.3)	5 (17.9)	7 (8.1)	5 (5.5)	5 (15.2)	5 (9.3)	4 (6.5)	1 (4.5)
Paraesthesia	0	0	0	2 (2.3)	0	0	0	2 (2.2)	1 (3.0)	0	2 (3.2)	1 (4.5)
Hypoglycaemia	9 (37.5)	7 (33.3)	5 (41.7)	16 (18.2)	19 (23.2)	13 (46.4)	16 (18.6)	35 (38.5)	8 (24.2)	12 (22.2)	14 (22.6)	6 (27.3)
Related to Prolactin	0	1 (4.8)	0	0	0	0	0	0	0	0	0	0
Depression, Broad SMQ	0	0	0	0	2 (2.4)	0	1 (1.2)	0	0	0	1 (1.6)	1 (4.5)
Suicide/Self Injury SMQ	0	0	0	1 (1.1)	0	0	0	0	2 (6.1)	0	3 (4.8)	0
Psychosis, Narrow SMQ	0	0	0	1 (1.1)	0	0	0	0	0	0	0	0
Psychosis, Broad SMQ	0	0	1 (8.3)	0	0	0	0	0	0	0	1 (1.6)	0
Gallbladder SMQ	0	1 (4.8)	0	1 (1.1)	0	0	0	1 (1.1)	0	0	0	0
Serotonin Syndrome terms	0	0	1 (8.3)	0	2 (2.4)	0	2 (2.3)	1 (1.1)	0	2 (3.7)	1 (1.6)	0
NMS, Broad SMQ	1 (4.2)	3 (14.3)	2 (16.7)	6 (6.8)	7 (8.5)	2 (7.1)	10 (11.6)	11 (12.1)	4 (12.1)	6 (11.1)	5 (8.1)	2 (9.1)
Dystonia, Narrow SMQ	0	0	0	0	0	0	0	0	0	0	0	0
Dystonia, Broad SMQ	2 (8.3)	0	0	2 (2.3)	4 (4.9)	1 (3.6)	3 (3.5)	2 (2.2)	1 (3.0)	4 (7.4)	6 (9.7)	1 (4.5)

Abbreviations: LOR, lorcaserin; PBO, placebo; BID, twice daily; QD, once daily; SMQ, Standard MedDRA Query; NMS, Neuroleptic Malignant Syndrome

Note: At each level of summarization, patients reporting more than one event were only counted once.

Table 78. Common Adverse Events and AEs of Interest by Starting Weight Subgroup in Pooled Phase 3 Studies APD356-009 and -011: Safety Population

AE Category Preferred Term	Quartile 1 (lowest)			Quartile 2			Quartile 3			Quartile 4 (highest)		
Starting Body Weight Quartile	PBO N=794	LOR 10 mg BID N=787	LOR 10 mg QD N=213	PBO N=808	LOR 10 mg BID N=790	LOR 10 mg QD N=215	PBO N=808	LOR 10 mg BID N=808	LOR 10 mg QD N=174	PBO N=775	LOR 10 mg BID N=810	LOR 10 mg QD N=199
Headache	78 (9.8)	149 (18.9)	42 (19.7)	87 (10.8)	156 (19.7)	40 (18.6)	84 (10.4)	138 (17.1)	21 (12.1)	88 (11.4)	125 (15.4)	31 (15.6)
Nausea	44 (5.5)	76 (9.7)	24 (11.3)	38 (4.7)	64 (8.1)	16 (7.4)	42 (5.2)	72 (8.9)	11 (6.3)	46 (5.9)	52 (6.4)	10 (5.0)
Dizziness	23 (2.9)	89 (11.3)	22 (10.3)	36 (4.5)	74 (9.4)	13 (6.0)	31 (3.8)	67 (8.3)	6 (3.4)	33 (4.3)	43 (5.3)	9 (4.5)
Paraesthesia	3 (0.4)	9 (1.1)	3 (1.4)	6 (0.7)	9 (1.1)	6 (2.8)	3 (0.4)	8 (1.0)	2 (1.1)	3 (0.4)	12 (1.5)	1 (0.5)
Hypoglycaemia	0	0	0	0	0	0	0	0	0	0	0	0
Related to Prolactin	0	0	0	2 (0.2)	1 (0.1)	0	1 (0.1)	0	0	0	3 (0.4)	0
Depression, Narrow SMQ	18 (2.3)	27 (3.4)	2 (0.9)	24 (3.0)	18 (2.3)	6 (2.8)	17 (2.1)	20 (2.5)	3 (1.7)	19 (2.5)	16 (2.0)	6 (3.0)
Depression, Broad SMQ	12 (1.5)	21 (2.7)	4 (1.9)	12 (1.5)	27 (3.4)	3 (1.4)	11 (1.4)	21 (2.6)	3 (1.7)	9 (1.2)	17 (2.1)	5 (2.5)
Suicide/Self Injury SMQ	1 (0.1)	2 (0.3)	1 (0.5)	6 (0.7)	5 (0.6)	2 (0.9)	2 (0.2)	8 (1.0)	2 (1.1)	5 (0.6)	4 (0.5)	1 (0.5)
Psychosis, Narrow SMQ	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	1 (0.1)	0
Psychosis, Broad SMQ	3 (0.4)	5 (0.6)	0	3 (0.4)	4 (0.5)	1 (0.5)	2 (0.2)	4 (0.5)	0	0	0	1 (0.5)
Gallbladder SMQ	4 (0.5)	5 (0.6)	1 (0.5)	5 (0.6)	9 (1.1)	0	3 (0.4)	9 (1.1)	3 (1.7)	4 (0.5)	3 (0.4)	1 (0.5)
Serotonin Syndrome terms	5 (0.6)	18 (2.3)	5 (2.3)	3 (0.4)	17 (2.2)	1 (0.5)	7 (0.9)	11 (1.4)	3 (1.7)	3 (0.4)	10 (1.2)	4 (2.0)
NMS, Broad SMQ	42 (5.3)	48 (6.1)	19 (8.9)	33 (4.1)	44 (5.6)	9 (4.2)	52 (6.4)	51 (6.3)	7 (4.0)	47 (6.1)	51 (6.3)	12 (6.0)
Dystonia, Narrow SMQ	0	0	0	0	0	0	0	1 (0.1)	0	0	0	0
Dystonia, Broad SMQ	23 (2.9)	15 (1.9)	4 (1.9)	14 (1.7)	12 (1.5)	6 (2.8)	19 (2.4)	19 (2.4)	3 (1.7)	14 (1.8)	21 (2.6)	3 (1.5)

Abbreviations: LOR, lorcaserin; PBO, placebo; BID, twice daily; QD, once daily; SMQ, Standard MedDRA Query; NMS, Neuroleptic Malignant Syndrome

Note: At each level of summarization, patients reporting more than one event were only counted once. AEs were coded with MedDRA version 12.0 for preferred terms.

Table 79. Common Adverse Events and AEs of Interest by Starting Weight Subgroup in Study APD356-010, Patients with Type 2 Diabetes: Safety Population

AE Category **Preferred Term**	**Quartile 1 (lowest)**			**Quartile 2**			**Quartile 3**			**Quartile 4 (highest)**		
Starting Body Weight Quartile	**PBO N=68**	**LOR 10 mg BID N=61**	**LOR 10 mg QD N=22**	**PBO N=68**	**LOR 10 mg BID N=67**	**LOR 10 mg QD N=16**	**PBO N=54**	**LOR 10 mg BID N=71**	**LOR 10 mg QD N=27**	**PBO N=62**	**LOR 10 mg BID N=57**	**LOR 10 mg QD N=30**
Headache	4 (5.9)	11 (18.0)	5 (22.7)	9 (13.2)	12 (17.9)	3 (18.8)	5 (9.3)	9 (12.7)	4 (14.8)	1 (1.6)	8 (14.0)	4 (13.3)
Nausea	6 (8.8)	8 (13.1)	1 (4.5)	5 (7.4)	6 (9.0)	2 (12.5)	4 (7.4)	7 (9.9)	2 (7.4)	5 (8.1)	3 (5.3)	3 (10.0)
Dizziness	3 (4.4)	5 (8.2)	2 (9.1)	9 (13.2)	5 (7.5)	2 (12.5)	1 (1.9)	6 (8.5)	7 (25.9)	3 (4.8)	2 (3.5)	0
Paraesthesia	0	0	0	1 (1.5)	2 (3.0)	0	1 (1.9)	1 (1.4)	0	0	1 (1.8)	2 (6.7)
Hypoglycaemia	15 (22.1)	20 (32.8)	12 (54.5)	17 (25.0)	15 (22.4)	5 (31.3)	9 (16.7)	24 (33.8)	7 (25.9)	12 (19.4)	16 (28.1)	8 (26.7)
Related to Prolactin	0	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Depression, Narrow SMQ	0	2 (3.3)	2 (9.1)	1 (1.5)	1 (1.5)	1 (6.3)	4 (7.4)	4 (5.6)	1 (3.7)	1 (1.6)	2 (3.5)	1 (3.3)
Depression, Broad SMQ	0	1 (1.6)	0	1 (1.5)	1 (1.5)	0	0	0	0	0	1 (1.8)	1 (3.3)
Suicide/Self Injury SMQ	0	0	0	0	0	0	1 (1.9)	0	1 (3.7)	0	3 (5.3)	1 (3.3)
Psychosis, Narrow SMQ	0	0	0	0	0	0	0	0	0	1 (1.6)	0	0
Psychosis, Broad SMQ	0	0	1 (4.5)	0	0	0	0	0	0	0	1 (1.8)	0
Gallbladder SMQ	0	1 (1.6)	0	1 (1.5)	0	0	0	1 (1.4)	0	0	0	0
Serotonin Syndrome terms	0	1 (1.6)	1 (4.5)	1 (1.5)	3 (4.5)	0	2 (3.7)	0	0	1 (1.6)	0	0
NMS, Broad SMQ	3 (4.4)	6 (9.8)	2 (9.1)	6 (8.8)	4 (6.0)	2 (12.5)	4 (7.4)	11 (15.5)	3 (11.1)	10 (16.1)	5 (8.8)	3 (10.0)
Dystonia, Narrow SMQ	0	0	0	0	0	0	0	0	0	0	0	0
Dystonia, Broad SMQ	3 (4.4)	2 (3.3)	1 (4.5)	4 (5.9)	2 (3.0)	0	1 (1.9)	2 (2.8)	1 (3.7)	3 (4.8)	6 (10.5)	1 (3.3)

Abbreviations: LOR, lorcaserin; PBO, placebo; BID, twice daily; QD, once daily; SMQ, Standard MedDRA Query; NMS, Neuroleptic Malignant Syndrome

Note: At each level of summarization, patients reporting more than one event were only counted once. AEs were coded with MedDRA version 12.0 for preferred terms.

7.13 Adverse Events in Single Dose Clinical Studies

Lorcaserin was generally well tolerated. No SAEs were reported in the single dose studies and no discontinuations due to AEs occurred (Table 80). AEs that were clearly associated with single-dose lorcaserin in a dose related manner included headache, nausea, vomiting, and dizziness (Table 81). These events were most frequent at doses ≥20 mg. The majority of the events were mild or moderate in intensity, and did not lead to study withdrawal. In the APD356-001A study, which enrolled both men and women, nausea (5 of 6 subjects), vomiting (5 of 5 subjects), and headache (12 of 17 subjects) occurred more often in women than in men who were exposed to lorcaserin. In that study, dose escalation was halted at 40 mg after the 2 women who received a 40 mg dose of lorcaserin reported experiencing mood and perceptual adverse events. Single doses of 20 mg, 40 mg and 60 mg were evaluated in a blinded, placebo-controlled abuse potential study of 34 men and women. Headache occurred in 85.3 and 83.9% of subjects who took 40 mg or 60 mg, respectively. Nausea occurred in approximately half of subjects at 40 and 60 mg.

No subjects have received greater than 60 mg lorcaserin as a single dose.

Table 80. Clinical Adverse Event Summary in Pooled Phase I Single Dose Studies

	Placebo		Lorcaserin									
			0.1 mg		1 mg		10 mg		20 mg		40 mg	
	(N =35)		(N = 20)		(N = 20)		(N = 114)		(N = 12)		(N = 6)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients with:												
One or more AE	11	31.4	5	25.0	1	5.0	66	57.9	11	91.7	6	100
No AE	24	68.6	15	75.0	19	95.0	48	42.1	1	8.3	0	0
Drug-related AE[a]	8	22.9	2	10.0	1	5.0	50	43.9	10	83.3	6	100
Laboratory AE[b]	0	0	0	0	0	0	2	1.8	1	8.3	0	0
SAE	0	0	0	0	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0	0	0	0	0
Discontinuation due to AE	0	0	0	0	0	0	0	0	0	0	0	0
Discontinuation due to drug-related AE	0	0	0	0	0	0	0	0	0	0	0	0
Discontinuation due to SAE	0	0	0	0	0	0	0	0	0	0	0	0
Discontinuation due to drug-related SAE	0	0	0	0	0	0	0	0	0	0	0	0

[a] Determined by the investigator to be possibly or probably drug related.

[b] AE related to an abnormal laboratory value

Table 81. Adverse Events Occurring in ≥5% (and n ≥ 2) of Subjects in Any Group: Pooled Phase 1 Single Dose Studies of Healthy Subjects

SOC	Placebo		Lorcaserin									
			0.1 mg		1 mg		10 mg		20 mg		40 mg	
	(N =35)		(N = 20)		(N = 20)		(N = 114)		(N = 12)		(N = 6)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Gastrointestinal disorders												
Abdominal pain upper	0	0	1	5.0	0	0	1	0.9	0	0	1	16.7
Nausea	1	2.9	0	0	0	0	10	8.8	4	33.3	2	33.3
Vomiting	0	0	0	0	0	0	5	4.4	0	0	2	33.3
General Disorders												
Feeling cold	0	0	0	0	0	0	1	0.9	0	0	2	33.3
Metabolism and nutrition disorders												
Anorexia/decreased appetite	0	0	0	0	0	0	6	5.3	0	0	1	16.7
Nervous system disorders												
Dizziness	0	0	0	0	1	5.0	9	7.9	1	8.3	2	33.3
Dizziness, postural	0	0	0	0	0	0	0	0	2	16.7	1	16.7
Headache	6	17.1	3	15.0	0	0	37	32.5	7	58.3	5	83.3
Psychiatric disorders												
Euphoric mood	0	0	0	0	0	0	2	1.8	0	0	4	66.7

Note: Although a patient may have had two or more clinical adverse events, the patient is counted only once within a category. The same patient may appear in different categories.

Source: Statistical Report for Pooled Phase 1 Analysis, Table 04

7.14 SAEs in Phase 2 Studies

No SAEs were reported in the 4-week APD356-003 study.

Five SAEs were reported in the 12-week APD356-004 study. All of the SAEs were reported by investigators to be unrelated or unlikely related to study drug.

One patient assigned to placebo had 2 SAEs (pneumonia, nephrolithiasis) and a second patient on placebo had a spontaneous abortion.

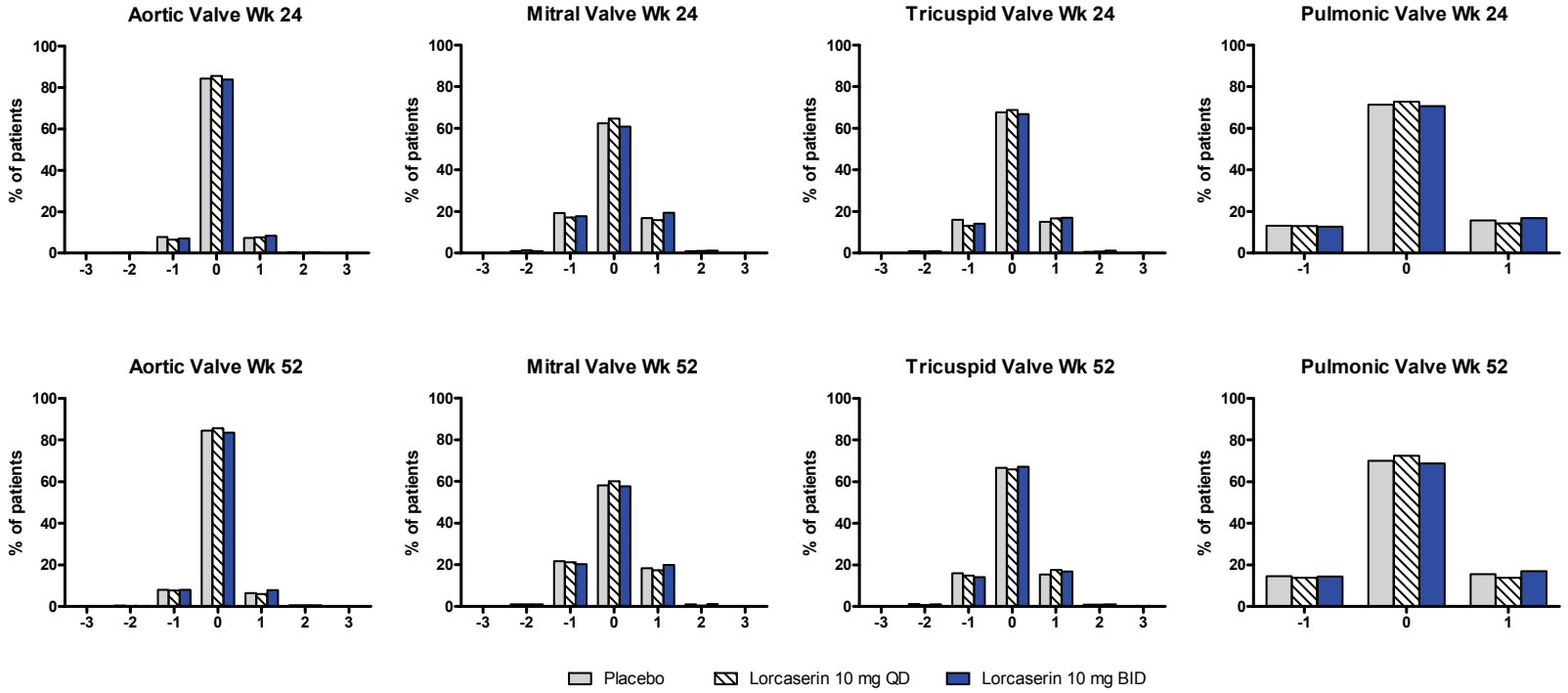
One patient assigned to lorcaserin 10 mg QD had a SAE of major depression, and one patient assigned to lorcaserin 10 mg BID had a SAE of convulsion. Narratives for each are as follows:

- Patient 08-012, a 38-year-old white female on lorcaserin 10 mg QD with a history of a mood disorder reported AEs of anxiety and depressive symptoms. At study exit visit, the patient was agitated and anxious; a psychological evaluation on that day indicated that the patient met the criteria for major depression. The patient was seen by a social worker for counseling. Within the month following the last dose of study medication, the patient's gynecologist started her on escitalopram which improved the symptoms. The Investigator considered the event of major depressive disorder as severe in nature, serious due to being an important medical event, and unlikely to be related to study drug.
- Patient 15-002, a 35-year old female patient who was receiving 10 mg lorcaserin BID, experienced an AE of generalized seizure on Study Day 72. She had no history or seizures and no contributory medical or social history. Idiopathic seizure disorder was diagnosed. The patient discontinued study drug following the AE, which the Investigator considered unlikely to be related to study drug, and she was subsequently lost to follow-up.

7.15 Shifts in Echocardiographic Valvular Regurgitation Scores

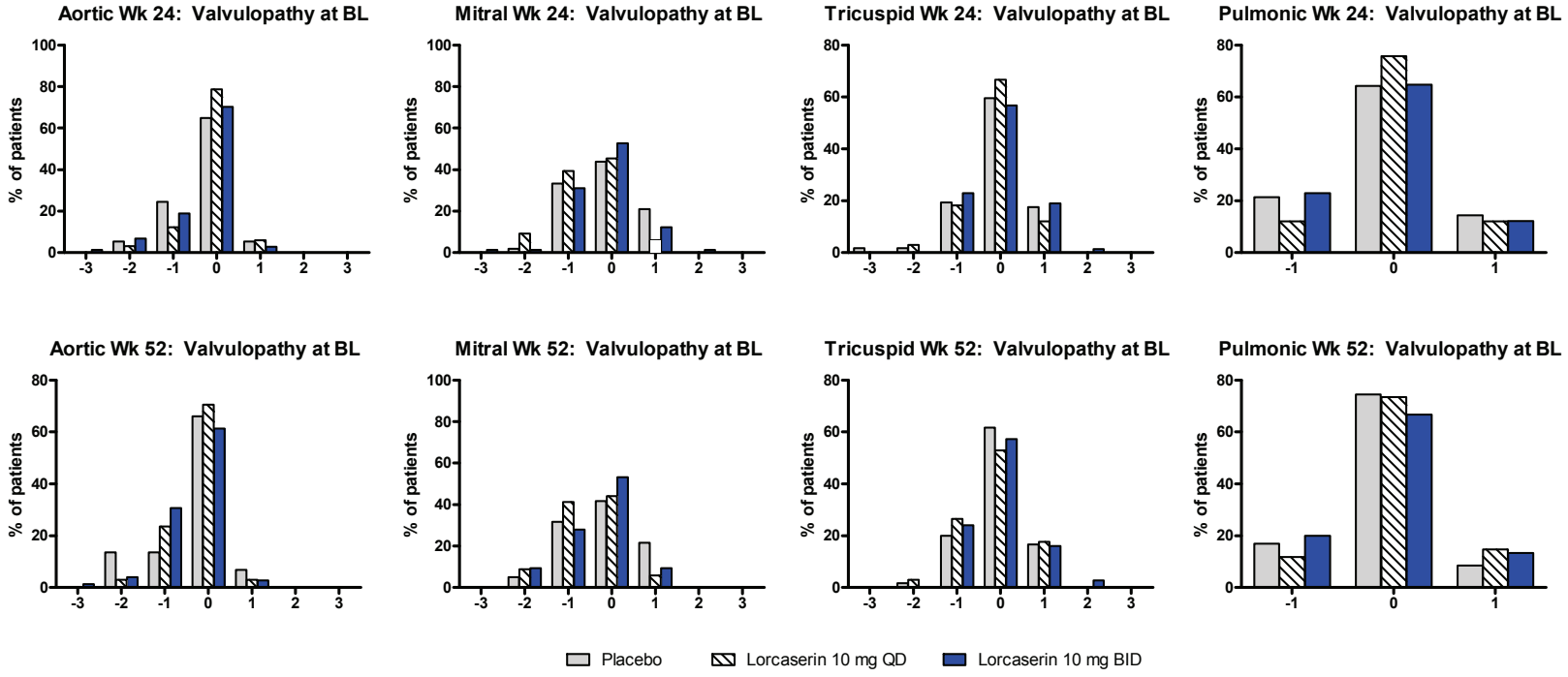
Figure 49, Figure 50, and Figure 51 present shifts in valvular regurgitant scores; these data are shown numerically in Figure 52.

Figure 49. Shifts in Echocardiographic Valvular Regurgitant Scores, Pooled Phase 3 Studies APD356-009, -011 and -010: All Patients



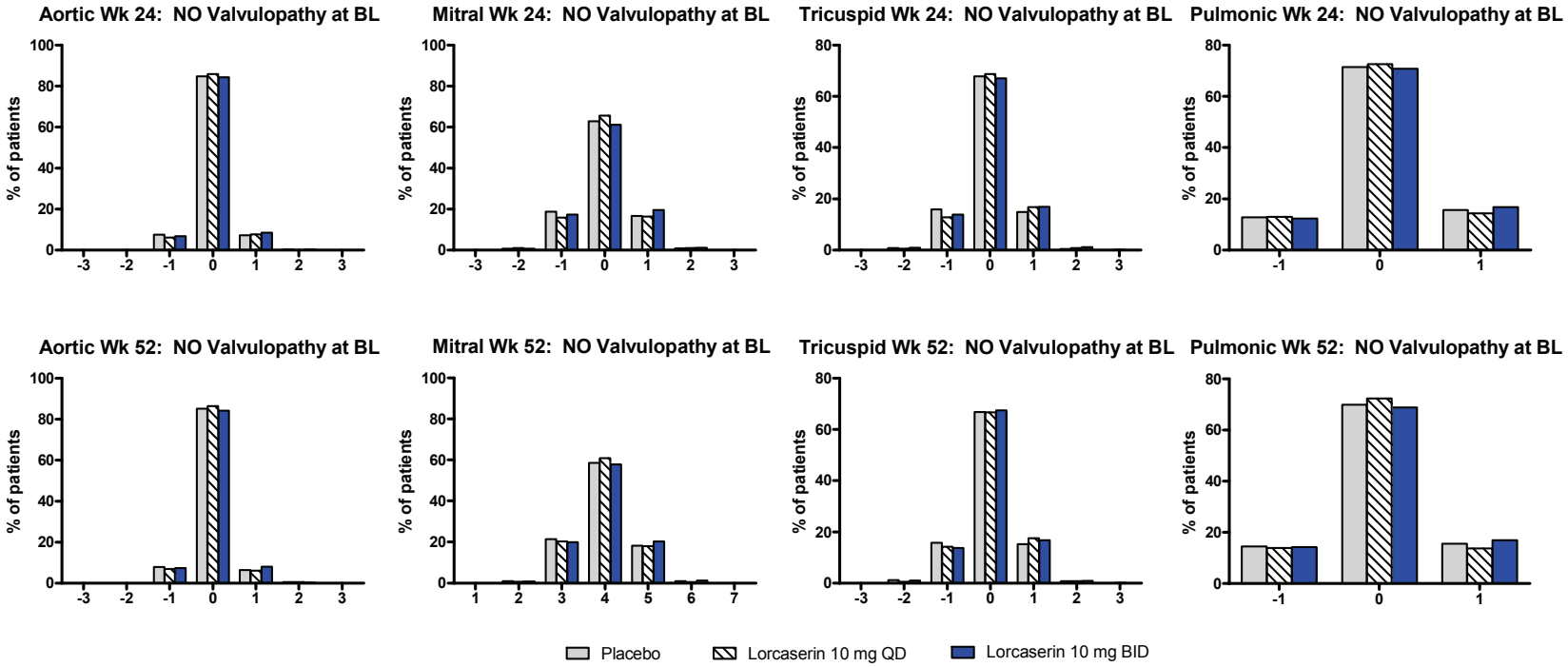
Note: Positive numbers indicate increased regurgitant scores ("worsening"); negative numbers indicate decreased regurgitant scores ("improvement")

Figure 50. Shifts in Echocardiographic Valvular Regurgitant Scores, Pooled Phase 3 Studies APD356-009, -011 and -010: Patients with Pre-existing FDA-Defined Valvulopathy at Baseline



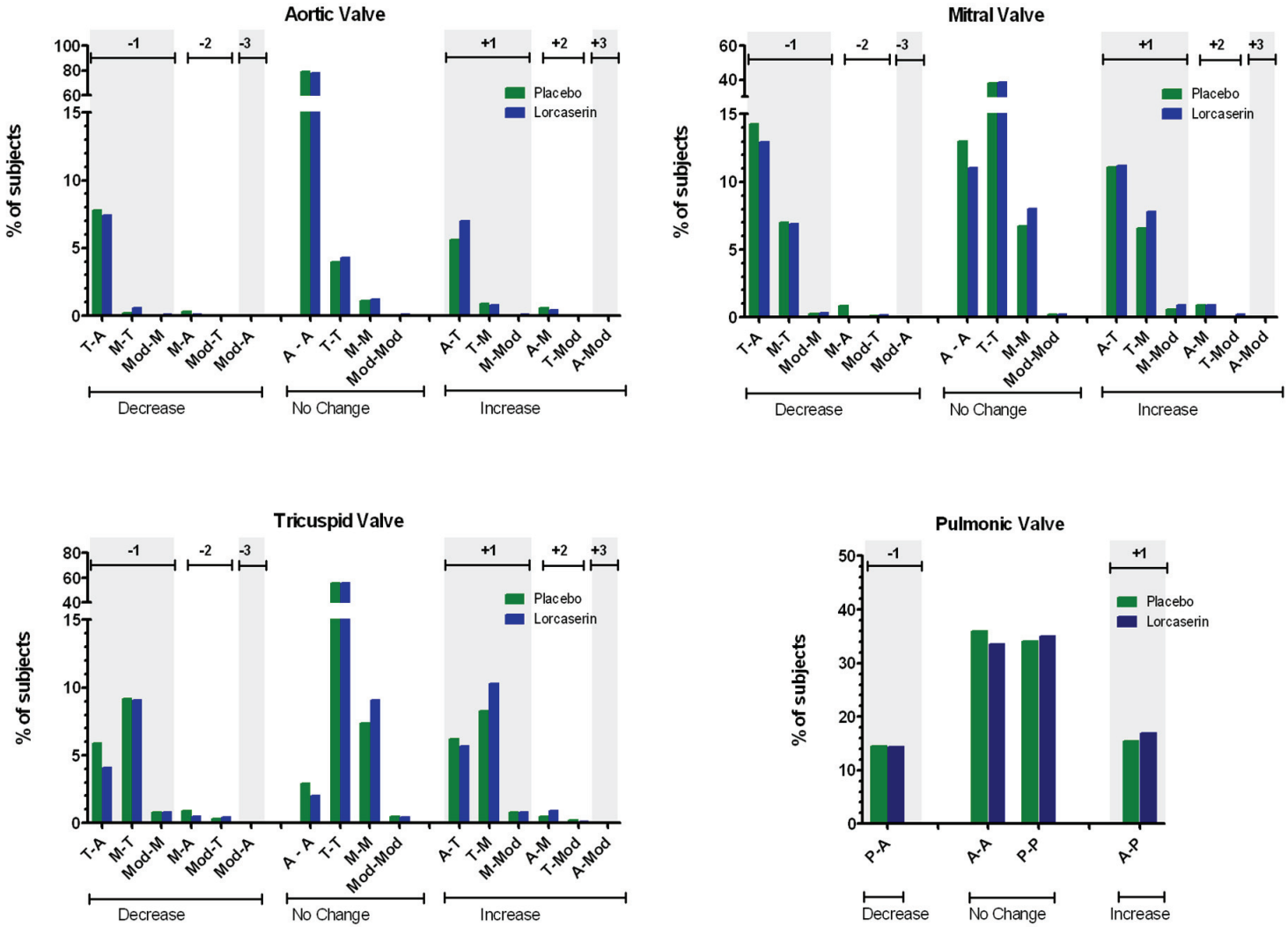
Note: Positive numbers indicate increased regurgitant scores ("worsening"); negative numbers indicate decreased regurgitant scores ("improvement")

Figure 51. Shifts in Echocardiographic Valvular Regurgitant Scores, Pooled Phase 3 Studies APD356-009, -011 and -010: Patients WITHOUT Pre-existing FDA-Defined Valvulopathy at Baseline



Note: Positive numbers indicate increased regurgitant scores ("worsening"); negative numbers indicate decreased regurgitant scores ("improvement")

Figure 52. Summary of Individual Shifts in Valvular Regurgitant Scores at Week 52 in Pooled Phase 3 Studies APD356-009, -010 and -011: All Patients



A= absent, T=trace, M=mild, Mod=moderate

Table 82. Tabular Summary of Shifts in Valvular Regurgitant Scores at Week 52 in Phase 3 Studies: All Patients

n(% of pts)	All Patients			Patients Without Baseline Valvulopathy			Patients With Baseline Valvulopathy		
Change	Placebo (N=2612)	Lorcaserin 10 mg BID (N=2771)	Lorcaserin 10 mg QD (N=736)	Placebo (N=2553)	Lorcaserin 10 mg BID (N=2696)	Lorcaserin 10 mg QD (N=702)	Placebo (N=59)	Lorcaserin 10 mg BID (N=75)	Lorcaserin 10 mg QD (N=34)
AORTIC VALVE									
-3	0	1 (0.04)	0	0	0	0	0	1 (1.33)	0
-2	8 (0.31)	3 (0.11)	1 (0.14)	0	0	0	8 (13.56)	3 (4.00)	1 (2.94)
-1	210 (8.04)	223 (8.05)	56 (7.61)	202 (7.91)	200 (7.42)	48 (6.84)	8 (13.56)	23 (30.67)	8 (23.53)
0	2210 (84.61)	2314 (83.51)	631 (85.73)	2171 (85.04)	2268 (84.12)	607 (86.47)	39 (66.10)	46 (61.33)	24 (70.59)
1	169 (6.47)	218 (7.87)	44 (5.98)	165 (6.46)	216 (8.01)	43 (6.13)	4 (6.78)	2 (2.67)	1 (2.94)
2	15 (0.57)	12 (0.43)	4 (0.54)	15 (0.59)	12 (0.45)	4 (0.57)	0	0	0
3	0	0	0	0	0	0	0	0	0
MITRAL VALVE									
-3	0	0	0	0	0	0	0	0	0
-2	25 (0.96)	27 (0.97)	7 (0.95)	22 (0.86)	20 (0.74)	4 (0.57)	3 (5.00)	7 (9.33)	3 (8.82)
-1	565 (21.62)	560 (20.21)	156 (21.20)	546 (21.39)	539 (19.99)	142 (20.23)	19 (31.67)	21 (28.00)	14 (41.18)
0	1521 (58.21)	1599 (57.70)	442 (60.05)	1496 (58.60)	1559 (57.83)	427 (60.83)	25 (41.67)	40 (53.33)	15 (44.12)
1	477 (18.25)	553 (19.96)	128 (17.39)	464 (18.17)	546 (20.25)	126 (17.95)	13 (21.67)	7 (9.33)	2 (5.88)
2	25 (0.96)	32 (1.15)	3 (0.41)	25 (0.98)	32 (1.19)	3 (0.43)	0	0	0
3	0	0	0	0	0	0	0	0	0
TRICUSPID VALVE									
-3	1 (0.04)	0	0	1 (0.04)	0	0	0	0	0
-2	31 (1.20)	27 (0.98)	5 (0.68)	30 (1.19)	27 (1.01)	4 (0.57)	1 (1.67)	0	1 (2.94)
-1	412 (15.92)	385 (14.03)	109 (14.83)	400 (15.82)	367 (13.75)	100 (14.27)	12 (20.00)	18 (24.00)	9 (26.47)
0	1727 (66.73)	1843 (67.14)	485 (65.99)	1690 (66.85)	1800 (67.42)	467 (66.62)	37 (61.67)	43 (57.33)	18 (52.94)
1	397 (15.34)	462 (16.83)	129 (17.55)	387 (15.31)	450 (16.85)	123 (17.55)	10 (16.67)	12 (16.00)	6 (17.65)
2	20 (0.77)	28 (1.02)	6 (0.82)	20 (0.79)	26 (0.97)	6 (0.86)	0	2 (2.67)	0
3	0	0	1 (0.14)	0	0	1 (0.14)	0	0	0
PULMONIC VALVE									
-1	365 (14.51)	382 (14.38)	101 (13.82)	355 (14.45)	367 (14.21)	97 (13.92)	10 (16.95)	15 (20.00)	4 (11.76)
0	1763 (70.07)	1827 (68.76)	529 (72.37)	1719 (69.96)	1777 (68.82)	504 (72.31)	44 (74.58)	50 (66.67)	25 (73.53)
1	388 (15.42)	448 (16.86)	101 (13.82)	383 (15.59)	438 (16.96)	96 (13.77)	5 (8.47)	10 (13.33)	5 (14.71)

Note: Last non-missing post baseline observation carried forward. Positive values indicate increased and negative numbers indicate decreased regurgitant score from Baseline to Week 52.

7.16 Search Terms used in Grouped Adverse Events of Interest

Below are the MedDRA Preferred Terms used for "adverse event of interest" searches. Standard MedDRA Queries (SMQs) that were used are included.

Depression Narrow (SMQ)	**Depression Broad (SMQ)**
Activation syndrome	Affect lability
Adjustment disorder with depressed mood	Alcohol abuse
Adjustment disorder with mixed anxiety and depressed mood	Alcohol problem
Agitated depression	Alcohol rehabilitation
Anhedonia	Alcoholism
Antidepressant therapy	Apathy
Childhood depression	Blunted affect
Decreased interest	Constricted affect
Depressed mood	Crying
Depression	Disturbance in attention
Depression postoperative	Drug abuse
Depressive symptom	Drug abuser
Dysphoria	Drug dependence
Dysthymic disorder	Drug dependence, antepartum
Electroconvulsive therapy	Drug dependence, postpartum
Feeling guilty	Dyssomnia
Feeling of despair	Emotional distress
Feelings of worthlessness	Hypersomnia
Major depression	Hyposomnia
Menopausal depression	Impaired self-care
Postpartum depression	Initial insomnia
	Intentional drug misuse
Suicide/self-injury (SMQ)	Listless
Completed suicide	Maternal use of illicit drugs
Depression suicidal	Memory impairment
Intentional overdose	Middle insomnia
Intentional self-injury	Mood altered
Multiple drug overdose intentional	Mood swings
Poisoning deliberate	Morose
Self injurious behavior	Negative thoughts
Self-injurious ideation	Neglect of personal appearance
Suicidal behavior	Polysubstance dependence
Suicidal ideation	Poor quality sleep
Suicide attempt	Psychomotor hyperactivity
	Psychomotor retardation
	Psychosocial support
Psychosis Narrow (SMQ)	Psychotherapy
Acute psychosis	Self esteem decreased
Alcoholic psychosis	Substance abuse
Alice in wonderland syndrome	Substance abuser
Brief psychotic disorder with marked stressors	Tearfulness
Brief psychotic disorder without marked stressors	Terminal insomnia
Brief psychotic disorder, with postpartum onset	
Charles Bonnet syndrome	**Psychosis Broad (SMQ)**
Childhood psychosis	Abnormal behavior

Clang associations	Abulia
Cotard's syndrome	Affect lability
Delusion	Affective disorder
Delusion of grandeur	Alcohol withdrawal syndrome
Delusion of reference	Anosognosia
Delusion of replacement	Apathy
Delusional disorder, erotomanic type	Asocial behaviour
Delusional disorder, grandiose type	Bipolar I disorder
Delusional disorder, jealous type	Blunted affect
Delusional disorder, mixed type	Bradyphrenia
Delusional disorder, persecutory type	Catatonia
Delusional disorder, somatic type	Childhood disintegrative disorder
Delusional disorder, unspecified type	Constricted affect
Delusional perception	Dyslogia
Delusions, mixed	Echolalia
Dementia of the Alzheimer's type, with delusions	Echopraxia
Depressive delusion	Flat affect
Derailment	Grandiosity
Epileptic psychosis	Hypomania
Erotomanic delusion	Idioglossia
Flight of ideas	Illogical thinking
Hallucination	Inappropriate affect
Hallucination, auditory	Incoherent
Hallucination, gustatory	Lack of spontaneous speech
Hallucination, olfactory	Logorrhoea
Hallucination, synaesthetic	Magical thinking
Hallucination, tactile	Major depression
Hallucination, visual	Mania
Hallucinations, mixed	Mutism
Hypnagogic hallucination	Obsessive rumination
Hypnopompic hallucination	Perseveration
Hysterical psychosis	Poverty of speech
Ideas of reference	Poverty of thought content
Illusion	Presenile dementia
Jealous delusion	Pressure of speech
Korsakoff's psychosis alcoholic	Senile dementia
Korsakoff's psychosis non-alcoholic	Social avoidant behaviour
Loose associations	Speech disorder
Neologism	Suspiciousness
Paranoia	Tachyphrenia
Paranoid personality disorder	Thinking abnormal
Paroxysmal perceptual alteration	Vascular dementia
Persecutory delusion	Verbigeration
Posturing	Wernicke-Korsakoff syndrome
Psychosis postoperative	
Psychotic behaviour	
Psychotic disorder	**Neuroleptic Malignant Syndrome Narrow (SMQ)**
Psychotic disorder due to a general medical condition	Hyperthermia malignant
Reactive psychosis	Neuroleptic malignant syndrome
Schizoaffective disorder	Serotonin syndrome
Schizoaffective disorder bipolar type	
Schizoaffective disorder depressive type	**Neuroleptic Malignant Syndrome Broad (SMQ)**
Schizophrenia	Body temperature increased

Schizophrenia simple	Hyperpyrexia
Schizophrenia, catatonic type	Pyrexia
Schizophrenia, disorganised type	Catatonia
Schizophrenia, paranoid type	Dyskinesia
Schizophrenia, residual type	Dystonia
Schizophrenia, undifferentiated type	Freezing phenomenon
Schizophreniform disorder	Hyperkinesia
Schizotypal personality disorder	Hypertonia
Senile psychosis	Muscle necrosis
Shared psychotic disorder	Muscle rigidity
Somatic delusion	Oculogyric crisis
Somatic hallucination	Opisthotonus
Tangentiality	Rhabdomyolysis
Thought blocking	Altered state of consciousness
Thought broadcasting	Autonomic nervous system imbalance
Thought insertion	Blood creatine phosphokinase abnormal
Thought withdrawal	Blood creatine phosphokinase increased
Transient psychosis	Blood creatine phosphokinase MM increased
Waxy flexibility	Blood pressure abnormal
	Blood pressure decreased
	Blood pressure fluctuation
Serotonin syndrome (Arena customized)	Blood pressure increased
Confusional state	Cardiovascular insufficiency
Disorientation	Coma
Delirium	Confusional state
Coma	Consciousness fluctuating
Hyperthermia	Delirium
Hyperhydrosis	Depressed level of consciousness
Hyperhidrosis	Disorientation
Sweating fever	Extrapyramidal disorder
Clonus	Heart rate abnormal
Myoclonus	Heart rate increased
Hypertonia	Hyperhidrosis
Opsoclonus myoclonus	Hypertension
Tremor	Hypotension
Intention tremor	Labile blood pressure
Essential tremor	Labile hypertension
Chills	Leukocytosis
Hyperreflexia	Loss of consciousness
Serotonin syndrome	Muscle enzyme increased
	Myoclonus
	Myoglobin blood increased
Breast neoplasms SMQ	Myoglobin blood present
Breast cancer	Myoglobin urine present
Breast cancer female	Myoglobinaemia
Breast cancer in situ	Myoglobinuria
Breast cancer male	Parkinsonian crisis
Breast cancer metastatic	Parkinsonian rest tremor
Breast cancer recurrent	Parkinsonism
Breast cancer stage I	Parkinson's disease
Breast cancer stage II	Stupor
Breast cancer stage III	Tachycardia
Breast cancer stage IV	Tremor

Breast lump removal	Unresponsive to stimuli
Breast neoplasm	White blood cell count abnormal
Breast sarcoma	White blood cell count increased
Breast sarcoma metastatic	
Breast sarcoma recurrent	**Dystonia Narrow SMQ**
Contralateral breast cancer	Dystonia
Cystosarcoma phyllodes	Emprosthotonus
Electron radiation therapy to breast	Meige's syndrome
Extended radical mastectomy	Oculogyric crisis
Gamma radiation therapy to breast	Opisthotonus
Inflammatory carcinoma of breast recurrent	Oromandibular dystonia
Inflammatory carcinoma of breast stage III	Pleurothotonus
Inflammatory carcinoma of breast stage IV	Spasmodic dysphonia
Inflammatory carcinoma of the breast	Torticollis
Malignant breast lump removal	Trismus
Malignant nipple neoplasm	
Malignant nipple neoplasm female	**Dystonia Broad SMQ**
Malignant nipple neoplasm male	Abasia
Mastectomy	Blepharospasm
Modified radical mastectomy	Drooling
Nipple neoplasm	Extrapyramidal disorder
Oestrogen receptor assay positive	Facial spasm
Paget's disease of the breast	Laryngospasm
Photon radiation therapy to breast	Motor dysfunction
Postmastectomy lymphoedema syndrome	Movement disorder
Progesterone receptor assay positive	Muscle contractions involuntary
Radical mastectomy	Muscle spasms
Radiotherapy to breast	Muscle spasticity
Simple mastectomy	Muscle tightness
X-ray therapy to breast	Muscle twitching
Antioestrogen therapy	Musculoskeletal stiffness
Biopsy breast abnormal	Oesophageal spasm
Breast calcifications	Oropharyngeal spasm
Breast dysplasia	Posture abnormal
Breast prosthesis implantation	Posturing
Breast reconstruction	Risus sardonicus
	Tic
	Tongue spasm
Gallbladder disease SMQ	Torticollis psychogenic
Biliary dyskinesia	Uvular spasm
Cholecystectomy	
Cholecystitis	**AEs related dizziness**
Cholecystitis acute	Dizziness postural
Cholecystitis chronic	Dizziness
Cholecystoenterostomy	
Cholecystostomy	**AEs related to Paraesthesia**
Cholelithiasis	Paraesthesia oral
Cholelithiasis obstructive	Paraesthesia
Cholelithotomy	
Gallbladder cholesterolosis	**AEs Related to Prolactin**
Gallbladder disorder	Hyperprolactinemia
Gallbladder enlargement	Blood prolactin abnormal
Gallbladder fistula	Blood prolactin increased

Gallbladder fistula repair	
Gallbladder injury	
Gallbladder mucocoele	
Gallbladder necrosis	
Gallbladder non-functioning	
Gallbladder obstruction	
Gallbladder oedema	
Gallbladder operation	
Gallbladder pain	
Gallbladder perforation	
Hydrocholecystis	
Hyperplastic cholecystopathy	
Porcelain gallbladder	

AE, adverse event; SMQ, Standard MedDRA Query

Appendix 6 Statistical Analysis of the Association Between Weight or BMI Change and Incidence of FDA-defined Valvulopathy

Singh and colleagues analyzed echocardiographic data obtained as part of the Framingham Offspring Study, using a subgroup of patients who had studies of acceptable technical quality and who lacked aortic or mitral stenosis.[5] They evaluated the prevalence and clinical determinants of mitral regurgitation (MR), aortic regurgitation (AR) and tricuspid regurgitation (TR). Age was positively associated with AR, MR and TR. Of relevance to the lorcaserin analyses, Singh et al. also identified a negative correlation between BMI and MR and between BMI and TR. In other words, as obesity increased, the apparent incidence of MR and TR decreased. The authors noted that the effect of adiposity could be technical (more difficult to detect regurgitation in more obese individuals) or could be related to cardiac structural or hemodynamic factors.

Based on the findings of Singh and colleagues, we hypothesized that weight loss (or decrease in BMI) among overweight or obese individuals might result in an apparent increase in the prevalence of FDA-defined valvulopathy at some point following weight loss as compared to a time point pre-weight loss.

The statistical methodology for the modeling is summarized below. The stepwise analyses were performed as follows:

- First, baseline factors associated with FDA-defined valvulopathy were identified using stepwise methods using only placebo data.
- Using the resulting logistic regression base model, the effect of weight change (or BMI change) as factors added to the base model was assessed.
- Using the parameter estimates from the placebo group, the predicted probabilities and predicted log odds for the lorcaserin group were obtained. The predicted probabilities and predicted log odds were used in two different methods to assess whether weight change (or BMI change) contributed to the observed incidence of valvulopathy in the lorcaserin group.
- The treatment-by-weight change, treatment-by-baseline weight and treatment-by-age interactions were analyzed using all patient data (as a way to identify whether associations with weight change, baseline weight and age were comparable for placebo and lorcaserin).
- The treatment effect on incidence of FDA-defined valvulopathy was assessed, adjusting for weight change (or BMI change). Some caution is needed in interpreting the results since treatment has an effect on weight change.

The resulting parameter estimates for the pooled datasets for placebo and lorcaserin 10 mg BID (since the models did not differ by treatment group) are presented in Table 83. While statistical significance was not achieved for the placebo alone model, inclusion of all data resulted in significant negative associations, with very little change in the parameter estimates.

Table 83. Association Analysis of Weight or BMI Change at Week 52 versus FDA-Defined Valvulopathy: Pooled Phase 3 Studies (APD356-009, -010, and -011)

Model	Parameter Estimate[a]	p-value	Odds Ratio (95% CI)	Predicted Risk with Given Change[b] -5 kg. -5% or -2 kg/m^2
Placebo Only				
Percent Change from Baseline in Body Weight	-0.0250	0.2456	0.975 (0.935, 1.017)	1.13
Change from Baseline in Body Weight (kg)	-0.0217	0.3010	0.979 (0.939, 1.020)	1.11
Change from Baseline in BMI (kg/m^2)	-0.0698	0.2408	0.933 (0.830, 1.048)	1.15
Placebo and Lorcaserin Combined				
Percent Change from Baseline in Body Weight	-0.0286	0.0256	0.972 (0.948, 0.997)	1.15
Change from Baseline in Body Weight (kg)	-0.0245	0.0597	0.976 (0.951, 1.001)	1.13
Change from Baseline in BMI (kg/m^2)	-0.0745	0.0411	0.928 (0.864, 0.997)	1.16

[a] Parameter estimate from Logistic Regression model with age, baseline weight (or baseline BMI)

[b] To calculate: exp ([change] x [parameter estimate])

According to this analysis, the apparent incidence of FDA-defined valvulopathy was negatively associated with percent change in body weight or with change in BMI. The association was more highly significant when 12 week weight or BMI change was used in place of Week 52. In other words, with greater weight loss, the incidence of detectable FDA valvulopathy increased, regardless of study treatment. The absence of a treatment effect independent of weight loss is supported by the fact that the initial model was developed using the placebo group only and did not differ significantly from the model developed using the lorcaserin group. Weight loss in the pooled population from all three Phase 3 studies was 5.6% in the lorcaserin BID group and 2.3% in the placebo group by MITT/LOCF analysis, and 7.3% and 3.2%, respectively, by Completer analysis. The models predict that this magnitude of change in BMI and weight will be associated with an odds ratio of 1.1 to 1.2 for FDA valvulopathy over a population with a stable weight. The odds ratio associated with the observed weight loss in the placebo group would be approximately half the lorcaserin BID value. Differential weight loss could therefore substantially explain the slight imbalance in incidence of FDA valvulopathy in the two pooled populations, further offsetting the risk that there is any difference in rates between these two groups.

A plausible explanation for the apparent increase in FDA-defined valvulopathy with weight loss in overweight/obese individuals is an improved image quality that is possible with less adipose tissue (chest wall and pericardial/epicardial fat) intervening between the probe and the heart valve.