# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 022529Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# OFFICE OF CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA: 22-529 | Submission Date(s): 12/23/2011 |
| Brand Name | BELVIQ |
| Generic Name | Lorcaserin |
| Reviewer | Immo Zadezensky, Ph.D. |
| Secondary Reviewer | Jaya Vaidyanathan, Ph.D. |
| Primary PM reviewer (TL) | Christine Garnett, Pharm.D. |
| Secondary PM reviewer | Kevin Krudys, Ph.D. |
| OCP Division | Clinical Pharmacology II |
| OND Division | Metabolism and Endocrinology Products |
| Sponsor | Arena Pharmaceuticals Inc. |
| Submission Type | 505 (b)(1) |
| Formulation | Tablet, 10 mg |
| Indication | Weight management, including weight loss and maintenance of weight loss |

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## 1 LIST OF TABLES AND FIGURES:

# 1. EXECUTIVE SUMMARY

## 1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed NDA 22-529 and finds it acceptable. See labeling recommendations in page 7.

## 1.2 PHASE IV REQUIREMENT

None.

## 1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

The sponsor, Arena Pharmaceuticals Inc., submitted a 505 (b)(1) new drug application (NDA 22-529) seeking a marketing approval for a 10 mg BID dose of lorcaserin hydrochloride (hemihydrate) immediate release tablets. The sponsor is seeking the indication for weight management, including weight loss and maintenance of weight loss, and usage in conjunction with a reduced-calorie diet and a program of regular exercise. The intended target population is 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).

Arena Pharmaceuticals submitted a New Drug Application for lorcaserin on December 18, 2009. The FDA issued a Complete Response Letter (CRL) on October 22, 2010. The CRL requested that Arena provide the final study report for the phase 3 trial in obese patients with Type 2 diabetes mellitus (APD356-10) and requested estimates of human brain exposure to lorcaserin to assess the safety margin of brain astrocytoma which was observed in non-clinical studies.

In the current resubmission, Arena has provided responses to the nonclinical and clinical deficiencies outlined in the CRL. The three clinical studies submitted with the complete response are:

1. APD356-010 (BLOOM-DM): 52-Week Safety and Efficacy of Lorcaserin in Overweight and Obese Patients with Type 2 Diabetes Mellitus
2. APD356-014 (TULIP): 56-Day Effect of Lorcaserin on Energy Metabolism and Food Intake in Overweight and Obese Patients
3. APD356-022: An Open Label Study to Assess the Pharmacokinetic Properties of Lorcaserin at Steady State in the Cerebrospinal Fluid of Healthy Volunteers. Lorcaserin concentration in the cerebrospinal fluid at steady state was measured to estimate brain exposure.

Please refer to the clinical pharmacology review for the original NDA in DARRTS dated10/01/2010 for details on the clinical pharmacology of lorcaserin. This review will focus on the exposure-response information from the BLOOM-DM study and the study in healthy volunteers to assess the steady state concentrations of lorcaserin in cerebrospinal fluid (CSF).

**What are the pharmacokinetic properties of lorcaserin in human CSF at steady state?**

Lorcaserin reaches maximum mean steady state plasma concentration ($C_{max,ss}$) of 63.1 ± 14.1 ng/mL (mean ± SD) at 2 h (range: 1 to 4 h). The maximum CSF concentration was 0.954 ± 0.458 ng/mL at 6 h (range: 2 to 8 h). At steady state, the $C_{min,ss}$ values for plasma and CSF were 27.4 ± 8.73 and 0.455 ± 0.162 ng/mL, respectively. The integrated exposure over 12 h in plasma and CSF ($AUC_{0-t}$) was 540 ± 157 h*ng/mL and 9.31 ± 3.87 h*ng/mL, respectively.

Mean plasma and CSF pharmacokinetic parameters of lorcaserin with summary statistics are presented in Table 1. Means and geometric means of CSF and plasma PK parameters are reported in Table 2.

Table 1 Individual and Arithmetic Mean Lorcaserin CSF and Plasma PK Parameters after 10 mg Lorcaserin HCl Twice Daily for 7 Days

| Subject ID | CSF | | | | Plasma | | | |
|---|---|---|---|---|---|---|---|---|
| | $C_{max,ss}$ (ng/mL) | $AUC_{0-t}$ (h·ng/mL) | $t_{max,ss}$[b] (h) | $C_{min,ss}$ (ng/mL) | $C_{max,ss}$ (ng/mL) | $AUC_{0-t}$ (h·ng/mL) | $t_{max,ss}$ (h) | $C_{min,ss}$ (ng/mL) |
| 001 | 0.669 | 6.53 | 8 | 0.407 | 57.1 | 469 | 4 | 27.7 |
| 003 | 1.01 | 11.4 | 2 | 0.579 | 71.1 | 627 | 2 | 33.8 |
| 004 | 1.97 | 16.9 | 8 | 0.59 | 88.6 | 832 | 2 | 40.7 |
| 005 | 0.656 | 6.41 | 6 | NA[a] | 50.6 | 363 | 2 | 17.7 |
| 006 | 1.22 | 11.8 | 6 | 0.583 | 66.9 | 573 | 4 | 31.6 |
| 007 | 0.507 | 5.12 | 4 | 0.232 | 42.6 | 361 | 2 | 18.5 |
| 008 | 1.05 | 9.90 | 6 | 0.273 | 69.6 | 570 | 2 | 24.9 |
| 009 | 0.983 | 10.4 | 4 | 0.638 | 70.8 | 660 | 4 | 35.6 |
| 011 | 0.520 | 5.29 | 4 | 0.335 | 50.7 | 402 | 1 | 16.1 |
| Mean | 0.954 | 9.31 | 6 | 0.455 | 63.1 | 540 | 2 | 27.4 |
| SD | 0.458 | 3.87 | 2 | 0.162 | 14.1 | 157 | 1 | 8.73 |
| CV (%)[c] | 48.0 | 41.6 | 8 | 35.6 | 22.4 | 29.1 | 4 | 31.9 |

[a] No CSF sample was taken at predose for subject 005

[b] Median (minimum – maximum)

[c] %CV = Standard Deviation / Mean × 100

Source: Clinical Study Report ADP356-022, Table 5, page 35

Table 2 Geometric Mean Lorcaserin CSF and Plasma PK Parameters after 10 mg Lorcaserin HCl Twice Daily for 7 Days

| Pharmacokinetic Parameters | Geometric Mean (90% Confidence Interval) | | |
|---|---|---|---|
| | CSF | Plasma | CSF/Plasma Ratio |
| $AUC_{0-t}$ (ng·h/mL) | 8.63 (6.68, 11.14) | 520 (435, 622) | 0.017 (0.015, 0.018) |
| $C_{max,ss}$ (ng/mL) | 0.87 (0.66, 1.15) | 61.7 (53.6, 71.0) | 0.014 (0.012, 0.016) |
| $C_{min,ss}$ (ng/mL) | 0.43 (0.33, 0.56) | 27.4 (22.1, 34.0) | 0.016 (0.013, 0.018) |
| $t_{max,ss}$(h)[a] | 6.00 (2.00, 8.00) | 2.00 (1.00, 4.00) | NA[b] |

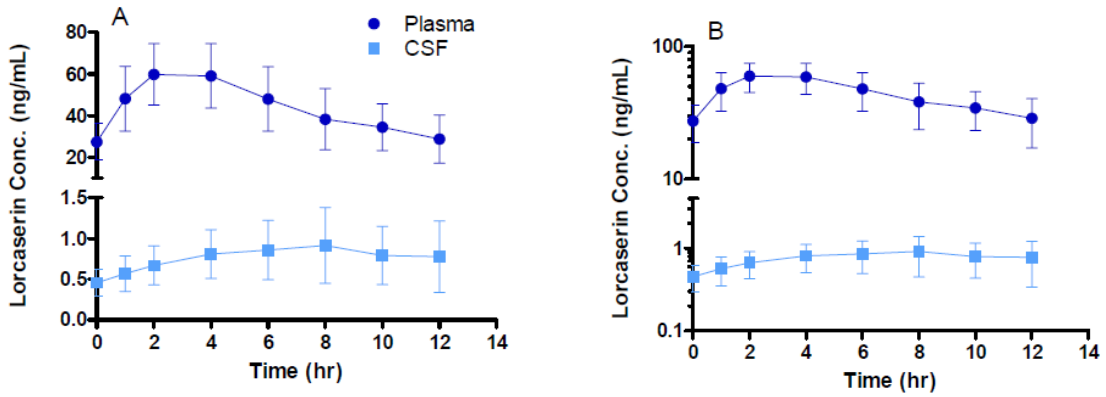
[a] Median (minimum – maximum)

[b] NA: Not applicable

Source: Clinical Study Report ADP356-022, Table 6, page 35

Mean plasma and CSF concentration-time profiles are presented in Figure 3 on a linear scale (panel A) and semi-logarithmic scale (panel B).

Figure 1 Lorcaserin Plasma and CSF Concentrations *vs.* Time Profiles on Day 7 after 10 mg Lorcaserin Twice Daily. A: linear plot; B: semilog plot; (Mean ± SD, n=9)



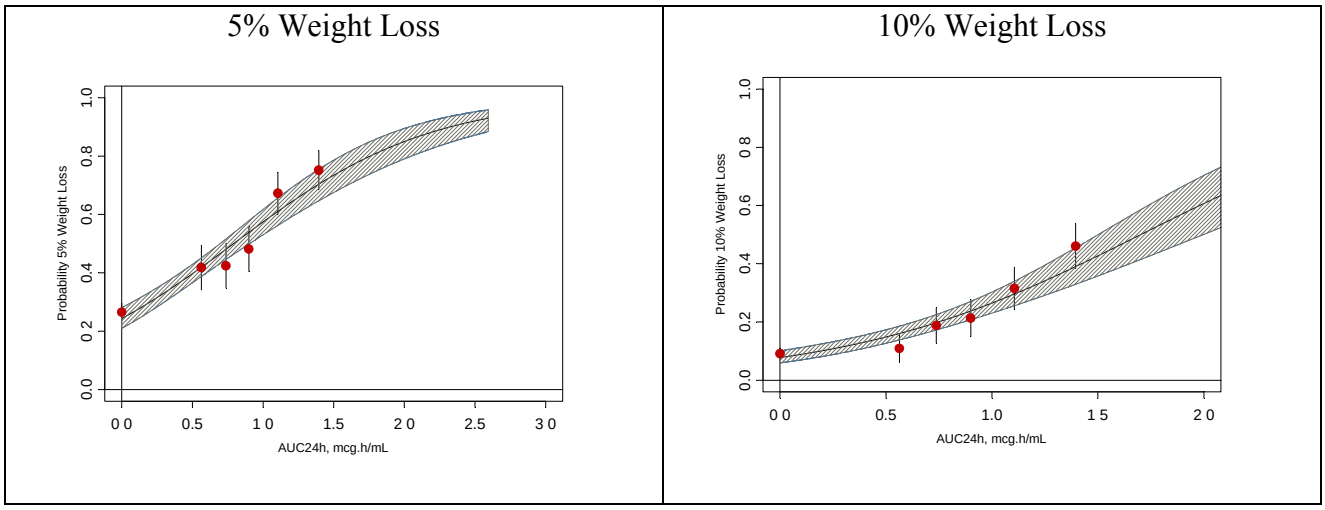

Refer to Pharmacology/toxicology review for the details as to how this information mitigates the concern raised from nonclinical findings. In brief, the clinical data submitted indicated that partitioning of lorcaserin to the CNS in human subjects is substantially lower than predicted by nonclinical studies in rats and non-human primates. A safety margin of 70-fold for astrocytoma in rats, based on estimated brain levels of lorcaserin, presents a negligible clinical risk.

**Does the exposure-response relationship for weight loss support the proposed dose in non-diabetic and diabetic patients?**

Although the proportion of patients who lost ≥5% of weight (primary endpoint) in study APD356-010 was higher in the 10 mg QD arm compared to the 10 mg BID arm (44.7% vs. 37.5%), the exposure-response relationship using pooled data from three clinical trials (APD356-010, APD356-011, and APD356-009) supports the proposed dose of 10 mg BID lorcaserin. The sponsor attributed the higher than expected weight loss in the 10 mg QD group to higher completion rates and different enrollment periods. This dose group was discontinued because of slow enrollment rate (protocol amendment 3). As a result, there were only 94 patients in the 10 mg QD group compared to 251 and 248 patients in the 10 mg BID and placebo groups, respectively.

The positive exposure-response analysis for probability of weight loss (Figure 4) supports the proposed dose of 10 mg BID lorcaserin. At a median AUC24h of 0.815 µg.h/ml, corresponding to the median exposure for 10 mg BID dose, the model-predicted probability of 5% and 10% weight loss is 51% and 22%, respectively. In comparison, at a median AUC24h of 0.425 µg.h/ml, corresponding to the median exposure at the 10 mg QD dose, the probability of 5% and 10% weight loss is 37% and 13.5%. There was no effect of diabetes status in the logistic regression models.

**Figure 2. Exposure-Response Analysis for 5% and 10% Weight Loss (Reviewer's Analysis)**




Based on a longitudinal PK/PD model conducted by the sponsor, the model-predicted mean (±SD) individual predicted percent weight loss at Week 52 in non-diabetic patients was 4% (±6%) for the placebo, 7% (±6%) for 10 mg QD and 9% (±6%) for 10 mg BID lorcaserin. For diabetic patients, model-predicted values were 3% (±4%) for the placebo, 6% (±5%) for 10 mg QD and 6% (±6%) for 10 mg BID lorcaserin.

**Are the labeling statements based on population PK model acceptable?**

No new labeling statements were proposed based on the current models.

*2* . Individual Study Review APD356-022

Pharmacokinetics in Cerebrospinal Fluid: APD356-022

This clinical study was titled: "An Open Label Study to Assess the Pharmacokinetic Properties of Lorcaserin at Steady State in the Cerebrospinal Fluid of Healthy Volunteers." The objective of this study was the pharmacokinetic properties of lorcaserin dosed to steady state in the cerebrospinal fluid of healthy volunteers.

## STUDY DESIGN

The study was a single site, open-label study of healthy overweight or obese adult men and women and enrolled 11 subjects. (detailed demographics see Table 3, with an age range between 18 to 65 years and a BMI of 27-35 kg/$m^2$. Subjects were given a 10 mg dose of lorcaserin BID for 7 days.

Table 3 Subject Demographic by Treatment Group

| Demographics | Lorcaserin 10 mg BID (N=11) |
|---|---|
| **Age (years)** | |
| Mean (SD) | 34.1 (8.6) |
| Median | 34.0 |
| Min - Max | 20 - 46 |
| **Age Group** | |
| 18-24 | 1 (9.1%) |
| 25-34 | 5 (45.5%) |
| 35-45 | 4 (36.4%) |
| 45-54 | 1 (9.1%) |
| **Race** | |
| White | 7 (63.6%) |
| Black or African American | 3 (27.3%) |
| American Indian or Alaska Native | 1 (9.1%) |
| **Sex** | |
| Male | 7 (63.6%) |
| Female | 4 (36.4%) |
| **Weight (kg)** | |
| Mean (SD) | 91.3 (9.5) |
| Median | 89.9 |
| Min - Max | 79.2 - 112.8 |
| **Height (cm)** | |
| Mean (SD) | 174.2 (7.0) |
| Median | 173.5 |
| Min - Max | 164.5 - 187.0 |

Source: Clinical Study Report ADP356-022, Table 3, page 30

## SAMPLE COLLECTION

Samples for pharmacokinetic assessment of lorcaserin were taken at the following time-points:

- On Days 1, 2, 3, 4, 5 and 6, blood samples (~4 mL) will be collected prior to the morning dose

- On Day 7, blood samples (~4 mL) and CSF samples (~0.5 mL at each time point) will be collected simultaneously up to 45 min pre-dose and at 1, 2, 4, 6, 8, 10, and 12 hrs post-dose

## PROTOCOL VIOLATIONS:

The majority of deviations are study procedures performed outside of window. However, one subject was given restricted medications (Subject was given the following medications: percocet, ibuprofen, adansetron, lorazepam, ducolax, naproxen). These medications were not allowed per protocol requirement. The overall outcome of the study seems to be unaffected by this protocol deviation.

## RESULTS

A total of 11 subjects were enrolled into the study, received at least one dose of study drug, and were included in the safety analyses. Of these, 9 subjects completed the study and were included in the PK analyses.

**Lorcaserin:**

Lorcaserin reaches maximum mean steady state plasma concentration ($C_{max,ss}$) of 63.1 ± 14.1 ng/mL (mean ± SD) at 2 h (range: 1 to 4 h). The maximum CSF concentration was 0.954 ± 0.458 ng/mL at 6 h (range: 2 to 8 h). At steady state, the $C_{min,ss}$ values for plasma and CSF were 27.4 ± 8.73 and 0.455 ± 0.162 ng/mL, respectively. The integrated exposure over 12 h in plasma and CSF ($AUC_{0-t}$) was 540 ± 157 h*ng/mL and 9.31 ± 3.87 h*ng/mL, respectively.

Mean plasma and CSF pharmacokinetic parameters of lorcaserin with summary statistics are presented in Table 4. Means and geometric means of CSF and plasma PK parameters are reported in Table 5.

*Reviewer comment: Mean lorcaserin plasma trough concentrations of 27.4 ng/mL observed in this study are comparable to trough concentrations observed in the pooled data from Phase 3 trial ADP356-009 and ADP356-011 during the original NDA.*

Table 4 Individual and Arithmetic Mean Lorcaserin CSF and Plasma PK Parameters after 10 mg Lorcaserin HCl Twice Daily for 7 Days

| Subject ID | CSF | | | | Plasma | | | |
|---|---|---|---|---|---|---|---|---|
| | $C_{max,ss}$ (ng/mL) | $AUC_{0-t}$ (h·ng/mL) | $t_{max,ss}$[b] (h) | $C_{min,ss}$ (ng/mL) | $C_{max,ss}$ (ng/mL) | $AUC_{0-t}$ (h·ng/mL) | $t_{max,ss}$ (h) | $C_{min,ss}$ (ng/mL) |
| 001 | 0.669 | 6.53 | 8 | 0.407 | 57.1 | 469 | 4 | 27.7 |
| 003 | 1.01 | 11.4 | 2 | 0.579 | 71.1 | 627 | 2 | 33.8 |
| 004 | 1.97 | 16.9 | 8 | 0.59 | 88.6 | 832 | 2 | 40.7 |
| 005 | 0.656 | 6.41 | 6 | NA[a] | 50.6 | 363 | 2 | 17.7 |
| 006 | 1.22 | 11.8 | 6 | 0.583 | 66.9 | 573 | 4 | 31.6 |
| 007 | 0.507 | 5.12 | 4 | 0.232 | 42.6 | 361 | 2 | 18.5 |
| 008 | 1.05 | 9.90 | 6 | 0.273 | 69.6 | 570 | 2 | 24.9 |
| 009 | 0.983 | 10.4 | 4 | 0.638 | 70.8 | 660 | 4 | 35.6 |
| 011 | 0.520 | 5.29 | 4 | 0.335 | 50.7 | 402 | 1 | 16.1 |
| Mean | 0.954 | 9.31 | 6 | 0.455 | 63.1 | 540 | 2 | 27.4 |
| SD | 0.458 | 3.87 | 2 | 0.162 | 14.1 | 157 | 1 | 8.73 |
| CV (%)[c] | 48.0 | 41.6 | 8 | 35.6 | 22.4 | 29.1 | 4 | 31.9 |

[a] No CSF sample was taken at predose for subject 005

[b] Median (minimum – maximum)

[c] %CV = Standard Deviation / Mean × 100

Source: Clinical Study Report ADP356-022, Table 5, page 35

Table 5 Geometric Mean Lorcaserin CSF and Plasma PK Parameters after 10 mg Lorcaserin HCl Twice Daily for 7 Days

| Pharmacokinetic Parameters | Geometric Mean (90% Confidence Interval) | | |
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| $C_{max,ss}$ (ng/mL) | 0.87 (0.66, 1.15) | 61.7 (53.6, 71.0) | 0.014 (0.012, 0.016) |
| $C_{min,ss}$ (ng/mL) | 0.43 (0.33, 0.56) | 27.4 (22.1, 34.0) | 0.016 (0.013, 0.018) |
| $t_{max,ss}$(h)[a] | 6.00 (2.00, 8.00) | 2.00 (1.00, 4.00) | NA[b] |

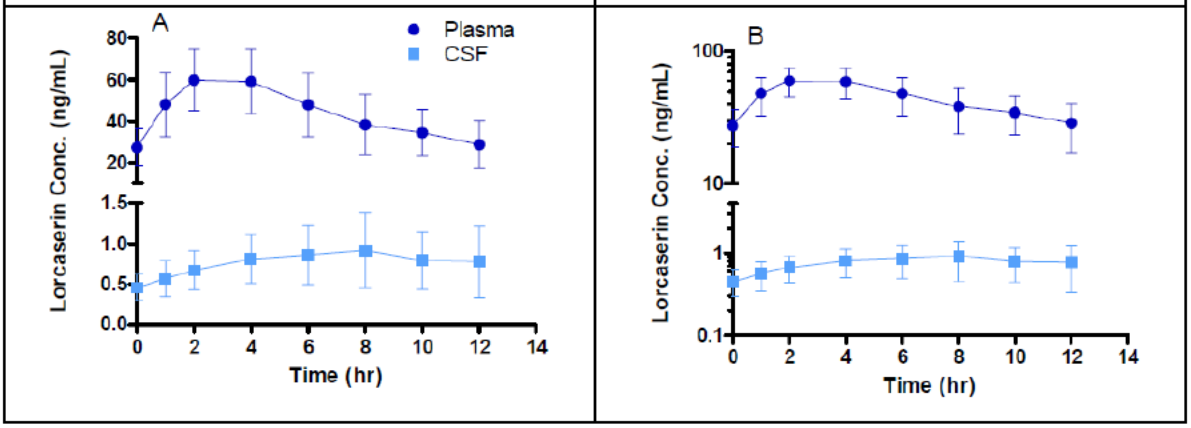
[a] Median (minimum – maximum)

[b] NA: Not applicable

Source: Clinical Study Report ADP356-022, Table 6, page 35

Mean plasma and CSF concentration-time profiles are presented in Figure 3 on a linear scale (panel A) and semi-logarithmic scale (panel B).

Figure 3 Lorcaserin Plasma and CSF Concentrations *vs.* Time Profiles on Day 7 after 10 mg Lorcaserin Twice Daily. A: linear plot; B: semilogarithmic plot; (Mean ± SD, n=9)




## ANALYTICAL METHOD

**Validation:**

Plasma:

The method was validated at [redacted] (b) (4) Samples were analyzed using a 200 µL aliquot volume and a protein precipitation, and [redacted] (b) (4) procedure followed by liquid chromatography/tandem mass spectrometry (LC/MS/MS) using atmospheric pressure chemical ionization. Lorcaserin standard curve covered the concentration range of 0.858 to 172 ng/mL( 0.858, 1.72, 3.44, 8.58, 34.4, 85.8, 150, 172 ng/mL) using APD356-$d_6$ as an internal standard. No significant interference at the analyte or internal standard retention times was observed from endogenous components. Long term stability was 265 days at -20°C and samples were stable over 5 freeze thaw cycles. For a summary of the QC validation results please refer to Table 6

CSF:

The method was validated at [redacted] (b) (4) Samples were analyzed using a 40.0 µL aliquot volume and a [redacted] (b) (4) procedure followed by liquid chromatography/tandem mass spectrometry (LC/MS/MS). An API 5000 was operated in the Selected Reaction Monitoring (SRM) mode under optimized conditions for detection of APD356 and APD356-$d_6$ positive ions formed by atmospheric pressure chemical ionization (APCI). Lorcaserin standard curve covered the concentration range of 0.200 to 30.0 ng/mL (0.200, 0.400, 1.00, 2.50, 10.0, 15.0, 27.0 and 30.0 ng/mL) using APD356-$d_6$ as an internal standard.

No significant interference at the analyte or internal standard retention times was observed from endogenous components. Long term stability was 588 days at -20°C and samples were stable over 4 freeze thaw cycles. For a summary of the QC validation results please refer to Table 6.

Table 6 Results of Quality Control from the bioanalytical method validation

| | Calibration | | | Quality control (between batch) | |
|---|---|---|---|---|---|
| Analyte / matrix | Curve range (ng/mL) | LLOQ (ng/mL) | %CV | %CV | %Bias |
| Lorcaserin/ plasma | 0.858 – 182 | 0.858 | 1.0 to 6.0 | 0.0 to 2.7% | -2.9 to 6.2% |
| Lorcaserin/ CSF | 0.200 – 30.0 | 0.200 | 1.1 to 8.5% | 0.0% to 4.5% | -2.5 to 4.0% |

Table 7 Results of Quality Control from the bioanalytical method

| | Calibration | | | Quality control (between batch) | |
|---|---|---|---|---|---|
| Analyte / matrix | Curve range (ng/mL) | LLOQ (ng/mL) | %CV | %CV | %Bias |
| Lorcaserin/ plasma | 1.00-200 | 1.00 | 1.3 to 4.5 | 1.5 to 2.6% | -10.0 to 2.7% |
| Lorcaserin/ CSF | 0.200 – 30.0 | 0.200 | 1.2 to 12.2 | 1.1 to 4.6% | -4.3 to -0.8% |

## CONCLUSIONS

Sponsor's conclusions:

- Plasma steady-state was achieved by Day 4. All subjects were at steady-state on Day 7.
- The plasma $C_{max,ss}$ was 63.1 ± 14.1 ng/mL (mean ± SD) at 2 h. The CSF $C_{max,ss}$ was 0.954 ± 0.458 ng/mL (mean ± SD) at 6 h.
- The CSF to plasma geometric mean ratios for $AUC_{0-t}$, $C_{max, ss}$ and $C_{min,ss}$, were 0.017, 0.014 and 0.016, respectively.

- Repeat oral administration of lorcaserin 10 mg twice daily to healthy obese or overweight volunteers produced a CSF to plasma exposure ratio at steady-state less than 0.02.
- 

***Reviewer comment:***

*The sponsor's conclusions are acceptable.*

3. Pharmacometric Review

# OFFICE OF CLINICAL PHARMACOLOGY:
# PHARMACOMETRIC REVIEW

| | |
|---|---|
| Application | NDA 022529 |
| Primary PM reviewer | Christine Garnett, Pharm.D. |
| Secondary PM reviewer | Kevin Krudys, Ph.D. |

## 2 SUMMARY OF FINDINGS

### 2.1 Key Review Questions

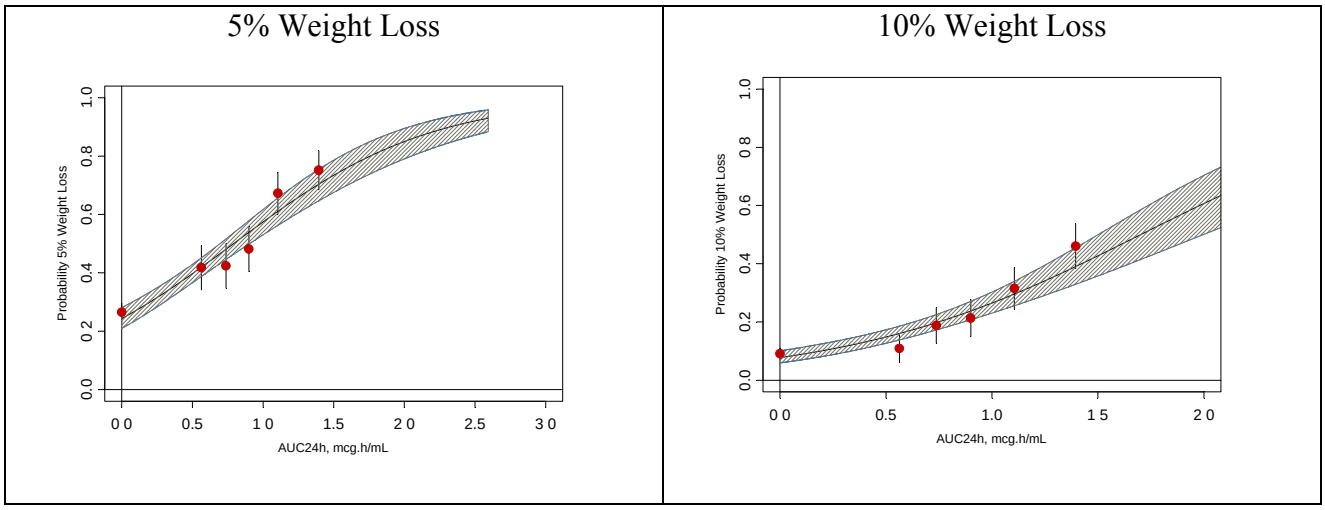
The purpose of this review is to address the following key questions.

#### 2.1.1 Does the exposure-response relationship for weight loss support the proposed dose in non-diabetic and diabetic patients?

Although the proportion of patients who lost ≥5% of weight (primary endpoint) in study APD356-010 was higher in the 10 mg QD arm compared to the 10 mg BID arm (44.7% vs. 37.5%), the exposure-response relationship using pooled data from three clinical trials (APD356-010, APD356-011, and APD356-009) supports the proposed dose of 10 mg BID lorcaserin. The sponsor attributed the higher than expected weight loss in the 10 mg QD group to higher completion rates and different enrollment periods. This dose group was discontinued because of slow enrollment rate (amendment 3). As a result, there were only 94 patients in the 10 mg QD group compared to 251 and 248 patients in the 10 mg BID and placebo groups, respectively.

The positive exposure-response analysis for probability of weight loss (Figure 4) supports the proposed dose of 10 mg BID locaserin. At a median AUC24h of 0.815 µg.h/ml, corresponding to the median exposure for 10 mg BID dose, the model-predicted probability of 5% and 10% weight loss is 51% and 22%, respectively. In comparison, at a median AUC24h of 0.425 µg.h/ml, corresponding to the median exposure at the 10 mg QD dose, the probability of 5% and 10% weight loss is 37% and 13.5%. There was no effect of diabetes status in the logistic regression models.

**Figure 4. Exposure-Response Analysis for 5% and 10% Weight Loss (Reviewer's Analysis)**




Based on a longitudinal PK/PD model conducted by the sponsor, the model-predicted mean (±SD) individual predicted percent weight loss at Week 52 in non-diabetic patients was 4% (±6%) for the placebo, 7% (±6%) for 10 mg QD and 9% (±6%) for 10 mg BID lorcaserin. For diabetic patients, model-predicted values were 3% (±4%) for the placebo, 6% (±5%) for 10 mg QD and 6% (±6%) for 10 mg BID lorcaserin.

### 2.1.2 Are the labeling statements based on population PK model acceptable?

No new labeling statements were proposed based on the current models.

## 2.2 Recommendations

## 2.3 Label Statements

**Labeling Statements based on Population PK analysis in section 12.2.** Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)

*Geriatric*. No dosage adjustment is required based on age alone. In a clinical trial of 12 healthy elderly (age >65 years) subjects and 12 matched adult patients, (b) (4) exposure (AUC and $C_{max}$) was equivalent in the two groups. $C_{max}$ was approximately 18% lower in the elderly group, and $T_{max}$ was increased from 2 hours to 2.5 hours in the elderly group as compared to the non-elderly adult group (b) (4)

(b) (4)

(b) (4)

## 3 PERTINENT REGULATORY BACKGROUND

Lorcaserin hydrochloride is a selective serotonin 2C (5-HT2c) receptor agonist being developed for weight loss. Arena Pharmaceuticals submitted a NDA for lorcaserin on December 18, 2009. The FDA issued a Complete Response Letter (CRL) on October 22, 2010. The CRL requested that Arena provide the final study report for phase 3 trial APD356-10 and requested estimates of human brain exposure to lorcaserin.

In the current resubmission, Arena has provided responses to the nonclinical and clinical deficiencies outlined in the CRL. The three clinical studies submitted with the complete response are

4. APD356-010 (BLOOM-DM): A 52-Week, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Safety and Efficacy of Lorcaserin Hydrochloride in Overweight and Obese Patients with Type 2 Diabetes Mellitus Managed with Oral Hypoglycemic Agent(s). This phase 3 trial evaluated the safety and efficacy of lorcaserin for weight loss in overweight and obese adults with type 2 diabetes mellitus that was managed with oral anti-diabetic agents. Secondarily, the study evaluated the effects of lorcaserin on glycemic control.
5. APD356-014 (TULIP): A 56-Day, Double-blind, Randomized, Placebo-controlled, Parallel group Study to Assess the Effect of Lorcaserin Hydrochloride on Energy Metabolism and Food Intake in Overweight and Obese Patients. This study evaluated the effects of lorcaserin on energy expenditure, metabolic rate, hunger, satiety, and other eating behaviors.
6. APD356-022: An Open Label Study to Assess the Pharmacokinetic Properties of Lorcaserin at Steady State in the Cerebrospinal Fluid of Healthy Volunteers. Lorcaserin concentration in the cerebrospinal fluid at steady state was measured to estimate brain exposure.

New pharmacokinetic information provided in this complete response includes updated population pharmacokinetic and PK/PD analyses that incorporate data from the APD356-010 study, and pharmacokinetic analysis of lorcaserin in human cerebrospinal fluid (CSF).

# 4 RESULTS OF SPONSOR'S ANALYSIS

## 4.1 Population Pharmacokinetics

### 4.1.1 Overview

The population pharmacokinetic analysis submitted with the original NDA has been updated for this complete response by the addition of data from the APD356-010 phase 3 study. Additional findings from the initial submission are as follow:

- The lorcaserin exposure data in APD356-010 were consistent with the previously developed Pop PK model.
- Lorcaserin exposure was slightly lower (lorcaserin clearance was slightly higher) among patients with type 2 diabetes than in non-diabetic patients.

### 4.1.2 Analysis Objectives

The primary objective was to describe the population PK of lorcaserin in healthy volunteers and obese/overweight patients including diabetics.

### 4.1.3 Clinical Data

Table 8 summarizes the data used for analysis. The final NONMEM dataset (File APD12911rINC10.csv) included a total of 6587 concentration-time records from 59 healthy volunteers and 945 obese/overweight patients (304 of them diabetics), giving a total of 1004 subjects.

**Table 8. Summary of the Source of Lorcaserin Concentration Data Used for Population PK Anlaysis (Sponsor's Table)**

| Study | Population | Dosing Regimen | Number of Concentrations |
|---|---|---|---|
| APD356-001 | Healthy Volunteers | Single Dose | 602 |
| APD356-002 | Healthy Volunteers | Once Daily | 485 |
| APD356-009 | Obese/overweight Patients | Twice Daily | 450 |
| APD356-010 | Diabetic Obese/overweight Patients | Once Daily | 645 |
| APD356-010 | Diabetic Obese/overweight Patients | Twice Daily | 1590 |
| APD356-011 | Obese/overweight Patients | Once Daily | 844 |
| APD356-011 | Obese/overweight Patients | Twice Daily | 1971 |

Source: Sponsor's Table 8:1, PK/PD Final Report page 34

### 4.1.4 Final Population PK Model

The final PK model for the Pop PK analysis of lorcaserin was a one-compartment model, with BSV estimated for CL/F, V/F and Ka, with a proportional error model for residual variability and covariance between CL/F and V/F (Table 9). The model included a power relationship between body weight and CL/F and a linear relationship between body weight and V/F, a fractional change in CL/F for diabetics and a formulation-dependent relative bioavailability (F1). Due to the presence of the effects of both formulation and diabetic status, there were some differences in lorcaserin PK parameters between the

three patient studies, as each study represented a unique combination of formulation and diabetic status. Goodness of fit plots are shown in Figure 5.

Due to the changes in weight during the course of the study, CL/F and derived exposure parameters differ slightly between Weeks 12, 24 and 52. A comparison of the summary of individual posterior predicted PK parameters is presented in Table 10. Goodness of fit plots are shown in Figure 6 and VPC in Figure 7. The percentage of lorcaserin concentrations outside of the 90% prediction intervals was 9.3% for BID dosing for study APD356-009; 14.9% and 7.9% for QD and BID dosing, respectively, for study APD356-010; and 9.0% and 10.1% for QD and BID dosing, respectively, for study APD356-010.

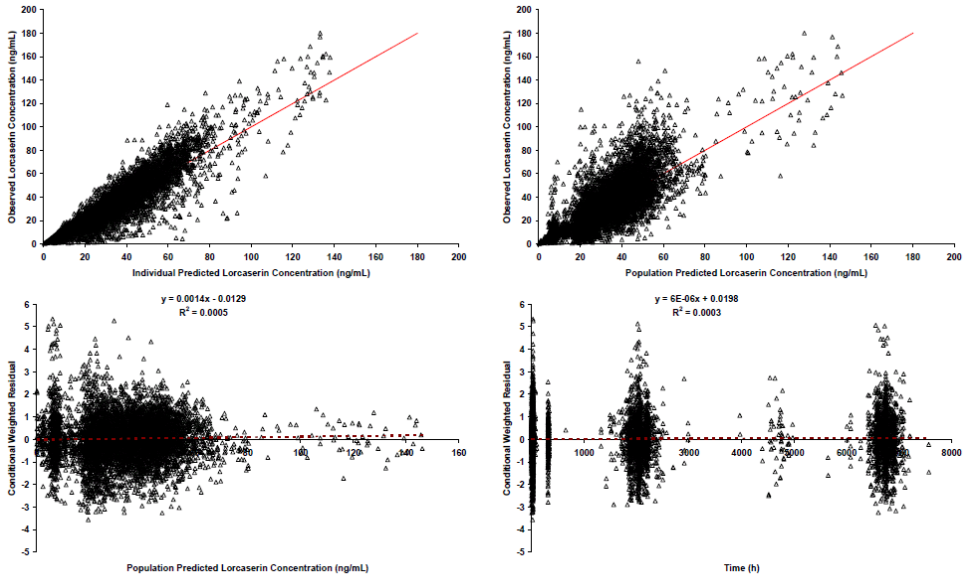
**Table 9. Lorcaserin Population PK Model (Sponsor's Table)**

| Parameter | Estimate [95% CI] | %RSE [b] |
|---|---|---|
| $CL/F = \Theta_{CL} * \Theta_{CL,WT} * \Theta_{CL,DIAB}$ | | |
| $\Theta_{CL}$ Males and females, all races, Non-diabetic (L/h) | 16.2 [15.5 – 16.9] | 2.23 |
| $\Theta_{CL,WT}$ $((BW/94.2)^{\Theta CL,WT})$ | 0.75 Fixed | |
| $\Theta_{CL,DIAB}$ [d] | 1.09 [1.04 – 1.14] | 2.36 |
| $V/F = \Theta_{V} * \Theta_{V,WT}$ | | |
| $\Theta_{V}$ Males and females, all races (L) | 241 [228 – 254] | 2.70 |
| $\Theta_{V,WT}$ $((BW/94.2)^{\Theta V,WT})$ | 1.0 Fixed | |
| $Ka = \Theta_{Ka}$ | | |
| $\Theta_{Ka}$ (1/h) | 1.44 [1.29 – 1.59] | 5.17 |
| $F1 = \Theta_{FORM}$ [e] | | |
| $\Theta_{F1,FORM5}$ | 0.893 [0.849 – 0.937] | 2.53 |
| $\Theta_{F1,FORM1-3}$ | 0.847 [0.789 – 0.905] | 3.48 |
| Inter-subject variability in CL/F (%CV) [a] [c] | 31.5 [6.29] | 6.71 |
| Inter-subject variability in V/F (%CV) [a] [c] | 17.5 [44.9] | 16.9 |
| Inter-subject variability in Ka (%CV) [a] [c] | 36.3 [70.9] | 30.3 |
| Correlation between CL/F and V/F (R) | 0.302 | 34.3 |
| Proportional residual variability in lorcaserin concentrations in healthy subjects and patients (%CV) [a] | 27.7 | 4.38 |

[a] The %CV for both inter-subject/patient and proportional residual variability is an approximation taken as the square root of the variance x 100. The approximation is due to the expansion of the exponential function only to first-order.
[b] RSE was calculated as the s.e. divided by the parameter estimate x 100.
[c] ETA Shrinkage % presented in parentheses.
[d] Fractional change from CL/F in non-diabetics.
[e] Formulation 4 capsule used in Study APD356-009 used as reference formulation. Formulation 5 was tablet administered in studies APD356-010 & APD356-011, Formulations 1-3 were administered in the Phase I studies.

Source: Sponsor's Table 8:12, PK/PD Final Report page 50

**Figure 5. Goodness of Fit Plots for Final Population PK Model (All Subjects)**




Source: Sponsor's Figure 11.9, PK/PD Final Report page 145

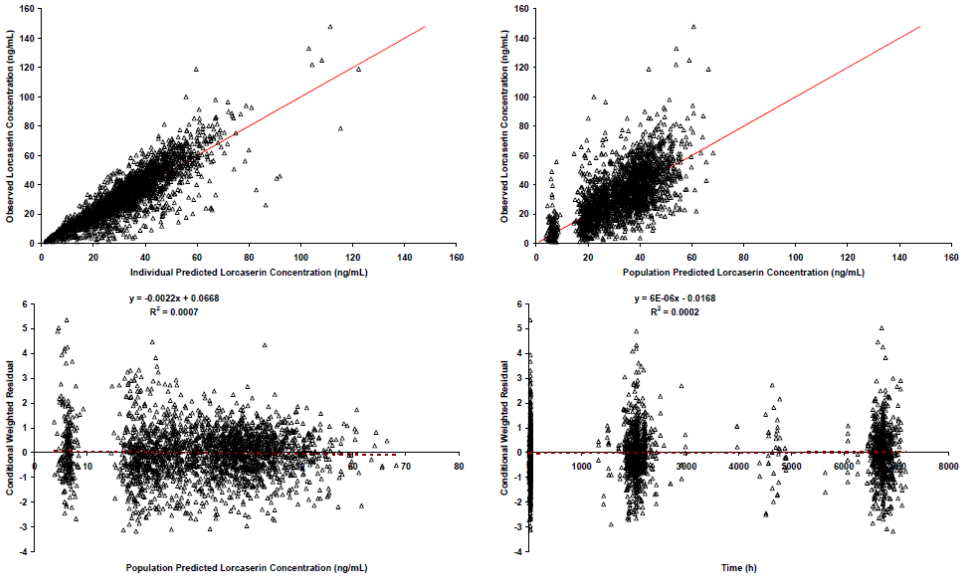
**Table 10. Individual Posterior Predicted Pharmacokinetic Parameters Following Administration of Lorcaserin in Diabetic Obese/Overweight Patients in Study APD356-010 (Sponsor's Table)**

| Parameter | Week 12 [(a)] (n=79) | Week 24 [(a)] (n=80) | Week 52[(a)] (n=72) | Week 12[(a)] (n=210) | Week 24 [(a)] (n=197) | Week 52[(a)] (n=169) |
|---|---|---|---|---|---|---|
| Dose | | 10 mg QD | | | 10 mg BID | |
| CL/F (L/h) | 18.4 (7.01) | 17.9 (6.67) | 17.6 (6.19) | 20.0 (6.86) | 19.5 (6.91) | 19.3 (6.86) |
| $AUC_{\tau}$ (µg.h/mL) | 0.469 (0.175) | 0.479 (0.174) | 0.482 (0.165) | 0.420 (0.141) | 0.432 (0.145) | 0.436 (0.151) |
| $AUC_{ss,24hr}$ (µg.h/mL) | 0.469 (0.175) | 0.479 (0.174) | 0.482 (0.165) | 0.840 (0.282) | 0.864 (0.290) | 0.873 (0.302) |
| $C_{ss}$ (ng/mL) | 19.6 (7.3) | 20.0 (7.2) | 20.1 (6.9) | 35.0 (11.7) | 36.0 (12.1) | 36.4 (12.6) |
| $C_{ss,max}$ (ng/mL) | 33.2 (9.4) | 33.6 (9.3) | 34.0 (9.0) | 44.1 (12.6) | 45.1 (13.0) | 45.7 (14.1) |
| $C_{ss,min}$ (ng/mL) | 8.3 (5.5) | 8.2 (5.3) | 8.2 (4.8) | 21.0 (10.0) | 21.7 (9.9) | 21.9 (10.5) |

[(a)] Nominal Week

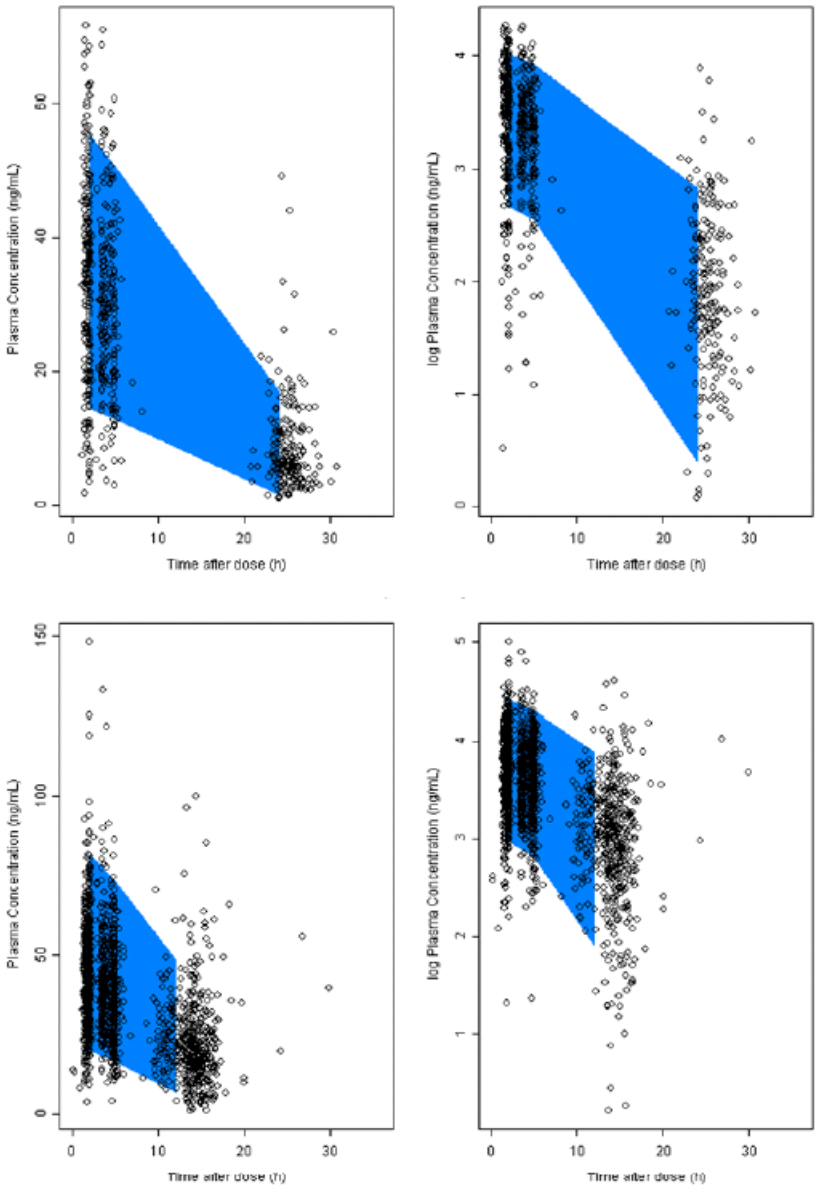
Source: Sponsor's Table 8:14, PK/PD Final Report page 51

**Figure 6. Goodness of Fit Plots for Final Population PK Model (APD356-010)**




Source: Sponsor's Figure 11.11, PK/PD Final Report page 147

**Figure 7. VPC of Population PK Model for Study APD356-010**




Note: Note: blue area = 90% PI (area between 5th and 95th percentile) of 250 model simulations; symbols = actual data; left panel = linear scale; right panel = log-linear scale

Source: Sponsor's Figure 8-9, PK/PD Final Report page 57

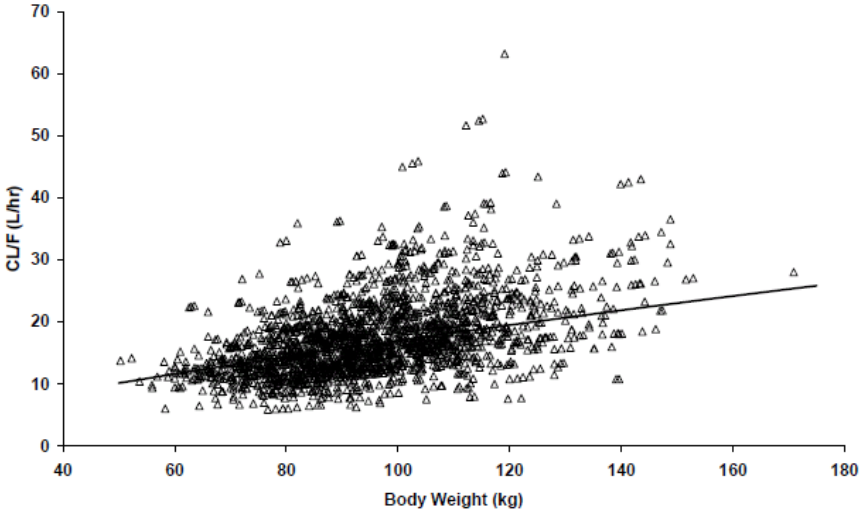
### 4.1.5 Impact of Covariates

The four significant covariates in the final population PK model are body weight on CL/F and V/F, presence of diabetes on CL/F, and formulation on bioavailability. There was no significant effect of gender and race.

Impact of Body Weight

Estimates of CL/F were centered for median body weight via a power relationship fixed at 0.75. The median point value, 25th and 75th percentiles for patients' body weight in the three Phase 3 studies were 94.2 kg, 85 kg to 107.3 kg, respectively. This relationship means that for a population with a median body weight of 94.2 kg, a CL/F of 16.2 L/h would be expected compared to CL/F values of 15.0 L/h and 17.9 L/h for populations with a body weight of 85 kg and 107.3 kg, respectively.

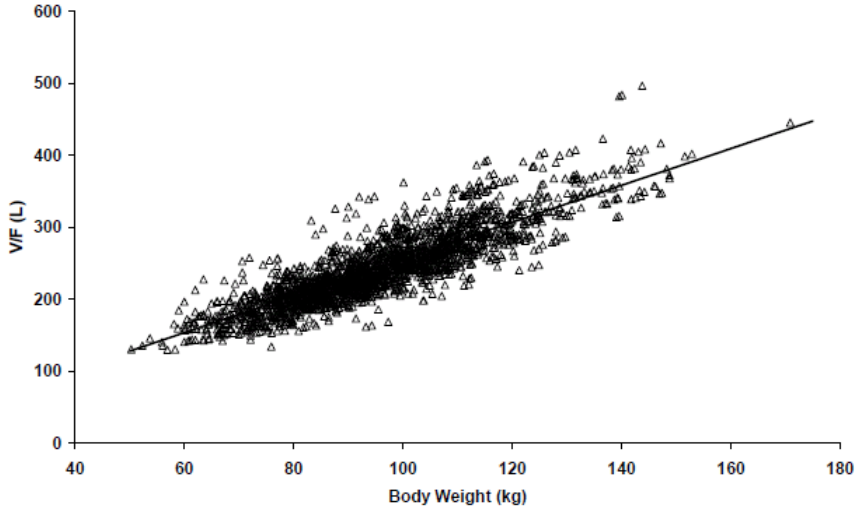
**Figure 8. Lorcaserin CL/F vs. Body Weight (Sponsor's Figure)**




Source: Sponsor's Figure 8-11, PK/PD Final Report page 60

Estimates of V/F were centered for median body weight via a power relationship fixed at 1.0, therefore, a linear relationship. This relationship means that for a population with a median body weight of 94.2 kg a V/F of 241 L would be expected, compared to V/F values of 223 L and 275 L for populations with a body weight of 85 kg and 107.3 kg, respectively.

**Figure 9. Lorcaserin V/F vs. Body Weight (Sponsor's Figure)**



Source: Sponsor's Figure 8-11, PK/PD Final Report page 60

Table 11 indicates that the predicted AUC24h was lower by, on average, 6 and 10% following QD and BID dosing, respectively, in patients weighing 107.3 kg compared to the corresponding values for the median weight of 94.2 kg. Conversely, patients weighing 85 kg had a 12% and 9% increase in $AUC_{ss,24hr}$ following QD and BID dosing, respectively, in comparison to subjects of median weight (94.2 kg).

**Table 11. Summary (Mean (%CV)) of Simulated (n=250) CL/F, $AUC_{ss,24hr}$ and Css Following QD and BID Administration of 10 mg Lorcaserin (Formulation 5) to a Non-Diabetic Patient with a Median Body Weight of 85 kg and 107.3 kg (Sponsor's Table)**

| Body Weight (kg) | Regimen | CL/F (L/h) | $C_{ss}$ (ng/mL) | $C_{ss,max}$ (ng/mL) | $C_{ss,min}$ (ng/mL) | $AUC_{ss,24hr}$ (µg.h/mL) | Percent change in $AUC_{ss,24hr}$ relative to the median body weight |
|---|---|---|---|---|---|---|---|
| 85 | QD | 15.7 (5.3) | 24.8 (7.8) | 38.1 (13.7) | 9.7 (5.9) | 0.595 (0.188) | +12% |
| 94.2 | QD | 17.3 (5.0) | 22.2 (6.7) | 34.2 (12.1) | 8.7 (5.7) | 0.532 (0.162) | - |
| 107.3 | QD | 18.5 (6.0) | 20.9 (6.8) | 31.1 (11.0) | 8.7 (5.8) | 0.503 (0.164) | -6% |
| 85 | BID | 15.9 (5.1) | 49.2 (16.4) | 56.4 (24.4) | 29.3 (15.6) | 1.180 (0.395) | +9% |
| 94.2 | BID | 17.4 (5.9) | 45.1 (15.3) | 51.7 (21.5) | 27.6 (14.7) | 1.082 (0.368) | - |
| 107.3 | BID | 19.5 (6.8) | 40.4 (13.9) | 45.1 (19.8) | 24.7 (14.0) | 0.969 (0.333) | -10% |

Source: Sponsor's Table 8:17, PK/PD Final Report page 66

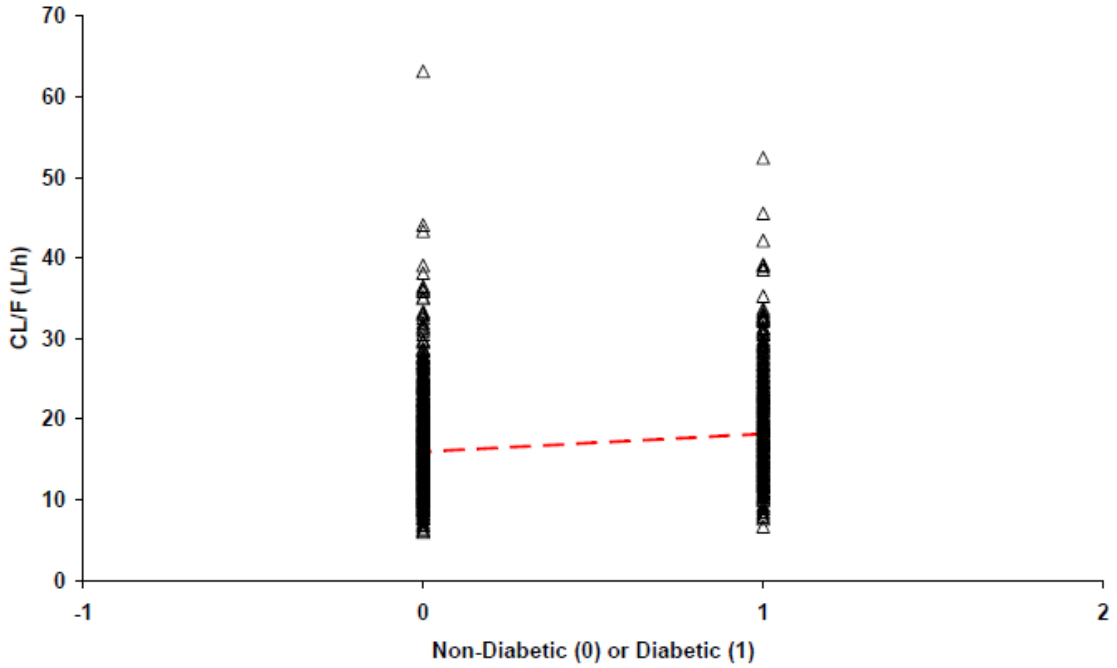
The sponsor concludes that differences in exposure due to changes in body weight both across and within patients do not warrant dose and/or dosing regimen adjustment.

*Reviewer's comments: Agree with sponsor's conclusions.*

Impact of Diabetes and Formulation

The categorical effects on CL/F for diabetic obese/overweight patients (APD356-010) increased by 9% in comparison to non-diabetic obese/overweight patients (APD356-009, APD356-011).

**Figure 10. Lorcaserin CL/F vs. Diabetes Status (Sponsor's Figure)**




Source: Sponsor's Figure 8-12, PK/PD Final Report page 61

In obese/overweight patients, the predicted PK parameters following administration of 10 mg lorcaserin in tablet form in study APD356-011 were slightly lower compared to the corresponding values for the capsule formulation administered in study APD356-009. On average, there was a 9% reduction in $AUC_{ss,24hr}$ following BID administration of 10 mg lorcaserin tablet in comparison to the capsule. This 9% reduction in lorcaserin exposure for the tablet versus capsule formulation is consistent with a previous bioequivalence study comparing the tablet and capsule formulations of lorcaserin (APD356-005 3).

**Table 12. Mean (±SD) of Individual Posterior Predicted Pharmacokinetic Parameters Following Administration of Lorcaserin in Capsule Form (APD356-009) to Obese/Overweight Patients and in Tablet Form to Obese/Overweight Patients (APD356-011) in Diabetics (APD356-010) (Sponsor's Table)**

| Parameter | Obese/Overweight Patients | | Diabetic Obese/Overweight Patients |
|---|---|---|---|
| | Study APD356-009 (Week 12[(a)]) (n=248) | Study APD356-011 (Week 12[(a)]) (n=264) | Study APD356-010 (Week 12[(a)]) (n=210) |
| Dose | 10 mg BID | 10 mg BID | 10 mg BID |
| Formulation (Number) | Capsule (Formulation 4) | Tablet (Formulation 5) | Tablet (Formulation 5) |
| CL/F (L/h) | 17.6 (6.73) | 17.2 (5.96) | 20.0 (6.86) |
| $AUC_{\tau}$ (µg.h/mL) | 0.537 (0.177) | 0.488 (0.161) | 0.420 (0.141) |
| $AUC_{ss,24hr}$ (µg.h/mL) | 1.075 (0.355) | 0.977 (0.321) | 0.840 (0.282) |
| $C_{ss}$ (ng/mL) | 44.8 (14.8) | 40.7 (13.4) | 35.0 (11.7) |
| $C_{ss,max}$ (ng/mL) | 52.7 (14.2) | 49.1 (14.1) | 44.1 (12.6) |
| $C_{ss,min}$ (ng/mL) | 25.2 (11.8) | 24.0 (11.5) | 21.0 (10.0) |

[(a)] Nominal Week

Source: Sponsor's Table 8:18, PK/PD Final Report page 68

The sponsor concludes that the effect of diabetes on CL/F and differences in the relative bioavailability of the tablet formulation are unlikely to be clinically significant.

*Reviewer's comments: Agree with sponsor's conclusions.*

### 4.1.6 Application of Population PK Model

The population model was used to support labeling statements (see section 2.3) and exposure metric (AUC) used in the PK/PD models for weight loss.

Reviewer's comments: Based on an independent review of the data and model codes submitted, the population PK model fit the data from the clinical trials well. It is reasonable to use model-based AUC in the PK/PD models. Exposure-Response Relationship for Weight Loss

### 4.1.7 Overview

The PK/PD model was revised to accommodate the lack of dose-response for weight loss in the once daily and twice daily dose groups in APD356-010.

- The revised model predicts minimal effect of body weight on lorcaserin exposure or weight loss.
- Patients with type 2 diabetes are predicted to have a lower placebo response than non-diabetic patients for weight loss.
- Diabetic status per se did not appear to impact probability of success for 5% or 10% weight loss.

- Significant covariates for the PK/PD weight loss models included ALT and creatinine clearance; however, the ALT relationship was opposite for 5% and 10% weight loss.

### 4.1.8 Longitudinal PK/PD Model for Weight Loss

The model for placebo effect on weight loss was an exponential function, parameterized in terms of maximal placebo effect (MAXP) and an exponential error term for the half-life (HL). Compared to the previous model in overweight patients, the maximum placebo effect in diabetes was 2.55% with a half-life of 8.1 weeks (sponsor's Table 8:19); therefore, the sponsor included a separate parameter in the model for maximum effect for diabetic patients. When combining data from both non-diabetic and diabetic trials, the base model for the placebo effect is shown in Table 13 and the final model which includes covariate effects in Table 14. Goodness-of-fit plots are shown in Figure 11.

**Table 13. Base PK/PD Model for Placebo Effect for Weight Loss**

| Parameter | Estimate [95% CI] | %RSE [c] |
|---|---|---|
| $f(x) = (\theta_{MAXP} \cdot (1\text{-}DIAB) + \theta_{MAXPD} \cdot DIAB) \cdot (1\text{-}exp(-ln(2)/\theta_{HL}) \cdot TIME)$ | | |
| *DIAB: 0 for non-diabetic and 1 for diabetic patients* | | |
| MAXP = $\theta_{MAXP}$ (%Weight Loss ) | 3.76 [3.18 – 4.34] | 7.93 |
| MAXPD = $\theta_{MAXPD}$ (%Weight Loss ) | 2.59 [1.94 – 3.24] | 12.9 |
| HL = $\theta_{HL}$ (weeks ) | 9.07 [7.56 – 10.6] | 8.48 |
| Inter-subject variability in MAXP (SD, %Weight Loss) [a] | ± 6.65 | 14.8 |
| Inter-subject variability in MAXPD (SD, %Weight Loss) [a] | ± 4.64 | 18.1 |
| Inter-subject variability in HL (%CV) [b] | 117 | 8.99 |
| Residual variability in %Weight Loss in placebo patients (SD, %Weight Loss) [a] | ± 1.33 | 4.71 |
| RUN# | PRW_PL_004 | |
| OFV | 18206.791 | |

[a] The SD for both inter-subject/patient and residual additive variability is taken as the square root of the variance. [b] The %CV for both inter-subject/patient and proportional residual variability is an approximation taken as the square root of the variance x 100. The approximation is due to the expansion of the exponential function only to first-order. [c] RSE was calculated as the s.e. divided by the parameter estimate x 100.

Source: Sponsor's Table 8:22, PK/PD Final Report page 73

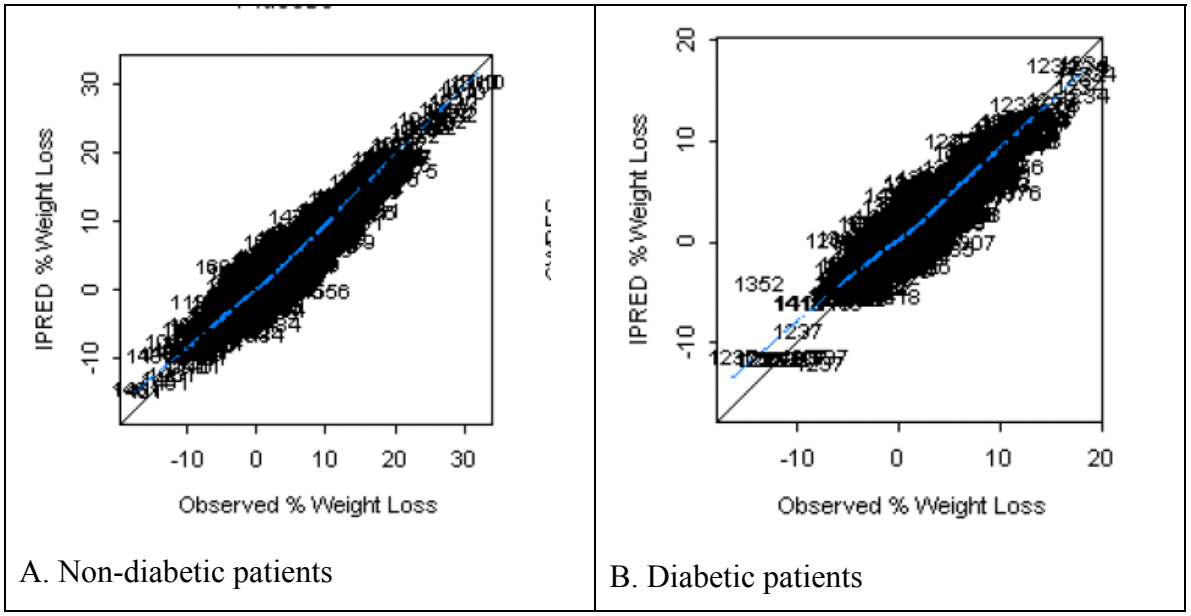
## Table 14. Final PK/PD Model for Placebo Effect for Weight Loss

| *Model structure* | | | | |
|---|---|---|---|---|
| $f(x) = (\theta_{MAXP} \cdot (1\text{-}DIAB) + \theta_{MAXPD} \cdot DIAB) \cdot (1\text{-}exp(-ln(2)/\theta_{HL}) \cdot TIME)$ | | | | |
| *DIAB: 0 for non-diabetic and 1 for diabetic patients* | | | | |
| Parameter | Estimate [95% CI] | %RSE [(c)] | %shr | bias |
| MAXP = $\theta_{MAXP}$ (%Weight Loss ) | 3.34 [2.77 – 3.91] | 8.77 | | |
| MAXPD = $\theta_{MAXPD}$ (%Weight Loss ) | 2.69 [2.01 – 3.37] | 12.8 | | |
| Effect of ALT on MAXP and MAXPD | -0.249 [-0.382 – -0.116] | 27.2 | | |
| Effect of BILI on MAXP and MAXPD | 0.160 [0.0644 – 0.256 | 30.5 | | |
| Effect of CRCL on MAXP and MAXPD | -1.25 [-1.46 – -1.04] | 8.40 | | |
| HL = $\theta_{HL}$ (weeks ) | 8.54 [7.29 – 9.79] | 7.49 | | |
| Inter-subject variability in MAXP (SD, %Weight Loss) [(a)] | ± 6.29 | 13.9 | 20.8 | -0.276 |
| Inter-subject variability in MAXPD (SD, %Weight Loss) [(a)] | ± 4.52 | 17.8 | 47.0 | -0.175 |
| Inter-subject variability in HL (%CV) [(b)] | 117% | 8.84 | 32.9 | -0.181 |
| Residual variability in %Weight Loss (SD, %Weight Loss) [(a)] | ± 1.30 | 4.67 | 1.54 | |
| RUN# | PLCOV_035N | | | |
| OFV | 17804.243 | | | |

[(a)] The SD for both inter-subject/patient and residual additive variability is taken as the square root of the variance. [(b)] The %CV for both inter-subject/patient and proportional residual variability is an approximation taken as the square root of the variance x 100. The approximation is due to the expansion of the exponential function only to first-order. [(c)] RSE was calculated as the s.e. divided by the parameter estimate x 100.

Source: Sponsor's Table 8:28, PK/PD Final Report page 81

**Figure 11. Goodness of fit: IPRED vs. Observed**




A. Non-diabetic patients

B. Diabetic patients

Source: Sponsor's Figure 11.22, PK/PD Final Report pages 187 and 190

The final continuous PK/PD model for percent weight loss included the maximal placebo percent weight loss for non-diabetic (MAXP) and diabetic (MAXPD) patients as fixed parameters, a slope parameter (SLOPE) for the association of lorcaserin exposure (lnAUCss,24hr) to percent weight loss and an exponential time function to describe the temporal change in percent weight loss. Final model parameters are shown in Table 15 and goodness-of-fit plots in Figure 12.

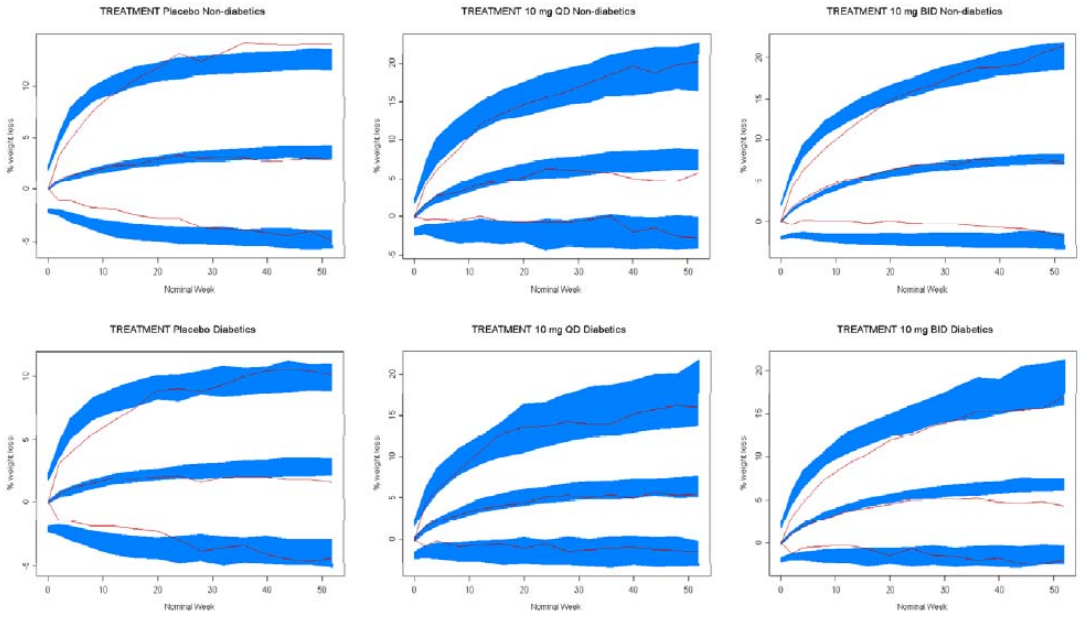
## Table 15. Final PK/PD Model for Weight Loss

| *Model structure* | | | | |
|---|---|---|---|---|
| $f(x) = (\theta_{MAXP} \cdot (1\text{-}DIAB) + \theta_{MAXPD} \cdot DIAB + \theta_{SLOPE} \cdot lnAUC_{ss,24hr}) \cdot (1\text{-}exp(-ln(2)/\theta_{HL}) \cdot TIME)$ | | | | |
| *DIAB: 0 for non-diabetic and 1 for diabetic patients* | | | | |
| Parameter | Estimate [95% CI] | %RSE [(c)] | %shr | bias |
| MAXP = $\theta_{MAXP}$ (%Weight Loss) | 3.34 FIXED to PLCOV_035N estimate | | | |
| MAXPD = $\theta_{MAXPD}$ (%Weight Loss) | 2.69 FIXED to PLCOV_035N estimate | | | |
| Effect of ALT on MAXP and MAXPD | -0.249 FIXED to PLCOV_035N estimate | | | |
| Effect of BILI on MAXP and MAXPD | 0.160 FIXED to PLCOV_035N estimate | | | |
| Effect of CRCL on MAXP and MAXPD | -1.25 FIXED to PLCOV_035N estimate | | | |
| SLOPE = $\theta_{SLOPE}$ (%Weight Loss · mL/µg.hr) | 0.362 [0.269 – 0.455] | 13.1 | | |
| Effect of CRCL on SLOPE | -1.31 [-1.86 – -0.755] | 21.6 | | |
| HL = $\theta_{HL}$ (weeks) | 6.67 [6.14 – 7.20] | 4.06 | | |
| Effect of ICR on HL | -1.20 [-1.46 – -0.937] | 11.2 | | |
| Effect of ALT on HL | -0.0898 [-0.141 – -0.0386] | 29.1 | | |
| Inter-subject variability in MAXP (SD, %Weight Loss) [(a)] | ± 5.43 | 9.86 | 24.7 | -0.099 |
| Inter-subject variability in MAXPD (SD, %Weight Loss) [(a)] | ± 4.24 | 14.3 | 49.3 | -0.272 |
| Inter-subject variability in SLOPE (%CV) [(b)] | 105% | 12.3 | 25.2 | -0.082 |
| Inter-subject variability in HL (%CV) [(b)] | 102% | 6.31 | 37.4 | -0.009 |
| Correlation between SLOPE and in HL (R) | 0.704 | 10.6 | | |
| Residual variability in %Weight Loss (SD, %Weight Loss) [(a)] | ± 1.25 | 3.19 | 6.18 | |
| RUN# | ACTPLCOV_031crN | | | |
| OFV | 41939.248 | | | |

[(a)] The SD for both inter-subject/patient and residual additive variability is taken as the square root of the variance.
[(b)] The %CV for both inter-subject/patient and proportional residual variability is an approximation taken as the square root of the variance x 100. The approximation is due to the expansion of the exponential function only to first-order. [(c)] RSE was calculated as the s.e. divided by the parameter estimate x 100.

Source: Sponsor's Table 8:31, PK/PD Final Report page 85

**Figure 12. VPC of Observed and Predicted Weight Loss**




Note: blue bands = 90% CI of 5th, 50th and 95th percentiles of 250 model simulations; red lines = 5th, 50th and 95th percentile of actual data

#### 4.1.8.1 Sponsor's PK/PD Modeling Conclusions

- The maximal percent weight loss for placebo, lorcaserin 10 mg QD and lorcaserin 10 mg BID in non-diabetic and diabetic obese/overweight patients was predicted to be achieved by about Week 32.
- Diabetic patients were predicted to have a lower placebo response than non-diabetic patients.
- For non-diabetic patients, the mean (±SD) individual predicted percent weight loss at Week 52 from the FINAL model was 4.00% (±5.77%) for the placebo, 6.99% (±6.19%) for 10 mg QD and 8.68% (±6.44%) for 10 mg BID lorcaserin administration.
- For diabetic patients, the mean (±SD) individual predicted percent weight loss at Week 52 from the FINAL model was 2.60% (±4.06%) for the placebo, 6.40% (±5.10%) for 10 mg QD and 6.20% (±5.67%) for 10 mg BID lorcaserin administration.

*Reviewer's Comments: Sponsor's PK/PD models are acceptable and provide a reasonable fit to the data.*

### 4.1.9 Logistic Regression Model for Weight Loss

The base logistic regression models for Week 52 weight loss included an intercept term and a slope parameter for the association of lorcaserin exposure (AUC24h) to weight loss (Table 17).

**Table 16. Base Logistic Regression Models**

| | weight loss ≥ 5% | | weight loss ≥ 10% | |
|---|---|---|---|---|
| Parameter | Estimate [95% CI] | %RSE[a] | Estimate [95% CI] | %RSE[a] |
| $\Theta_{intercept}$ | -1.13 [-1.29, -0.973] | 7.09 | -2.48 [-2.72, -2.24] | 4.88 |
| $\Theta_{slope}$ | 1.43 [1.22, 1.64] | 7.62 | 1.46 [1.20, 1.72] | 9.18 |
| Prop EX24=0[b] | 24% | | 8% | |
| Prop EX24=0.848[c] | 52% | | 22% | |
| RUN# | LOCF001 | | LOCF101 | |
| OFV | 2025.351 | | 1384.100 | |

[a] RSE was calculated as the s.e. divided by the parameter estimate x 100.
[b] Proportion of predicted successful response following placebo administration calculated as $e^{\Theta intercept} / (1+ e^{\Theta intercept})$
[c] Proportion of predicted successful response at median exposure (0.848 µg.h/mL), calculated as $e^{(\Theta intercept + \Theta slope \cdot 0.848)} / (1+ e^{(\Theta intercept + \Theta slope \cdot 0.848)})$

Source: Sponsor's Table 8:35, PK/PD Final Report page 95

The final ≥ 5% weight loss model predicts a successful placebo response for 16 to 38% of the patients (Table 17). At median exposure, 37 to 66% of the patients are predicted to achieve weight loss ≥5%. There may be a greater probability of achieving weight loss ≥5% for patients with low CRCL values and high ALT values. Plot of the model is shown in Figure 13.

The final ≥ 10% weight loss model predicted a placebo response for 3 to 18% of the patients and 9 to 38% of the patients were predicted to achieve weight loss ≥10% at the median exposure (Table 18). For Black patients, lower rates of success are predicted, 1-12% for placebo and 3-28% at median exposure. Plot of the model is shown in Figure 14.

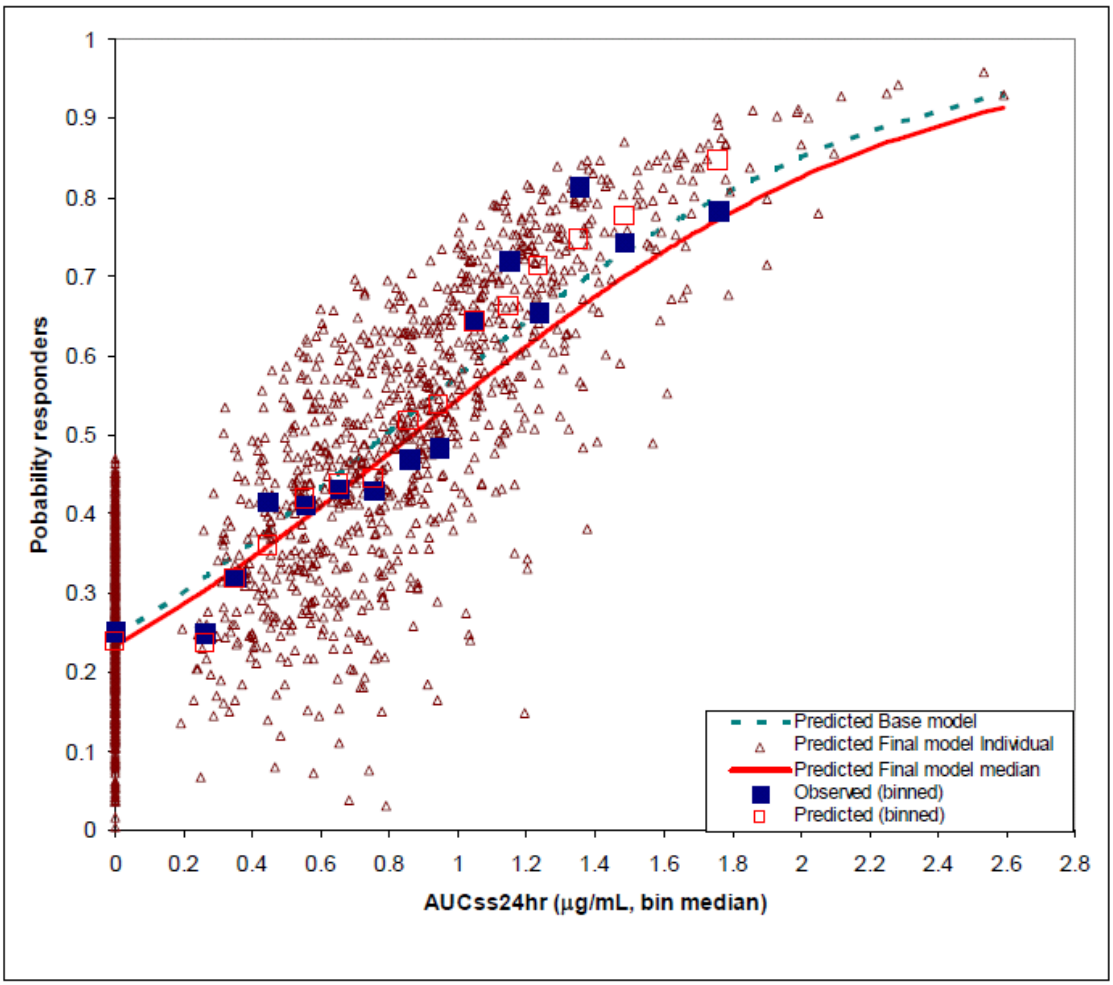
**Table 17. Logistic Regression Model for Weight Loss ≥5%**

| Parameter | Estimate [95% CI] | %RSE[a] | CRCL | ALT |
|---|---|---|---|---|
| $\Theta_{intercept}$ | -1.19 [-1.35, -1.03] | 7.03 | | |
| $\Theta_{slope}$ | 1.37 [1.16, 1.58] | 7.96 | | |
| $\Theta_{CRCL}$ | 2.38 [1.55, 3.21] | 17.7 | | |
| $\Theta_{ALT}$ | -0.566 [0.371, 0.761] | 17.6 | | |
| Prop EX24=0[b] | 38% | | 10th | median |
| Prop EX24=0[b] | 28% | | median | 10th |
| Prop EX24=0[b] | **23%** | | median | median |
| Prop EX24=0[b] | 19% | | 90th | median |
| Prop EX24=0[b] | 16% | | median | 90th |
| Prop EX24=0.848[c] | 66% | | 10th | median |
| Prop EX24=0.848[c] | 56% | | median | 10th |
| Prop EX24=0.848[c] | **49%** | | median | median |
| Prop EX24=0.848[c] | 43% | | 90th | median |
| Prop EX24=0.848[c] | 37% | | median | 90th |
| RUN# | LOCF001_005 | | | |
| OFV | 1920.095 | | | |

[a] RSE was calculated as the s.e. divided by the parameter estimate x 100.
[b] Proportion of predicted successful response following placebo administration calculated as $e^{\Theta intercept} / (1+ e^{\Theta intercept})$.
[c] Proportion of predicted successful response at median exposure (0.848 µg.h/mL), calculated as $e^{(\Theta intercept + \Theta slope \cdot 0.848)} / (1+ e^{(\Theta intercept + \Theta slope \cdot 0.848)})$

Source: Sponsor's Table 8:41, PK/PD Final Report page 102

**Figure 13. Exposure-Response Relationship for Weight Loss ≥5%**




Source: Sponsor's Figure 8.27, PK/PD Final Report page 103

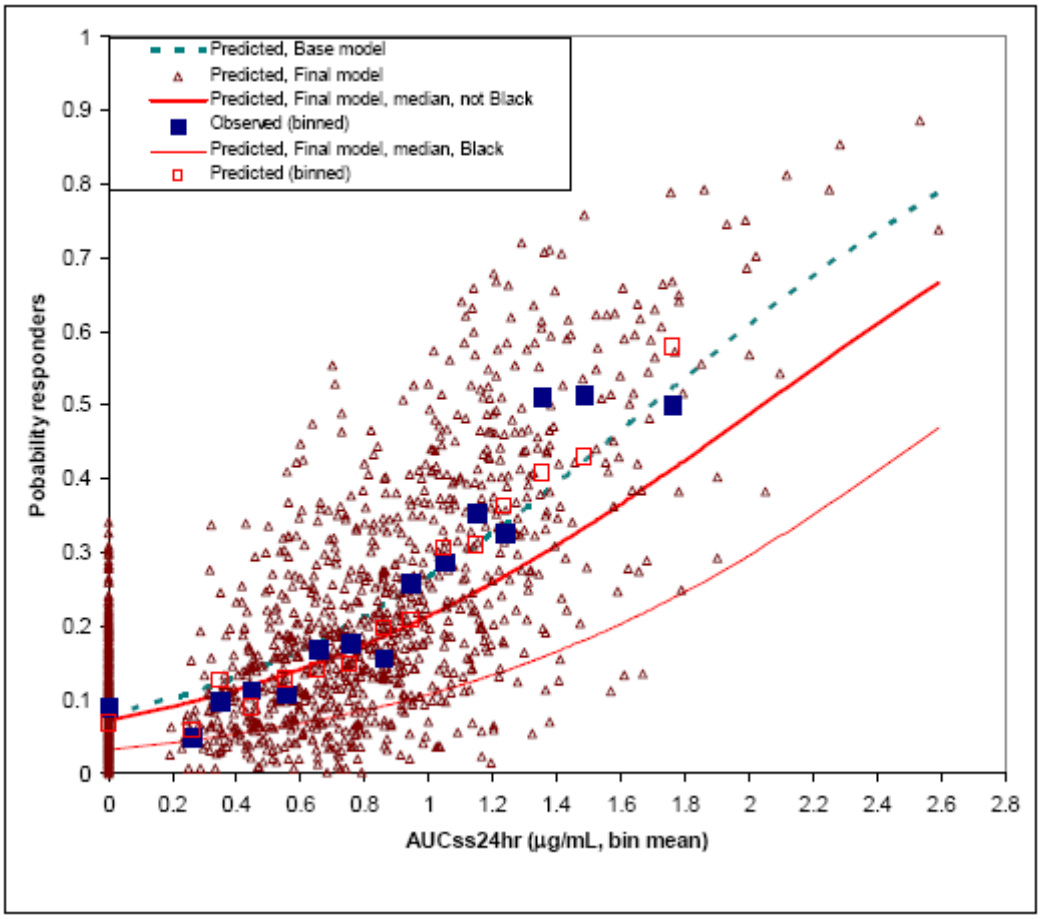
**Table 18. Logistic Regression Model for Weight Loss ≥10%**

| Parameter | Estimate [95% CI] | %RSE[a] | CRCL | ALT | Not Blacks | Blacks |
|---|---|---|---|---|---|---|
| $\Theta_{intercept}$ | -2.55 [-2.82, -2.28] | 5.33 | | | | |
| $\Theta_{slope}$ | 1.25 [0.993, 1.51] | 10.5 | | | | |
| $\Theta_{CRCL}$ | 1.43 [1.05, 1.81] | 13.6 | | | | |
| $\Theta_{ALT}$ | 0.460 [0.295, 0.625] | 18.3 | | | | |
| $\Theta_{RACI}$ | 1.32 [1.09, 1.55] | 8.86 | | | | |
| Prop EX24=0[b] | | | 10th | median | 18% | 12% |
| Prop EX24=0[b] | | | median | 10th | 11% | 6% |
| Prop EX24=0[b] | | | median | median | 7% | 3% |
| Prop EX24=0[b] | | | 90th | median | 5% | 2% |
| Prop EX24=0[b] | | | median | 90th | 3% | 1% |
| Prop EX24=0.848[c] | | | 10th | median | 38% | 28% |
| Prop EX24=0.848[c] | | | median | 10th | 27% | 16% |
| Prop EX24=0.848[c] | | | median | median | 18% | 9% |
| Prop EX24=0.848[c] | | | 90th | median | 14% | 6% |
| Prop EX24=0.848[c] | | | median | 90th | 9% | 3% |
| RUN# | LOCF101_004 | | | | | |
| OFV | 1261.386 | | | | | |

[a] RSE was calculated as the s.e. divided by the parameter estimate x 100.
[b] Proportion of predicted successful response following placebo administration calculated as $e^{\Theta intercept} / (1+ e^{\Theta intercept})$
[c] Proportion of predicted successful response at median exposure (0.848 µg.h/mL), calculated as $e^{(\Theta intercept + \Theta slope \cdot 0.848)} / (1+ e^{(\Theta intercept + \Theta slope \cdot 0.848)})$

Source: Sponsor's Table 8:42, PK/PD Final Report page 105

Figure 14. Exposure-Response Relationship for Weight Loss ≥5%




Source: Sponsor's Figure 8.29, PK/PD Final Report page 107

#### 4.1.9.1 Sponsor's Logistic Regression Modeling Conclusions

- The final logistic model for weight loss ≥5% predicted a 23% probability of a successful placebo response. At median lorcaserin exposure, approximately 49% of the patients will achieve weight loss ≥5%.
- The final logistic model for weight loss ≥10% predicted a 7% probability of a successful placebo response. At median lorcaserin exposure, approximately 18% of the patients will achieve weight loss ≥10%.
- Some statistically significant covariate effects on the achievement of weight loss ≥5% or ≥10% were identified (CRCL, ALT, race); however, their overall significance on the pharmacodynamic profile of lorcaserin is considered minimal.
- Diabetic status appears to have no significant effect on the achievement of weight loss ≥5% or ≥10% after one year of treatment

*Reviewer's Comments: Reviewer performed independent logistic regression analysis in SAS to confirm findings (see section 5) and obtained comparable parameter estimates for the base logistic models. However, using stepwise covariate modeling building in SAS, different covariates were identified as being significant in the model. These differences*

*can be attributed to different structural forms of the covariate-parameter relationships—the sponsor used power function centered at the median covariate value and reviewer used linear function as implemented in SAS.*

# 5 REVIEWER'S ANALYSIS

## 5.1 Introduction

Logistic regression was performed to independently confirm the sponsor's findings.

## 5.2 Objectives

Analysis objective is to evaluate the exposure-response relationship for 5% and 10% weight loss using logistic regression analysis.

## 5.3 Methods

Proc Logistic as implemented in SAS was used for logistic regression analysis. S-plus was used to generate plots.

### 5.3.1 Data Sets

Data set used is summarized in Table 19.

**Table 19. Analysis Data Set**

| File Name | Link to EDR |
|---|---|
| pdlabs.xpt | \\cdsesub1\EVSPROD\NDA022529\\0034\m5\datasets\0604-009\analysis\pdlabs.xpt |

### 5.3.2 Software

SAS 9.2 was used for logistic regression modeling. Graphics were performed using S-plus.

### 5.3.3 Model Code

Logistic Regression Code for Weight Loss (code shown for 5%)

```
proc logistic data=pkpd plots(only)= (effect(clband x=(ex24 bbmi
alt crcl)) oddsratio (type=horizontalstat));
class trt(ref='0') diab sex (ref='0') race (ref='0');
model p05 (event ='1') =ex24 trt diab sex race bbmi age alt bili
crcl ex24*age ex24*bbmi ex24*alt ex24*bili ex24*crcl ex24*sex
ex24*race /clodds=pl selection=stepwise slentry=0.01 slstay=0.001
details lackfit; output out=pred predicted=phat lower=lcl
upper=ucl;score data = scored2 out=scored2;
run;
```

## 5.4 Results

The median AUC24h for the 10 mg QD and 10 mg BID dose groups in trial APD356-010 is 0.425 µg.h/ml and 0.815 µg.h/ml, respectively. These values were computed from the

variable ex24 in dataset pdlabs.xpt. Results of logistic regression model are shown in Table 13 through Table 14.

**Table 20. FDA Analysis: Logistic Regression Model for ≥5% Weight Loss**

| Parameter | Estimate (SE) | p-value | Odds Ratio (95% Wald CI) |
|---|---|---|---|
| Intercept | -1.14 | <0.0001 | -- |
| Slope-AUC24h | 1.43 | <0.0001 | 4.20 (3.40, 5.18) |

c-statistic: 0.693

Probability of response for placebo=24.3%

Probability of response for median AUC24h (0.815 µg.h/ml)=50.8%

**Table 21. FDA Analysis: Final Covariate Logistic Regression Model for ≥5% Weight Loss**

| Parameter | Estimate (SE) | p-value | Odds Ratio (95% Wald CI) |
|---|---|---|---|
| Intercept | -0.627 | 0.1595 | -- |
| Slope-AUC24h | 1.59 | <0.0001 | 4.90 (3.82, 6.28) |
| Baseline BMI | 0.0643 | <0.0001 | 1.07 (1.04, 1.09) |
| ALT | -0.0252 | <0.0001 | 0.976 (0.966, 0.985) |
| CrCL | -0.0182 | <0.0001 | 0.982 (0.987, 0.986) |

c-statistic: 0.763, Hosmer and Lemeshow goodness-of-fit: 0.1798

**Table 22. FDA Analysis: Logistic Regression Model for ≥10% Weight Loss**

| Parameter | Estimate (SE) | p-value | Odds Ratio (95% Wald CI) |
|---|---|---|---|
| Intercept | -2.47 | <0.0001 | -- |
| Slope-AUC24h | 1.45 | <0.0001 | 4.28 (3.33, 5.12) |

c-statistic: 0.706

Probability of response for placebo =7.8%

Probability of response for median AUC24h (0.815 µg.h/ml) = 21.6%

Probability of response for median AUC24h (0.425 µg.h/ml) = 13.5%

**Table 23. FDA Analysis: Final Covariate Logistic Regression Model for ≥10% Weight Loss**

| Parameter | Estimate (SE) | p-value | Odds Ratio (95% Wald CI) |
|---|---|---|---|
| Intercept | -0.306 | 0.701 | -- |
| Slope-AUC24h | 1.5725 | <0.0001 | 4.82 (3.61, 6.43) |

| | | | |
|---|---|---|---|
| Baseline BMI | 0.0990 | <0.0001 | 1.1 (1.07, 1.14) |
| Age | -0.0412 | <0.0001 | 0.960 (0.943, 0.977) |
| Bilirubin | 1.236 | 0.0001 | 3.441 (1.825, 6.487) |
| CrCL | -0.0359 | <0.0001 | 0.9654 (0.958, 0.971) |

c-statistic: 0.794, Hosmer and Lemeshow goodness-of-fit: 0.5988

## 6 LISTING OF ANALYSES CODES AND OUTPUT FILES

| **File Name** | **Description** | **Location in \\cdsnas\pharmacometrics** |
|---|---|---|
| Lorcaserin.logsitic.sas | Logistic models for 5% and 10% weight loss | \\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lorcaserin_NDA22529_CG\ER Analyses\Final Model |
| WeightLoss_ER_BINS_CG.ssc | Plots of logistic regression model | \\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lorcaserin_NDA22529_CG |

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IMMO ZADEZENSKY
05/30/2012

CHRISTINE E GARNETT
05/31/2012

KEVIN M KRUDYS
05/31/2012

JAYABHARATHI VAIDYANATHAN
05/31/2012

## ONDQA BIOPHARMACEUTICS REVIEW

| | |
|---|---|
| **NDA#:** | **22-529 Resubmission** |
| **Submission Date:** | 12/23/2011 |
| **Brand Name:** | LORQESS |
| **Generic Name:** | Lorcaserin HCl |
| **Formulation:** | Tablets |
| **Strength:** | 10 mg |
| **Applicant:** | Arena Pharmaceuticals, Inc. |
| **Reviewer:** | John Duan, Ph.D. |
| **Submission Type:** | NDA Resubmission |

## SYNOPSIS

***Background:*** Lorqess is a selective serotonin 2C agonist indicated for weight management, including weight loss and maintenance of weight loss used in conjunction with a reduced-calorie diet and a program of regular exercise. The original NDA was submitted on 12/22/09 and a Complete Response Letter was issued by FDA on 10/22/2010.

***Resubmission:*** On 12/27/122, the Applicant filed the resubmission of NDA 22-59 providing their responses to the deficiencies identified in the complete response letter.

***Review:*** The biopharmaceutics related issues were resolved during the 1st review cycle of the original NDA submission, including the following;

1. A BCS Class I designation was granted for Lorcaserin HCl Tablets based on the BCS committee recommendation.

2. The following dissolution method and acceptance criterion were recommended and the Applicant accepted the recommendation and modified the NDA accordingly.

   Apparatus: USP Apparatus 2 (paddles)
   Agitation speed: 50 rpm
   Medium: 0.1 N HCl
   Volume: 900 mL
   Temperature: 37°C ± 0.5°C.
   Acceptance criteria: Q = (b) (4) at 15 min

However, in the resubmission, the dissolution acceptance criterion listed in the Certificate of Analysis (CoA) was not consistent with the agreement made during the 1st review cycle. Therefore, an IR Letter was sent to the Applicant on 4/12/2012. In their response dated 4/16/2012, the Applicant justified this discrepancy (see Appendix) and the revised CoA and the updated specifications table for the drug product was provided.

**RECOMMENDATION**

From the biopharmaceutics viewpoint, the Resubmission of NDA 22-529 for LORQESS (lorcaserin) HCl Tablets is recommended for approval.

_____ _____

John Duan, Ph.D. Date
**Reviewer**
**ONDQA Biopharmaceutics**

_____ _____

Angelica Dorantes, Ph.D. Date
**ONDQA Biopharmaceutics Lead**

cc: *Resubmission NDA 22-529/DARRTS*

# Appendix

**The Information Request sent and the response from the Applicant.**

**IR:** Please clarify why the dissolution acceptance criterion listed in the CoA (Certificate of Analysis) of the NDA resubmission is not consistent with the acceptance criterion of Q (b) (4) at 15 minutes previously agreed upon on 8/3/2010. Please revise the CoA and provide a copy of the updated specifications table for your product.

## Arena Response

The drug product batch used in the APD356-022 study, lot 0943B013, was manufactured in October 2009 by Arena Pharmaceuticals GmbH as part of the drug product validation campaign for the commercial-scale (b) (4) process. At that time, the dissolution acceptance criterion was Q = (b) (4) at 30 minutes, but data were also collected at the 15-minute timepoint and met the agreed upon acceptance criterion of Q = (b) (4) at 15 minutes.

When the more stringent dissolution acceptance criterion was agreed upon on 8/3/2010 in Sequence No. 0023, the CoA was not revised. However, it has now been revised with the Q = (b) (4) at 15 minutes acceptance criterion and this result is now reflected on the certificate of analysis for bulk lot 0943B013 provided with this submission.

The specification provided on 8/3/2010 in Sequence No. 0023 (See Table 1 of 3.2.P.5.1) reflects the agreed upon dissolution acceptance criterion of Q = (b) (4) at 15 minutes and has been implemented for production batches. A copy of the current drug product production specification is provided with this submission (Note: the material number was changed following process validation).

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/s/

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JOHN Z DUAN
04/24/2012

ANGELICA DORANTES
04/24/2012

# OFFICE OF CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA: 22-529 | Submission Date(s): 12/18/2009 |
| Brand Name | TBD |
| Generic Name | Lorcaserin HCl |
| Reviewer | Immo Zdrojewski, Ph.D. |
| Secondary Pharmacometric Reviewer | Nitin Mehrotra, Ph.D. |
| Pharmacometric Team Leader (acting) | Christine Garnett, Ph.D. |
| Clinical Pharmacology Team Leader | Sally Choe, Ph.D. |
| OCP Division | Clinical Pharmacology II |
| OND Division | Metabolism and Endocrinology Products |
| Sponsor | Arena Pharmaceuticals Inc. |
| Submission Type | 505 (b)(1) |
| Formulation | Tablet, 10 mg |
| Indication | Weight management, including weight loss and maintenance of weight loss |

TABLE OF CONTENTS

**List of Tables and Figures:**

## 1. Executive Summary

### 1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed NDA 22-529 and finds it acceptable.

### 1.2 PHASE IV REQUIREMENT

None

### 1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

The sponsor, Arena Pharmaceuticals Inc., submitted a 505 (b)(1) new drug application (NDA 22-529) seeking a marketing approval for a 10 mg BID dose of lorcaserin hydrochloride (hemihydrate) immediate release tablets. The sponsor is seeking the indication for weight management, including weight loss and maintenance of weight loss, and usage in conjunction with a reduced-calorie diet and a program of regular exercise. The intended target population is 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).

Lorcaserin is a $5HT_{2c}$ agonist with its activity of modulating appetite at the $5HT_{2c}$ receptor. The sponsor claims that its activity at $5HT_{2c}$ prevails over activities at other 5HT receptors, especially $5HT_{2a}$ and $5HT_{2b}$ receptors. Lorcaserin is a highly soluble and highly permeable compound and is not a substrate of Pgp transporter. 92.3% of a radioactive dose is recovered in urine and 2.2% is recovered in feces. The extent of lorcaserin binding to plasma proteins is approximately 70%. *In-vitro* data indicate that lorcaserin is extensively metabolized in the liver. The major circulatory metabolite (lorcaserin sulfamate, M1) and the major urinary metabolite (N-carbamoyl lorcaserin, M5) are inactive metabolites. Lorcaserin is metabolized by multiple CYP P450 enzymes (1A1, 1A2, 2A6, 2B6, 2C19, 2D6, 2E1, 3A4), UGT enzymes (1A9, 2B7, 2B15, 2B17), and SULT enzymes (1A1, 1A2, 2A1, 1E1). Lorcaserin is a competitive inhibitor of CYP2D6 mediating dextromethorphan O-demethylation, but does not significantly inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4-mediated metabolism. Lorcaserin did not induce CYP1A2 and the induction potential for CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5 is low.

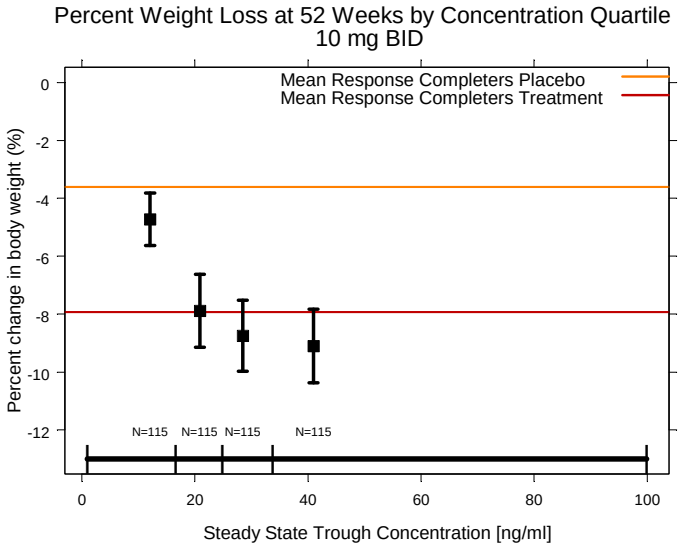
The sponsor evaluated 10 mg BID and 10 mg QD doses in two placebo-controlled Phase 3 trials (APD356-009 and APD356-011) based on the 12 week weight loss data from Phase 2 trials. The draft FDA guidance titled" Guidance for Industry Developing Products for Weight Management" states that "a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:

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

In each of the Phase 3 trials, lorcaserin demonstrated marginal efficacy, with the placebo subtracted weight loss being 3.0 to 3.3% for the 10 mg BID dose and 1.9% for the 10 mg QD dose. However, in both Phase 3, the proportion of subjects who lost at least 5% of their baseline body weight was > 35% and was approximately double the proportion of subjects compared to those in placebo group while this difference between groups was statistically significant.

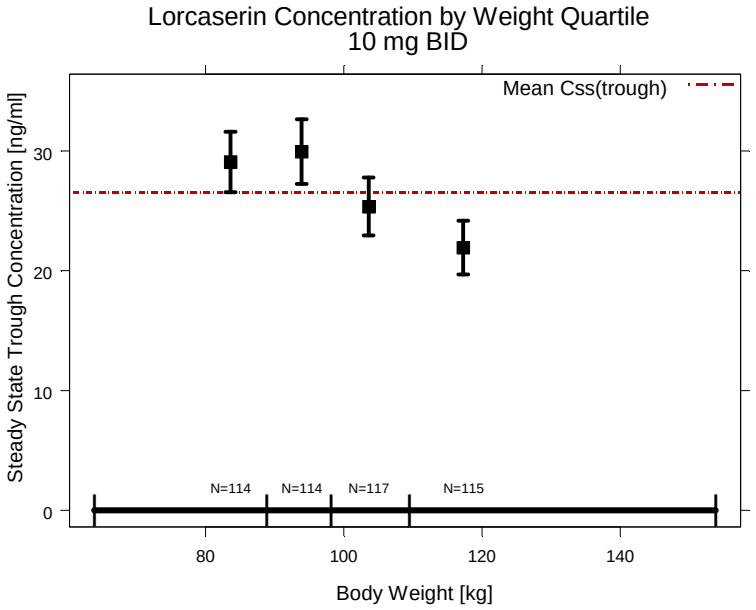
Exposure measurements of lorcaserin were available from 520 subjects (16.2%) receiving BID doses during the Phase 3 trials. Exposure-response relationship for percent change in body weight at Week 52 from baseline was established. This analysis demonstrated that patients with lower steady state trough ($C_{min(ss)}$) concentrations have less weight loss at 52 weeks than those with higher $C_{min(ss)}$ as illustrated in Figure 1. Furthermore, population PK analysis demonstrated that body weight is the most significant covariate affecting the clearance of lorcaserin. This implies that lower exposures of lorcaserin are expected in patients with higher body weight, which is demonstrated in Figure 2. Therefore, subjects with higher baseline body weight might potentially benefit from a higher dose to match their exposures to the exposures observed in lower body weight quartiles, in order to maximize efficacy. However, a weak correlation was observed between the lorcaserin exposure and the body weight in Phase 3 trials (Figure 3). Figure 2 also demonstrates significant concentrations overlapped in all four body weight quartiles. Only 41% of the subjects in the lowest concentration quartile in Figure 1 belonged to the highest body weight quartile (109.9 to 153.8 kg). This means that 59% of subjects in lowest exposure quartile belong to other body weight quartiles and administering a higher dose to these patients might lead to unnecessary higher exposures. Higher exposures, however, pose safety concerns based on pre-clinical findings, which demonstrated lorcaserin to be a potential human carcinogen with an unidentified safety margin in one pre-clinical species. Pharmacology/Toxicology review also revealed the uncertainty about the $EC_{50}$ values at other potential off target serotonin receptor subtypes, $5HT_{2a}$ and $5HT_{2b}$ receptors. See the Pharmacology/Toxicology Review by Dr. Fred Alavi for more detailed information. Furthermore, one patient receiving a single dose of 40 mg in the single ascending dose study, which is 4 times higher than the proposed clinical dose, demonstrated severe side effects around the $t_{max}$ of lorcaserin, including euphoria, feeling of drunkenness and other related adverse events. In conclusion, since the specific population that can benefit from an increased dose was not identified and higher lorcaserin concentrations pose several potential safety concerns, this reviewer does not recommend dose adjustment based on body weight.

**Figure 1** Percent weight loss at 52 weeks by concentration quartile in the PK subpopulation during the Phase 3 trials [a].



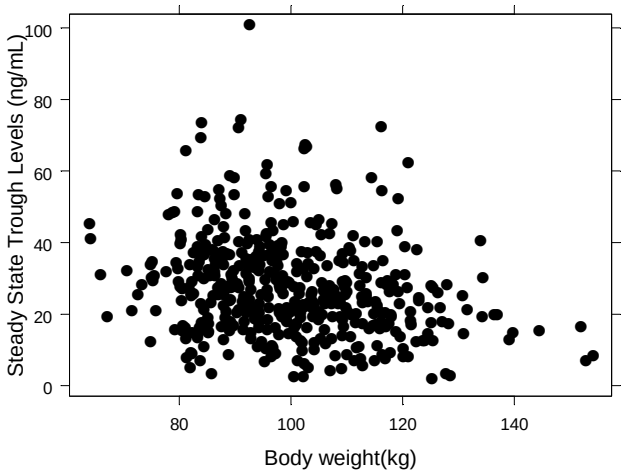

[a] The vertical black bars represent the mean with 95% confidence interval. The exposure range in each trough quartile is denoted by the horizontal black line along with the number of subjects in each quartile. Exposures are demonstrated as black squares at the median exposure of each quartile. The mean response demonstrated here is less than the mean response in the PK subpopulation, since the PK subpopulation was mainly composed of completers (subjects taking drug for 52 weeks and having a 52 week weight measurement)

**Figure 2** Lorcaserin steady state trough concentrations after administration of 10 mg BID dose in the Population PK subpopulation.[a]




[a] The vertical black bars represent the mean with 95% confidence interval. The body weight range in each weight quartile is denoted by the horizontal black line along with the number of subjects in each quartile. Exposures are demonstrated as black squares at the median body weight of each quartile.

**Figure 3** Exposures (steady state trough levels) observed in the PK subpopulation by body weight




## Intrinsic factors:

The sponsor evaluated the effect of renal impairment on lorcaserin pharmacokinetics in subjects with mild, moderate, severe renal impairment, or end stage renal disease. Creatinine clearance was calculated by Cockgroft-Gault equation based on ideal body weight (IBW). $C_{max}$ decreased, but AUC of lorcaserin did not change significantly with decreasing renal function. Lorcaserin sulfamate metabolite (M1) exposure increased approximately 1.7-fold and N-carbamoyl-lorcaserin metabolite (M5) increased approximately 2.8-fold in patients with moderate renal impairment.

Metabolites M1 and M5 increased by approximately 4-fold and 6-fold, respectively in patients with severe renal impairment, and increased 3-fold and 26-fold, respectively in patients with end-stage renal disease. Lorcaserin and M1 were not removed from the circulation by hemodialysis, and M5 was only modestly extracted (18%) by hemodialysis. Based on the exposure changes of M1 and M5 in moderate and severe renal impairment, and end stage renal disease, this reviewer agrees with the sponsor's proposal that lorcaserin should be used with a caution in patients with moderate renal impairment, and should not be used in patients with severe renal impairment or end-stage renal disease.

In patients with mild or moderate hepatic impairment, AUC and $C_{max}$ of lorcaserin were not meaningfully affected. Lorcaserin $C_{max}$ was 7.8% and 14.3% lower, respectively, than that in healthy matched controls. Mean AUC values were 24% and 30% higher, respectively, than that in the healthy matched controls. The sponsor did not evaluate the effect of severe hepatic impairment on the pharmacokinetics of lorcaserin. Considering the population pharmacokinetic estimate of approximately 33% for the between subject variability after adjustment of body weight, a 30% increase in AUC in patients with mild and moderate hepatic impairment is acceptable. Therefore, this reviewer agrees with the sponsor's proposal of not recommending a dose adjustment for patients with mild or moderate hepatic impairment. However, a label statement stating that lorcaserin has not been evaluated in severe hepatic impairment and cautionary use in patients with severe hepatic impairment is recommended.

In subjects ages 65 and above, lorcaserin $C_{max}$ was approximately 17% lower compared to those obtained from adults (18-65 years). Both subject groups were obese or overweight with a BMI of 27 to 45 $kg/m^2$. $AUC_{0-t}$, and $AUC_{0-inf}$ geometric mean ratios and their 90% confidence intervals were contained within a range of 0.80 to 1.25. Since lower $C_{max}$ concentrations do not pose a safety concern, the AUC did not change significantly, and the population pharmacokinetic analysis did not reveal any significant effect of age on the pharmacokinetics of lorcaserin, this reviewer agrees with the sponsor's conclusion that no dose adjustment is necessary based on the patients age.

**Extrinsic factors:**

The sponsor evaluated the pharmacokinetic properties of a single oral dose of lorcaserin in the fed versus fasted state. In study APD356-015, lorcaserin was administered in 12 overweight or obese patients with a BMI of 27-45 $kg/m^2$. In the fed state, lorcaserin was administered after a high fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800–1000 calories) meal. The 90% confidence intervals around the geometric mean ratios for comparing non-fasting and fasting regimens with respect to lorcaserin $C_{max}$, $AUC_{0-t}$ and $AUC_{0-inf}$ regimens were contained within the range of 0.80 to 1.25. Lorcaserin can be administered with or without regards to meals.

The sponsor evaluated the drug-drug interaction potential *in-vitro* and *in-vivo*. In *in-vitro*, the sponsor tested the inhibition potential of lorcaserin and lorcaserin sulfamate (M1) on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2C8, and CYP3A4, and the potential of lorcaserin or lorcaserin sulfamate as an inducer of CYP enzymes. The *in-vitro* data showed that lorcaserin is a competitive inhibitor of CYP2D6 while lorcaserin and lorcaserin sulfamate did not show any interaction potential with other enzymes tested. Based on the *in-vitro* [I]/Ki results of 0.14, the sponsor conducted Study APD356-012, which demonstrated that lorcaserin is an moderate inhibitor of CYP2D6 mediated metabolism as demonstrated by the increase in dextromethorphan exposure by approximately 2-fold after concomitant administration. A cautionary statement should be included in the label for patients concomitantly taking CYP2D6 substrates with lorcaserin.

## 2. Question Based Review

### *2.1. GENERAL ATTRIBUTES OF THE DRUG*

*2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?*

Lorcaserin is a new molecular entity (NME) developed by Arena Pharmaceuticals Inc. for the indication of weight management, including weight loss and maintenance of weight loss, and usage in conjunction with a reduced-calorie diet and a program of regular exercise. Lorcaserin is a 5-$HT_{2c}$ agonist.

*2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?*

Lorcaserin hydrochloride (lorcaserin HCl) is a new molecular entity (NME). The anhydrous HCl salt was observed to have three polymorphs, (b) (4) Anhydrous lorcaserin HCl was used for Phase 1, Phase 2, and one Phase 3 clinical (APD356-009) trials, but all anhydrous forms (b) (4) (b) (4) upon exposure to typical humidities. Lorcaserin hydrochloride hemihydrate (lorcaserin HCl HH) is a (b) (4). The hemihydrate was selected as the drug substance for two Phase 3 clinical trials, formulation development, and commercialization. The structural formula of lorcaserin HCl hemihydrate is illustrated in Figure 4. Lorcaserin HCL HH is a monobasic compound having pKa 9.53 and logP 2.56, and has a molecular weight of 241.16 g/mol.

**Figure 4** Structural formula of lorcaserin HCl hemihydrate

(b) (4)

The tablet dosage form was used in two of three Phase 3 trials (APD356-009 and APD356-011). Other clinical dosage forms included an oral solution used in Phase 1, and (b) (4) (b) (4) capsules used in Phase 1, Phase 2, and one Phase 3 clinical (APD356-009) trials. The prototype tablet formulation used in Phase 3 trials has the same composition as the market-image tablet formulation except for the color where the prototype tablet is white and the market-image tablet is blue.

The Biopharmaceutics Classification System (BCS) Committee concluded that lorcaserin hydrochloride can be classified as a BCS Class I drug.

*2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?*

The sponsor proposes that lorcaserin [redacted] (b) (4)

The sponsor proposes the indication for this drug for weight management, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced-calorie diet and a program of regular exercise. Furthermore, lorcaserin is proposed to be indicated for obese patients with an initial body mass index ≥30 kg/m2, or overweight patients with a body mass index ≥27 kg/m2 in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea).

*2.1.4 What are the proposed dosage(s) and route(s) of administration?*

Lorcaserin is to be administered orally as a dose of 10 mg BID without regards to meals. No dose adjustment is proposed for any specific population. While the sponsor is proposing a cautionary statement for use in patients with moderate renal impairment, this reviewer recommends that lorcaserin should not be used in patients with severe renal impairment and end stage renal disease. Lorcaserin has not been studied in patients with severe hepatic impairment and this reviewer recommends using lorcaserin in patients with severer hepatic impairment with caution.

## *2.2. GENERAL CLINICAL PHARMACOLOGY*

*2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

The clinical pharmacology program consists of the following 13 in-vivo studies:

- 3 intrinsic factor studies
  - renal impairment
  - hepatic impairment
  - obese elderly vs. obese adult pharmacokinetics
- 4 extrinsic factor studies
  - 2 fasted vs. fed pharmacokinetic studies (both tablet and capsule formulation)
  - 2 drug-drug interaction studies with CYP 2D6 probe dextromethorphan (both tablet and capsule formulation)
- 4 pharmacokinetic studies
  - maximum tolerated dose (single and multiple dose)
  - mass balance study
  - relative bioavailability (capsule vs. tablet formulation)
- 1 PK/PD study
  - Effect of lorcaserin on body weight, appetite, and food intake
- 1 thorough QT study

During the clinical program, the sponsor conducted two Phase 2 studies, APD356-003 and APD356-004 with a total duration of 28 days and 3 month, respectively. Study APD356-003 assessed doses of 1 mg, 5 mg, and 15 mg given once daily, and placebo. Study APD356-004 evaluated doses of 10 mg and 15 mg given once daily, 10 mg given twice daily, and placebo. Additionally, two Phase 3 safety and efficacy studies, APD356-009 and APD356-011, were conducted. An additional Phase 3 study, APD356-010, in overweight and obese patients with type 2 diabetes mellitus is still ongoing.

Study APD356-009 evaluated the efficacy for weight loss and weight maintenance at 10 mg BID dose comparing that of placebo over 104 weeks. For the efficacy for weight loss, the weight loss in the 10 mg BID dosing group was compared to placebo at week 52. Efficacy for weight maintenance was assessed during the second year of the trial: at Week 52, while patients assigned to lorcaserin were re-randomized 2:1 to remain on lorcaserin or to switch to placebo, all patients on placebo remained on placebo. Safety assessments included echocardiograms (for FDA-defined valvulopathy assessment) at screening, Week 24, Week 52, Week 76, and Week 104.
Study APD356-011 evaluated doses of 10 mg QD and 10 mg BID compared to placebo; the total duration of the study was 52 weeks. Safety assessments included echocardiograms at baseline, Week 24, and Week 52, and prolactin samples at baseline and at weeks 4, 12, 24, and 52 (pre dose, and 2 h post dose sample).

Studies APD356-009 and APD356-011 evaluated the following co-primary endpoints:

- 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

Additionally, the sponsor included population pharmacokinetic analysis, exposure-response analysis, and 14 in-vitro studies in the application. The in-vitro studies included protein binding and blood/plasma ratio, Caco-2 permeability, and metabolism studies, as well as CYP inhibition and induction studies.

*2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?*

The FDA draft guidance for industry titled "Developing Products for Weight Management" recommends that the efficacy of a weight-management product should be assessed by analyses of both mean (the difference in mean percent loss of baseline body weight in the active-product versus placebo-treated group) and categorical changes (the proportion of subjects who lose at least 5 percent of baseline body weight in the active-product versus placebo-treated group) in body weight. The sponsor conducted the analysis based on both mean and categorical changes.

According to the draft guidance, in general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:

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

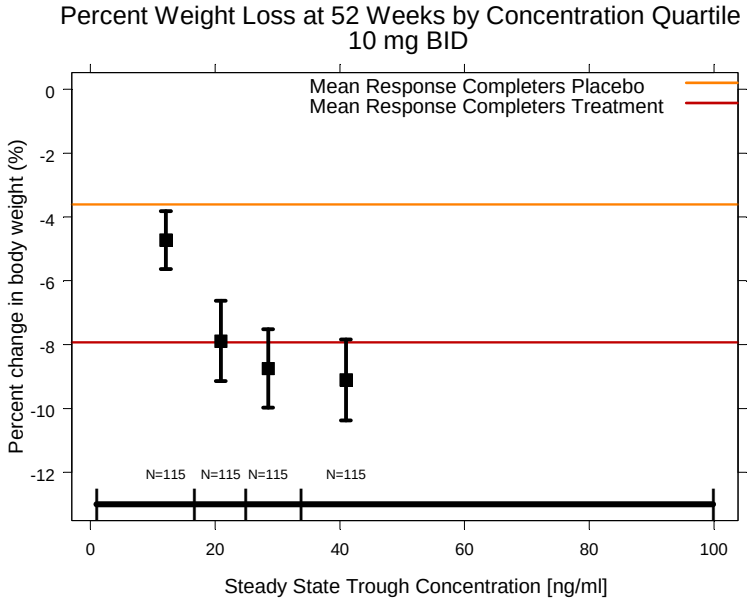
*2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

Yes, please refer to the Analytical Section (section 2.6) for details.

*2.2.4 What are the characteristics of the exposure-response relationship (dose response, concentration-response)?*

The exposure response relationship for efficacy was evaluated in the subjects randomized to 10 mg BID during the Phase 3 trials (last observation carried forward population). There were 520 out of 3198 patients (16.2%) receiving the BID dose in both Phase 3 clinical trials that had exposure measurements and completed the trial. Figure 5 demonstrates the exposure response relationship. Subjects demonstrated increasing weight loss from baseline after 52 weeks with increasing exposures. Sponsor also demonstrated dose-response in phase-2 trials and selected 10 mg QD and 10 mg BID for the Phase-3 trials (Figure 8).

**Figure 5** Percent weight loss at 52 weeks by concentration quartile in the PK subpopulation during the Phase 3 trials[a].




[a] The vertical black bars represent the mean with 95% confidence interval. The exposure range in each trough quartile is denoted by the horizontal black line along with the number of subjects in each quartile. Exposures are demonstrated as black squares at the median exposure of each quartile.

*2.2.5 What are the characteristics of the dose/exposure-response relationship for safety?*

During the review of most frequent adverse events, this reviewer observed a trend in the increase in adverse events with increasing dose for nervous system disorders and psychiatric disorders (Table 1).

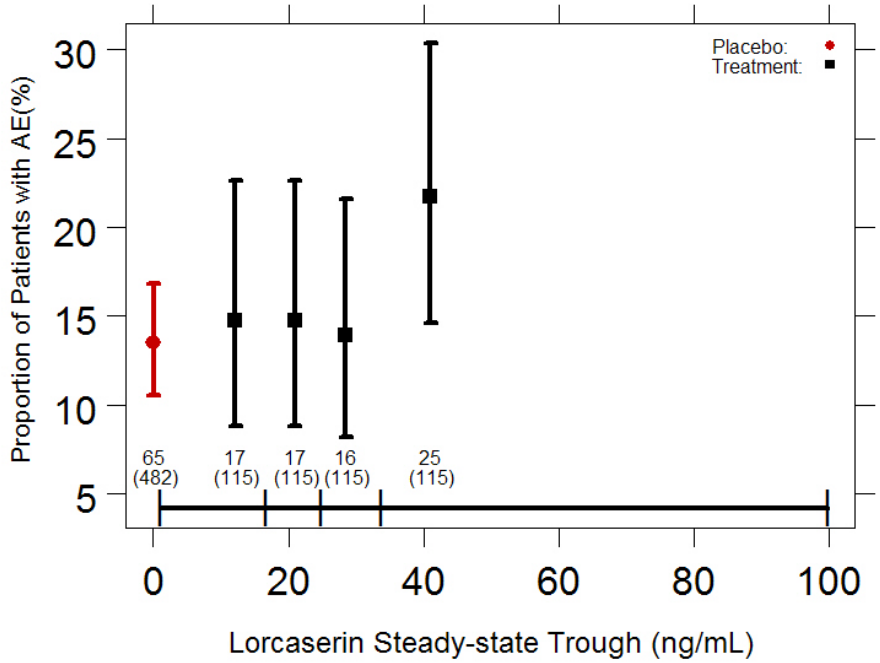
**Table 1** Summary of Most Frequent Adverse Events (≥1% of patients in any group) Considered to be Possibly or Probably Related to Study Drug in Pooled Phase 3 Studies: Safety Population.

| System Organ Class<br>Preferred Term | Pooled Placebo (N=3185) | Pooled Lorcaserin 10 mg BID (N=3195) | Lorcaserin 10 mg QD (N=801) | Any Lorcaserin Dose (N=3996) |
|---|---|---|---|---|
| Number of Patients Reporting AEs | 799 (25.1) | 1186 (37.1) | 267 (33.3) | 1453 (36.4) |
| Gastrointestinal Disorders | | | | |
| Nausea | 85 (2.7) | 152 (4.8) | 28 (3.5) | 180 (4.5) |
| Dry mouth | 64 (2.0) | 144 (4.5) | 25 (3.1) | 169 (4.2) |
| Constipation | 61 (1.9) | 90 (2.8) | 18 (2.2) | 108 (2.7) |
| Diarrhoea | 50 (1.6) | 78 (2.4) | 11 (1.4) | 89 (2.2) |
| Vomiting | 16 (0.5) | 33 (1.0) | 7 (0.9) | 40 (1.0) |
| General Disorders And Administration Site Conditions | | | | |
| Fatigue | 45 (1.4) | 127 (4.0) | 23 (2.9) | 150 (3.8) |
| Metabolism And Nutrition Disorders | | | | |
| Decreased appetite | 27 (0.8) | 37 (1.2) | 21 (2.6) | 58 (1.5) |
| Nervous System Disorders | | | | |
| Headache | 171 (5.4) | 329 (10.3) | 83 (10.4) | 412 (10.3) |
| Dizziness | 64 (2.0) | 189 (5.9) | 29 (3.6) | 218 (5.5) |
| Somnolence | 16 (0.5) | 38 (1.2) | 5 (0.6) | 43 (1.1) |
| Psychiatric Disorders | | | | |
| Insomnia | 42 (1.3) | 32 (1.0) | 8 (1.0) | 40 (1.0) |

A dose-response relationship was evaluated for FDA defined valvulopathy. There were 31 (2.06%) events in the placebo group for the completer population for the pooled Phase 3 trials. This compares to 9 (2.0%) FDA defined valvulopathy events in the10 mg QD dose group in APD356-009 trial and 40 (2.29%) in the completer population for the pooled Phase 3 trials for the 10 mg BID dose. Based on this dose-response data, this reviewer evaluated whether there is an exposure-response relationship for these safety events.

This reviewer was unable to determine a conclusive exposure-response relation for safety for these adverse events. The exposure-response relationships for the all System Organ Class (SOC) classification including Nervous system disorders and Psychiatric disorder in particular were evaluated. The SOC is comprised of all adverse events related to psychiatric disorders.
The adverse events included in the SOC are coded as preferred terms. There was no significant exposure-response relationship for any single safety related preferred term within this SOC. This is most likely because event rates in each preferred term were low and PK data is limited. When evaluating the more general adverse event category SOC Psychiatric disorder, the exposure-response relationship demonstrated a slight trend of higher AEs with higher exposures. The proportion of patients experiencing psychiatric disorders (all grade) were slightly higher in the fourth quartile compared to first three concentration quartiles **(**Figure 6). Furthermore, the AEs in the first three concentration quartiles overlap with placebo. This relationship, however, includes all adverse events coded as preferred terms in the psychiatric disorders category and might not be associated with single specific events. Hence, this relationship is not conclusive and should be interpreted with caution.

**Figure 6** Proportion of patients with adverse events (SOC Psychiatric Disorders) by observed steady state trough concentration quartile




Overall, the results from the exposure-response evaluation for safety are inconclusive, because:

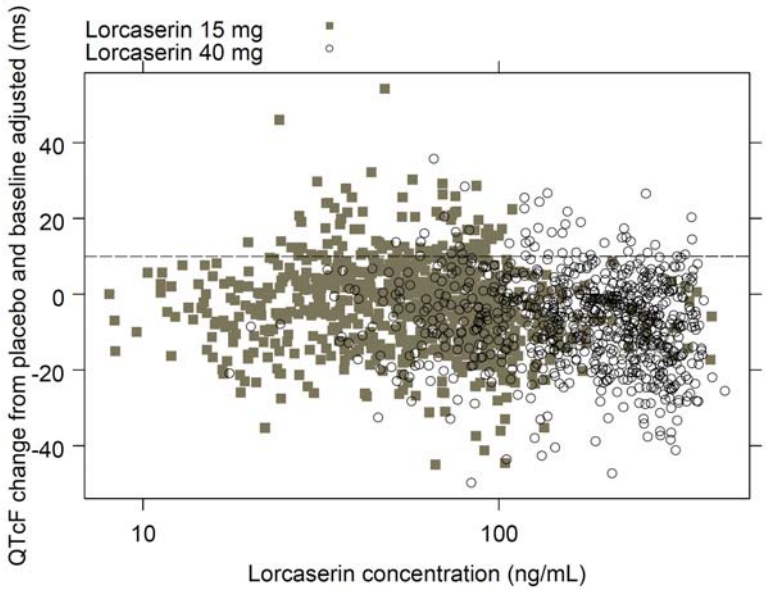
- The number of preferred term adverse events in the population randomized to PK sampling was low, which did not allow for evaluation of exposure response relationship on the adverse event preferred term level
- Exposure-response relationship analysis for safety on the system organ class (SOC) level is confounded by the variety of preferred term events included in the SOC.

*2.2.6 Does lorcaserin prolong the QT or QTc interval?*

The effect of lorcaserin on the QT interval was assessed in a double-blind, randomized, parallel design trial (APD356-007). In this randomized, blinded, four-treatment, parallel study, 244 healthy subjects received lorcaserin 15 mg, lorcaserin 40 mg, placebo, and a single oral dose of moxifloxacin 400 mg. The sponsor submitted the study report under IND 69,888.

In brief, no significant QT prolongation effect of lorcaserin (15 mg QD and 40 mg QD) was detected in this thorough QT study (Figure 7). The largest upper bounds of the 2-sided 90% CI for the mean difference between lorcaserin (10 mg and 40 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance. For the full review, see Dr. Christine Garnett's report in DAARTS dated 06/30/2008.

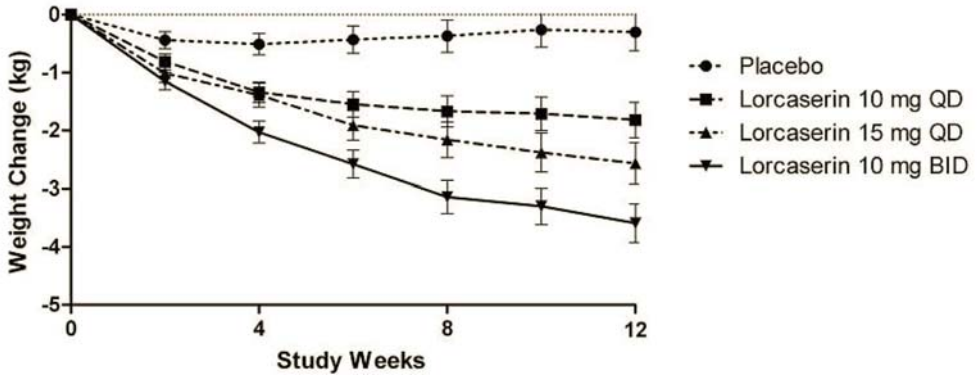
**Figure 7** ΔΔQTcF vs. Lorcaserin Concentrations




*2.2.7 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?*

Dose selection was appropriate as demonstrated in the results from two Phase 2 studies dose finding studies, APD356-003 and APD356-004 with a total duration of 28 days and 3 month, respectively. Study APD356-003 assessed doses of 1 mg, 5 mg, and 15 mg given once daily, and placebo. Study APD356-004 evaluated doses of 10 mg and 15 mg given once daily, 10 mg given twice daily, and placebo. In Study APD356-004 the sponsor demonstrated that the 10 mg dose given twice daily resulted in the highest weight loss compared to placebo over a period of 3 month (Figure 8).

**Figure 8** Change in Body Weight from Baseline to Week 12 in APD356-004: Completer Analysis

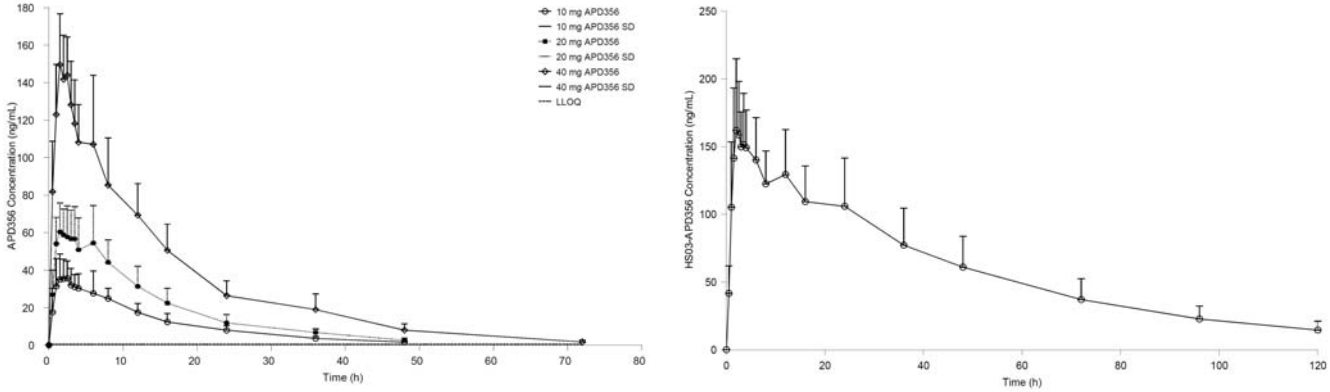



*2.2.8 What are the single dose and multiple dose PK parameters?*

Single dose administration ranged from 10 to 40 mg in healthy male and female volunteers with a BMI between 23-32 kg/m$^2$ under fasting conditions. For lorcaserin, median $t_{max}$ ranged from 1.75 to 2.25 hours and the mean $t_{1/2}$ ranged from 10.16 to 11.2 hours. Plasma samples were not analyzed for the $HSO_3$-lorcaserin metabolite in the 10 and 20 mg dosing group. The sponsor measured $HSO_3$-lorcaserin concentrations in the 40 mg dose level group.

Multiple doses (QD) of 3, 10, and 20 mg were evaluated in male and female healthy volunteers with a BMI of ≥25 kg/m$^2$. PK parameters for the parent drug were similar on day 1 and day 14. Accumulation of the 10 mg QD dose was approximately 35%. The estimated accumulation for a proposed marketed dose of 10 mg BID dose based on an 11 h half-life is approximately 70%. The mean fraction of the administered dose excreted as unchanged APD356 for the 3, 10, and 20 mg dose levels were lower than 1.5%. Both $C_{max}$ and AUC appeared to increase dose proportionally between the 3 and 20 mg dose (please see section 2.2.14 for more details on dose proportionality).

**Figure 9** Mean (+SD) Plasma Concentration-Time Profiles of Lorcaserin (ng/ml) [left] HSO3-Lorcaserin[a] [right] (ng/mL) After Administration of Single Oral Doses of Lorcaserin to Healthy Male and Female Subjects




[a] $HSO_3$-Lorcaserin was only measured in subjects receiving a single 40 mg dose of lorcaserin

Median $t_{max}$ for $HSO_3$-lorcaserin ranged between 2.25 and 3.25 hours during the multiple dose study. Mean apparent elimination half-life of $HSO_3$-lorcaserin in plasma ranged from approximately 32 to 45 hours on Day 1 and from approximately 47 to 52 hours on Day 14. The mean accumulation index or $HSO_3$-lorcaserin for the 3, 10, and 20 mg dose given once daily were 2.698, 2.596, and 2.075, respectively. The estimated accumulation for BID dosing is approximately 6-fold based on an observed half-life of 47 hours.

**Table 2** Summary of Plasma Lorcaserin Pharmacokinetic Parameters at 3mg, 10 mg, and 20 mg, daily on day 1 and day 14

| Pharmacokinetic Parameters | Treatment A 3 mg Daily for 14 Days | Treatment B 10 mg Daily for 14 Days | Treatment C 20 mg Daily for 14 Days |
|---|---|---|---|
| **Day 1** | | | |
| $T_{max}$ (hr)* | 2.000 (2.00 – 3.00) | 1.500 (1.50 – 2.50) | 1.750 (1.00 – 2.50) |
| $C_{max}$ (ng/mL) | 11.16 (3.842) | 39.07 (11.144) | 83.77 (16.584) |
| $AUC_{(0-t)}$ (ng·hr/mL) | 132.1 (47.46) | 436.1 (130.01) | 878.7 (206.85) |
| $AUC_{(0-\tau)}$ (ng·hr/mL) | 132.3 (47.56) | 436.6 (130.19) | 879.9 (207.23) |
| $AUC_{(0-inf)}$ (ng·hr/mL) | 172.0 (69.08) | 516.9 (159.41) | 1086.2 (299.03) |
| $T_{½z}$ (hr) | 11.381 (1.9918) | 8.866 (1.8053) | 9.546 (2.8174) |
| **Day 14** | | | |
| $T_{max}$ (hr)* | 1.750 (1.00 – 2.50) | 2.500 (1.50 – 3.00) | 2.000 (1.00 – 3.50) |
| $C_{max}$ (ng/mL) | 13.70 (4.192) | 50.85 (15.745) | 85.02 (33.622) |
| $C_{min}$ (ng/mL) | 2.604 (1.8236) | 9.297 (4.7587) | 12.694 (14.0964) |
| $C_{avg}$ (ng/mL) | 7.17 (2.578) | 24.74 (8.500) | 37.47 (18.925) |
| $AUC_{(0-t)}$ (ng·hr/mL) | 172.2 (61.86) | 593.8 (204.01) | 899.2 (454.20) |
| $AUC_{(0-\tau)}$ (ng·hr/mL) | 172.2 (61.86) | 593.8 (204.01) | 899.2 (454.20) |
| $T_{½z}$ (hr) | 10.229 (2.8697) | 10.281 (2.4270) | 11.264 (3.7134) |
| Cl/F (L/hr) | 19.81 (8.600) | 18.07 (4.352) | 26.07 (9.675) |
| AI | 1.327 (0.2578) | 1.358 (0.1808) | 1.051 (0.4561) |
| $C_{max}$ Ratio | 1.2739 (0.32255) | 1.3121 (0.20441) | 1.0695 (0.48292) |

* Median (range) presented

**Table 3** Summary of Plasma $HSO_3$-lorcaserin Pharmacokinetic Parameters at 3mg, 10 mg, and 20 mg, daily on day 1 and day 14

| Pharmacokinetic Parameters | Treatment A 3 mg Daily for 14 Days | Treatment B 10 mg Daily for 14 Days | Treatment C 20 mg Daily for 14 Days |
|---|---|---|---|
| **Day 1** | | | |
| $T_{max}$ (hr)* | 2.750 (2.50 – 4.00) | 2.250 (2.00 – 6.00) | 3.000 (2.00 – 3.50) |
| $C_{max}$ (ng/mL) | 9.29 (2.648) | 50.07 (16.125) | 138.97 (104.215) |
| $AUC_{(0-t)}$ (ng·hr/mL) | 160.8 (46.66) | 823.5 (306.74) | 2382.3 (1991.20) |
| $AUC_{(0-\tau)}$ (ng·hr/mL) | 161.2 (46.82) | 825.7 (307.70) | 2388.9 (1997.09) |
| $AUC_{(0-inf)}$ (ng·hr/mL) | 506.5 (238.77) | 1857.1 (726.85) | 6257.5 (5901.47) |
| $T_{½z}$ (hr) | 44.59 (15.275) | 32.37 (4.120) | 33.27 (9.681) |
| **Day 14** | | | |
| $T_{max}$ (hr)* | 3.250 (2.00 – 4.00) | 3.250 (2.03 – 8.00) | 2.500 (1.50 – 6.00) |
| $C_{max}$ (ng/mL) | 23.00 (9.649) | 120.45 (59.176) | 293.22 (373.532) |
| $C_{min}$ (ng/mL) | 14.50 (7.790) | 68.52 (36.214) | 166.63 (212.488) |
| $C_{avg}$ (ng/mL) | 18.35 (8.002) | 90.61 (44.212) | 229.94 (290.751) |
| $AUC_{(0-t)}$ (ng·hr/mL) | 440.3 (192.09) | 2174.7 (1061.08) | 5518.6 (6978.02) |
| $AUC_{(0-\tau)}$ (ng·hr/mL) | 474.2 (193.62) | 2599.5 (1404.41) | 5518.6 (6978.02) |
| $T_{½z}$ (hr) | 52.36 (18.345) | 46.78 (0.406) | 47.23 (12.043) |
| AI | 2.698 (0.6117) | 2.596 (0.4685) | 2.075 (0.9402) |
| $C_{max}$ Ratio | 2.432 (0.4574) | 2.368 (0.6121) | 1.875 (0.9842) |

* Median (Min-Max)

*2.2.9 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?*

Most Phase 1 studies enrolled overweight subjects (BMI >23 kg/$m^2$), which is the intended population to be treated. Since lorcaserin pharmacokinetic properties have been established in the intended target population, a comparison to healthy subjects is not necessary.

*2.2.10 What are the characteristics of drug absorption?*

Lorcaserin is highly permeable across Caco-2 cell monolayer and appears not to be a substrate or an inhibitor of P-gp. Studies to indentify the involvement of other drug transporters in the absorption of lorcaserin have not been conducted. Absolute bioavailability of lorcaserin has not been evaluated. In a mass balance study, approximately 92% of the radioactive dose of lorcaserin was recovered in urine. Lorcaserin reaches peak plasma concentrations after approximately 2 hours.

*2.2.11 What are the characteristics of drug distribution?*

Lorcaserin is mainly distributed to human plasma, based on the human whole blood to plasma partition coefficient which is approximately 0.63. Lorcaserin is moderately bound to plasma proteins (approximately 70%).

*2.2.12 Does the mass balance study suggest renal or hepatic as the major route of elimination?*

Overall, lorcaserin is eliminated both by renal and hepatic route. Lorcaserin was extensively metabolized and the parent drug as well as the metabolites was excreted mainly in urine. A mean $^{14}C$ recovery of 94.5% was achieved in 6 subjects by the end of the study period. On average, 92.3% of the total radioactivity administered as a 10 mg dose was recovered in urine. Approximately, 2.2% was recovered in feces (Table 4).
HSO3-lorcaserin was identified as the major metabolite observed in circulation, representing approximately 38% of radioactivity in pooled plasma. Parent drug was the second most abundant radioactive peak with approximately 12% of radioactivity in plasma. In addition, five minor metabolites, M5 (N-carbamoyl glucuronide), M8 (1-carboxyl glucuronide), M10 (phenolic sulfate),

M13 (N-glucuronide), and M14 (ether glucuronide), were found in plasma. Each of these five minor metabolites represented less than 10% of the radioactivity in circulation. Ten metabolites were identified in urine. M5 (N-carbamoyl glucuronide) was identified as the major metabolite in urine, and represented approximately 36% of total administered dose additionally, one urinary metabolite, M8 (1-carboxyl glucuronide) was excreted in urine greater than 10% of dose. While lorcaserin sulfamate (HSO3- lorcaserin) was the major metabolite in plasma, it was a minor metabolite in urine, representing approximately 3% of dose. Nine other metabolites excreted in urine were identified as either glucuronide or sulfate conjugates of oxidative metabolites.

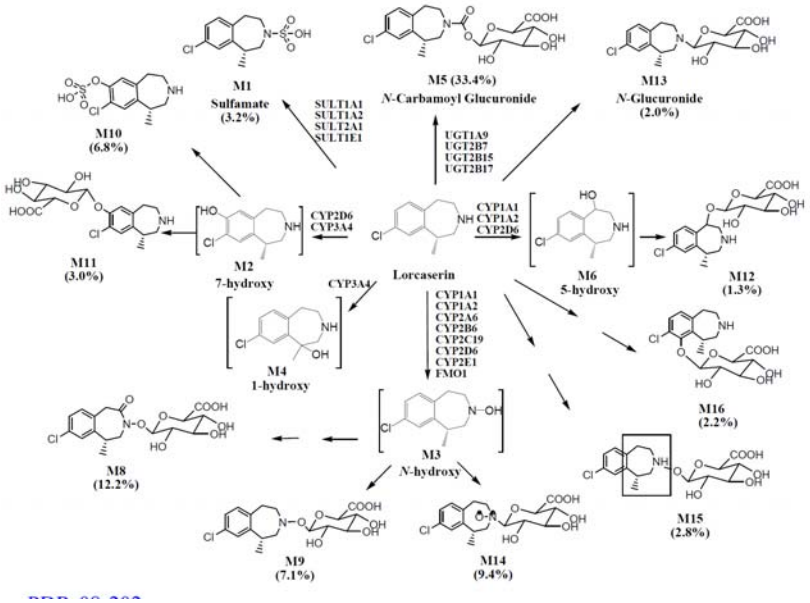
**Table 4** Mass Balance of Total Radioactivity Excretion Following 1 x 10 mg [14C]-lorcaserin Containing 100 μCi of Total Radioactivity

| Subject Number | Cum % dose in Urine | Cum % dose in Feces | % of Total Dose |
|---|---|---|---|
| 1 | 92.3 | 2.33 | 94.6 |
| 2 | 93.4 | 1.18 | 94.5 |
| 3 | 94.8 | 3.41 | 98.2 |
| 4 | 90.1 | 2.38 | 92.5 |
| 5 | 89.5 | 1.39 | 90.9 |
| 6 | 93.8 | 2.46 | 96.3 |
| | | | |
| N | 6 | 6 | 6 |
| Mean | 92.3 | 2.19 | 94.5 |
| SD | 2.1 | 0.81 | 2.6 |
| CV (%) | 2.3 | 36.94 | 2.8 |
| SEM | 0.9 | 0.33 | 1.1 |
| Minimum | 89.5 | 1.18 | 90.9 |
| Maximum | 94.8 | 3.41 | 98.2 |

*2.2.13 What are the characteristics of drug metabolism?*

*In-vitro* data indicate that lorcaserin is extensively metabolized in the liver. The main circulatory metabolite (lorcaserin sulfamate, M1) and the main urinary metabolite (N-carbamoyl lorcaserin, M5) are inactive metabolites. Lorcaserin is metabolized by multiple CYP P450 enzymes (1A1, 1A2, 2A6, 2B6, 2C19, 2D6, 2E1, 3A4), UGT enzymes (1A9, 2B7, 2B15, 2B17), and SULT enzymes (1A1, 1A2, 2A1, 1E1). A minor metabolite (7-OH lorcaserin) formed by CYP 2D6 was detected in some patients in the mass balance study. Lorcaserin is a competitive inhibitor of CYP2D6 mediating dextromethorphan O-demethylation, but does not significantly inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4-mediated metabolism. Lorcaserin did not induce CYP1A2 and the induction potential for CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5 was low. The proposed metabolic pathway in humans is illustrated in Figure 10.

**Figure 10** Proposed Lorcaserin Metabolic Pathways in Humans (percentage of dose excreted in urine, n=6)




*2.2.14 What are the characteristics of drug excretion?*

Based on the mass balance study, lorcaserin is extensively metabolized. It seems that the major metabolite in plasma, $HSO_3$-lorcaserin (38%) is further metabolized since only 3.2% were recovered in urine. On the other hand, the major urinary metabolite N-carbamoyl glucuronide (~36%) represented only <10% of plasma radioactivity. The mean elimination half life after multiple oral administrations in patients was between 8.8 and 11.6 h following 3 mg to 20 mg doses. The mean apparent elimination half-life of $HSO_3$-lorcaserin in plasma ranged from approximately 32 to 45 hours on Day 1 and from approximately 47 to 52 hours on Day 14. Lorcaserin and the main metabolites are almost completely eliminated within 10 days post dose.

*2.2.15 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?*

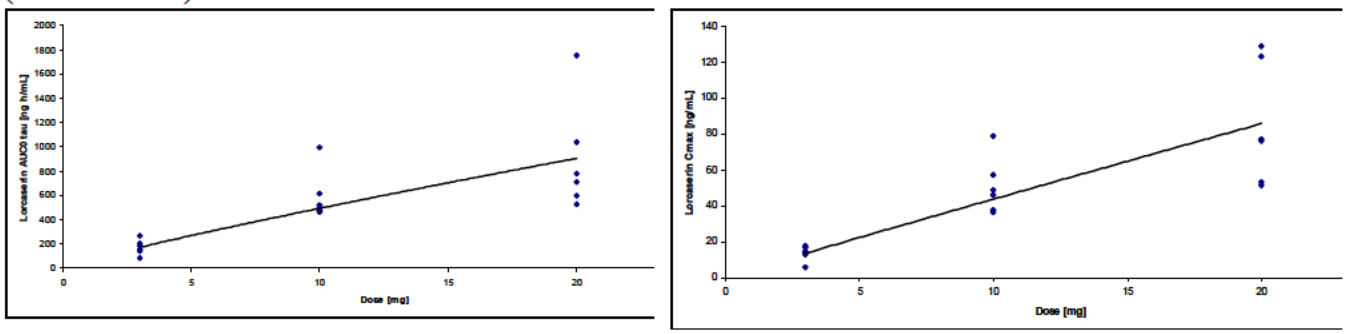
Dose proportionality was estimated using the power model, ($Y = \alpha * Dose^{\beta}$ where Y, $\alpha$ and $\beta$ correspond to the PK parameter (AUC or Cmax), proportionality constant and an exponent, respectively). If the 90% CI for the exponent, $\beta$ contains 1, the relationship between dose and the PK parameters is considered to be dose proportional.

Dose proportionality was evaluated using lorcaserin AUC and Cmax obtained from the multiple dose ascending studies in subjects with a BMI ≥25 kg/m$^2$. Dose proportionality was demonstrated on all days evaluated (1 and 14). Point estimates and 90% confidence intervals for the dose-proportionality parameter (slope of the linear regression) were calculated from the multiple ascending dose study (APD356-002), where doses of 3, 10, and 20 mg were administered daily for 14 days and are shown below (Figure 11):

- $C_{max}$ Day 1: 1.08 [0.92-1.24]
- $C_{max}$ Day 14: 0.97 [0.78-1.16]
- $AUC_{inf}$ Day 1: 0.98 [0.81-1.16]
- $AUC_{\tau}$ Day 14: 0.87 [0.67-1.07]

During the single ascending dose study (APD356-001A), doses of 10, 20, and 40 mg were administered. Even though the $C_{max}$ and AUC appear to increase approximately double with doubling of dose, strict dose proportionality in this dose range could not be established since some of the 90 % confidence intervals excluded 1.

**Figure 11** Lorcaserin $AUC_{0\text{-}tau}$ (left) and $C_{max}$ (right) on Day 14 in overweight/obese subjects (APD356-002)




*2.2.16 What is the inter- and intra-subject variability of PK parameters in patients, and what are the major causes of variability?*

Inter-subject variability of ≤ 30% was observed in pharmacokinetics parameters of $AUC_{0\text{-}inf}$ and $C_{max}$. Some of the studies that can be used to get an estimate of the inter-subject variability for AUC and $C_{max}$ of lorcaserin are shown in Table 5.

**Table 5 Variability estimates (%CV) for $AUC_{0\text{-}inf}$ and $C_{max}$ of lorcaserin 10 mg dose.**

| **Study** | | **Inter-subjects variability (%CV)** | |
|---|---|---|---|
| | | **$C_{max}$** | **$AUC_{0\text{-}inf}$** |
| **APD356-001A** | Single dose PK | 27 | 27.3 |
| **APD356-002** | Multiple dose PK | 28 | 30 |

The population analysis estimated that the inclusion of body weight as a covariate reduced the inter-individual variability of the apparent clearance from 36.2% to 32.2%.

## *2.3. INTRINSIC FACTORS*

*2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?*

- **Age and Gender**

The sponsor has evaluated the effect of age on the pharmacokinetics of lorcaserin in the dedicated PK study APD356-018. The sponsor conducted study APD356-018 to compare the single-dose pharmacokinetic (PK) parameters of lorcaserin in the obese or overweight elderly (>65 years) to those obtained from the obese or overweight adult (18-65 years). Subjects received a single 10 mg dose of lorcaserin. In this study, the 90% confidence intervals when comparing adult and to elderly subjects with respect to lorcaserin $AUC_{0-t}$, and $AUC_{0-inf}$ regimens were similar. $C_{max}$ was approximately 17% lower in elderly subjects compared to adult subjects. The 90% confidence interval of the geometric mean ratio with regards to $C_{max}$ was 71-97% (Table 6).

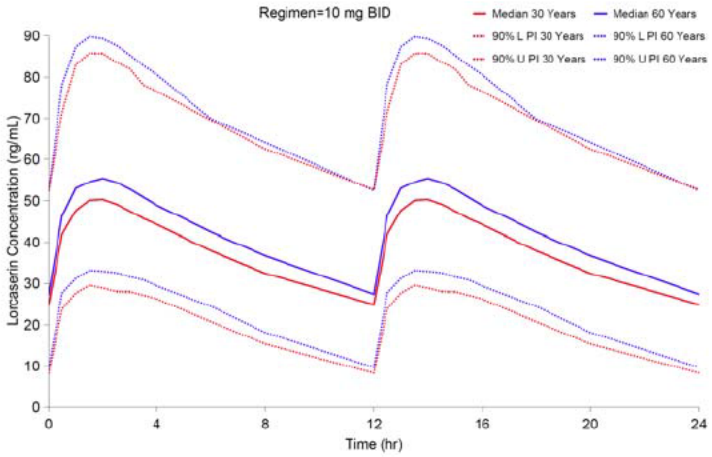
**Table 6** Analysis of Pharmacokinetic Parameters of Lorcaserin-PK Population

| Parameter | Geometric Mean | | Geometric Mean Ratio (Elderly/Adult) | |
|---|---|---|---|---|
| | Adult | Elderly | Ratio | 90%CI |
| $C_{max}$ (ng/mL) | 33.0 | 27.5 | 0.83 | 0.71-0.97 |
| $AUC_{0-t}$ (ng.hr/mL) | 442.8 | 437.8 | 0.99 | 0.80-1.22* |
| $AUC_{0-inf}$ (ng.hr/mL) | 460.7 | 453.5 | 0.98 | 0.80-1.22* |
| *Note: Denotes 90% confidence interval fell within the recommended 0.80-1.25 limits of equivalence when analyzed on logarithmic scale | | | | |

The results of the population PK analysis (multivariate analysis) support the results of the dedicated age effect study (APD356-018). Even though the population PK analysis indicated that CL/F decreased with age and the effect of age on CL/F was responsible for a small but significant increase (> 10.84 points) in OFV upon its removal, it resulted in only a very small improvement in inter-individual variability (IIV) for CL/F (32.2% to 31.8%).

Simulations showed that there was less than a 10% increase in lorcaserin concentrations following a doubling of age. From 250 simulations median and 90% prediction interval (PI) lorcaserin concentrations were very similar for a population of median weight of 92.5 kg but aged 30 and 60 years (Figure 12). Therefore, the sponsor concluded that the effect of age on CL/F not to be clinically significant and consequently as the effect was dropped from the final PK model for lorcaserin.

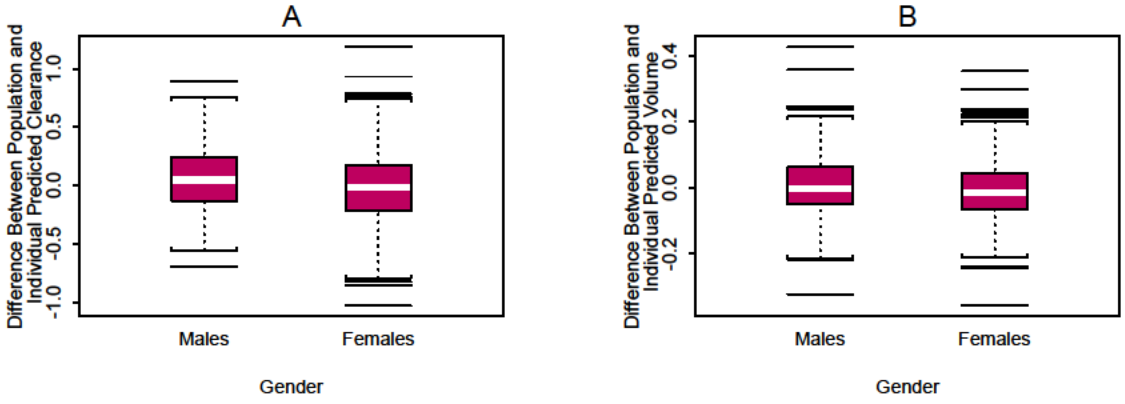
**Figure 12** Simulated (N=250) Median and 90% prediction interval (PI) following Administration of 10 mg Lorcaserin BID to a Population with a Median Age 30 Years and 60 Years




Source: Sponsor PK/PD report page 43,Figure 8-2

There is no difference in pharmacokinetics of lorcaserin between male and female subjects. Figure 13 shows that after adjusting for body weight, there is no significant difference in the differences between individual and population predicted clearance and volume of distribution (ETA1 and ETA 2).

**Figure 13** Difference in clearance (panel A) and Volume (panel B) in the pharmacokinetic population by gender.




Source: CL and V vs. gender plot.

***Reviewer comment:***

- *No dosage adjustment is proposed based on age and gender. This is acceptable.*

**• Renal Impairment**

The effect of renal impairment on the pharmacokinetics of lorcaserin, the main circulatory metabolite (lorcaserin sulfamate) and the main urinary metabolite (N-carbamoyl glucuronide) were evaluated in study APD356-016.

$C_{max}$ decreased, but AUC of lorcaserin did not change significantly with decreasing renal function. Overall, the changes in lorcaserin exposure seem unlikely to be clinically relevant.

Table 7 Geometric Mean Ratios of Lorcaserin Plasma Pharmacokinetic Parameters

| Pharmacokinetic Parameters | Geometric Mean Ratios of LSM (90% Confidence Intervals) of Lorcaserin Relative to Normal Renal Function Group (n=8 per Group) | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| $C_{max}$ | 0.991 (0.764, 1.29) | 0.697 (0.537, 0.904) | 0.686 (0.529, 0.891) |
| $AUC_{0-t}$ | 1.31 (1.01, 1.69) | 1.02 (0.791, 1.32) | 0.933 (0.723, 1.20) |
| $AUC_{0-inf}$ | 1.30 (1.01, 1.67) | 1.03 (0.806, 1.32) | 0.931 (0.727, 1.19) |

The results of the reviewer's analysis for subjects with ESRD are provided in Table 8.

**Table 8** Geometric Mean Ratios of Lorcaserin Plasma Pharmacokinetic Parameters (patients with end stage renal disease with and without dialysis)

| Pharmacokinetic Parameters | Geometric Mean Ratios of LSM (90% Confidence Intervals) of Lorcaserin Relative to Normal Renal Function Group (n=8 per Group) | |
|---|---|---|
| | ESRD (no dialysis) | ESRD (dialysis) |
| $C_{max}$ | 0.692 (0.51, 0.92) | 0.74 (0.55, 0.99) |
| $AUC_{0-t}$ | 1.21 (0.91, 1.60) | 1.10 (083, 1.47) |
| $AUC_{0-inf}$ | 1.64 (1.23, 2.19) | 1.32 (0.97, 1.79) |

Lorcaserin sulfamate (M1) exposure increased approximately 1.7-fold (Table 9) and N-carbamoyl-lorcaserin (M5) increased approximately 2.8-fold in patients with moderate renal impairment (Table 10).
Metabolites M1 and M5 increased by approximately 4-fold and 6-fold, respectively in patients with severe renal impairment, and increased 3-fold and 26-fold, respectively in patients with end-stage renal disease. Lorcaserin and M1 were not removed from the circulation by hemodialysis, and M5 was only modestly extracted (18%) by hemodialysis.

**Table 9** Geometric Mean Ratios of Lorcaserin sulfamate Plasma Pharmacokinetic Parameters

| Pharmacokinetic Parameters | Geometric Mean Ratios of LSM (90% Confidence Intervals) of $HSO_3$-Lorcaserin Relative to Normal Renal Function Group (n=8 per Group) | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| $C_{max}$ | 1.33 (0.84, 2.10) | 0.97 (0.61, 1.53) | 1.71 (1.08, 2.71) |
| $AUC_{0-t}$ | 1.61 (1.07, 2.42) | 1.72 (1.15, 2.59) | 4.13 (2.75, 6.19) |
| $AUC_{0-inf}$ | 1.73 (1.06, 2.83) | 2.27 (1.39, 3.71) | 10.5 (6.47, 17.3) |

| Pharmacokinetic Parameters | Geometric Mean Ratios of LSM (90% Confidence Intervals) of $HSO_3$-Lorcaserin Relative to Normal Renal Function Group (n=8 per Group) | |
|---|---|---|
| | ESRD (no dialysis) | ESRD (dialysis) |
| $C_{max}$ | 1.99 (1.26, 3.15) | 4.50 (3.15, 6.44) |
| $AUC_{0-t}$ | 2.93 (1.95, 4.39) | 6.71 (4.58, 9.82) |
| $AUC_{0-inf}$ | NC | 75.6 (41.0, 139) |

NC: not calculated

**Table 10** Geometric Mean Ratios of N-carbamoyl Lorcaserin Plasma Pharmacokinetic Parameters

| Pharmacokinetic Parameters | Geometric Mean Ratios of LSM (90% Confidence Intervals) of N-carbamoyl glucuronide Relative to Normal Renal Function Group (n=8 per Group) | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| $C_{max}$ | 0.91 (0.68, 1.21) | 1.39 (1.04, 1.85) | 2.14 (1.61, 2.85) |
| $AUC_{0-t}$ | 1.45 (0.99, 2.13) | 2.74 (1.87, 4.02) | 5.96 (4.07, 8.74) |
| $AUC_{0-inf}$ | 1.37 (0.95, 1.98) | 2.51 (1.74, 3.62) | 5.07 (3.51, 7.31) |

| Pharmacokinetic Parameters | Geometric Mean Ratios of LSM (90% Confidence Intervals) of N-carbamoyl glucuronide Relative to Normal Renal Function Group (n=8 per Group) | |
|---|---|---|
| | ESRD (no dialysis) | ESRD (dialysis) |
| $C_{max}$ | 4.03 (3.03, 5.36) | 3.21 (2.33, 4.41) |
| $AUC_{0-t}$ | 26.2 (17.9, 38.5) | 23.0 (15.3, 34.4) |
| $AUC_{0-inf}$ | 24.2 (16.8, 35.0) | 25.0 (16.1, 39.0) |

Based on the exposure changes of M1 and M5 in moderate and severe renal impairment, and end stage renal disease, we agree with the sponsor's proposal that lorcaserin should be used with caution in patients with moderate renal impairment, and should not be used in patients with severe renal impairment or end-stage renal disease.

***Reviewer comment:***
*The half life for lorcaserin sulfamate increases with increasing degree of renal impairment (from 36.2 hours in patients with normal renal function to 220 h in patients with end stage renal disease). For details see section 4.1.5. It is questionable, whether a washout of 7 days between the non-dialyses and dialysis phase is adequate to excrete all metabolite from the system and avoid carryover into the dialysis phase of the study. This is also apparent by the sponsor's statement that residual M1 from Period 1 (non-dialysis) was apparently present at the initiation of Period 2 (dialysis), leading to higher M1 plasma concentrations throughout Period 2 as compared to Period 1.*

- **Hepatic Impairment**

The effect of hepatic impairment on lorcaserin pharmacokinetics and the main circulatory metabolite (lorcaserin sulfamate) was evaluated in study APD356-017.
Lorcaserin $C_{max}$ was 7.8% and 14.3% lower, respectively, than in healthy matched controls. Mean AUC values were 24% and 30% higher, respectively, than in the healthy controls (Table 11). The sponsor did not evaluate the effect of severe hepatic impairment on the pharmacokinetics of lorcaserin. Considering the population pharmacokinetic estimate of approximately 33% between subject variability after adjustment of body weight a 30% increase in AUC with mild and moderate hepatic impairment is acceptable. Therefore, we agree with the sponsor's proposal of not recommending a dose adjustment for patients with mild or moderate hepatic impairment. However, a label statement stating that lorcaserin has not been evaluated in severe hepatic impairment should be added to the label.

**Table 11** Geometric Mean Ratios of Lorcaserin Plasma Pharmacokinetic Parameters and 90% Confidence Interval in Subjects with Varying Degree of Hepatic Impairment

| Pharmacokinetic Parameters[a] | Group 2: Mild Hepatic Impairment | Group 3: Moderate Hepatic Impairment |
|---|---|---|
| $AUC_{0-t}$ | 1.25 (1.01, 1.54) | 1.31 (1.06, 1.61) |
| $AUC_{0-inf}$ | 1.24 (1.01, 1.52) | 1.30 (1.06, 1.60) |
| $C_{max}$ | 0.922 (0.763, 1.11) | 0.857 (0.710, 1.04) |

$C_{max}$ and $AUC_{0-t}$ of $HSO_3$-lorcaserin tended to increase with increasing degree of hepatic impairment Total exposure increased approximately 34% and 42% in subjects with mild and moderate renal impairment, respectively. $C_{max}$ was approximately 47% and 23% increased in subjects with mild and moderate hepatic impairment, respectively (Table 12).

**Table 12** Geometric Mean Ratios of Lorcaserin Sulfamate Plasma Pharmacokinetic Parameters and 90% Confidence Interval in Subjects with Varying Degree of Hepatic Impairment

| Pharmacokinetic Parameters[a] | Group 2: Mild Hepatic Impairment | Group 3: Moderate Hepatic Impairment |
|---|---|---|
| $AUC_{0-t}$ | 1.34 (1.00-1.79) | 1.42 (1.06-1.89) |
| $AUC_{0-inf}$ | 1.31 (0.98-1.74) | 1.34 (1.00-1.78) |
| $C_{max}$ | 1.47 (1.04-2.07) | 1.23 (0.88-1.73) |

***Reviewer comment:***

- *The parent drug (lorcaserin) $C_{max}$ and $AUC_{0-t}$ increase since lorcaserin is metabolized by multiple enzymes in the liver*
- *The $HSO_3$-lorcasein metabolite $C_{max}$ and $AUC_{0-t}$ increased accordingly. This might be because the $HSO_3$-metabolite seems to be further metabolized and then possibly excreted as the N-carbamoyl-glucuronide, as the results of the mass balance study indicate.*
- *Increases in metabolite seem not to be a safety concern, since the metabolite is not active and brain concentrations are far less than those of the parent drug.*
- *No dose adjustment is needed for mild HI or moderate HI.*

## *2.4. EXTRINSIC FACTORS*

*2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?*

- **Food**

The results from the dedicated food effect study (APD356-015) demonstrate that there was no significant effect of a high-fat meal on lorcaserin $C_{max}$ and $AUC_{0-inf}$ (Figure 14).
When administered with a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800–1000 calories) meal, the $C_{max}$ was approximately 9% higher and the $AUC_{0-inf}$ was approximately 5% higher than those under fasting conditions. Although increases in the mean $C_{max}$ and AUC $_{0-inf}$ were observed, the 90% confidence intervals for comparing non-fasting and fasting regimens with respect to lorcaserin $C_{max}$, $AUC_{0-t,}$ and $AUC_{0-inf}$ regimens were contained within the range of 0.80 to 1.25 (Table 13). $T_{max}$ was delayed under fed conditions from 3.3 h to 2.1 h.

**Figure 14** Mean Plasma Concentration (ng/mL) of Lorcaserin over Time by Group – PK Population

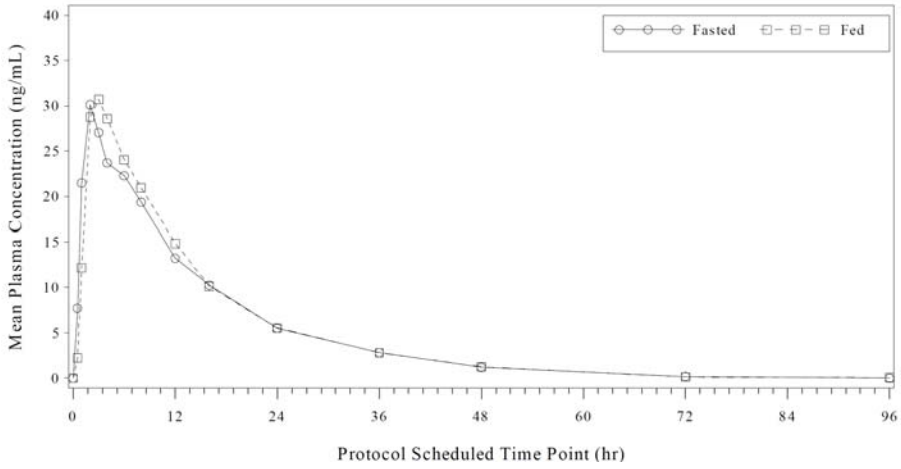



**Table 13** Analysis of Pharmacokinetic Parameters of Lorcaserin-PK Population

| Parameter | Geometric Mean | | Geometric Mean Ratio (Fed/Fasted Periods) | |
|---|---|---|---|---|
| | Fed Period | Fasted Period | Ratio | 90%CI |
| $C_{max}$ (ng/mL) | 32.7 | 30.1 | 1.086 | 0.995, 1.186* |
| $AUC_{0-t}$ (ng.hr/mL) | 442.4 | 423.3 | 1.045 | 0.976, 1.119* |
| $AUC_{0-inf}$ (ng.hr/mL) | 456.8 | 440.0 | 1.038 | 0.974, 1.107* |

Note: *Denotes 90% confidence interval fell within the recommended 0.80-1.25 limits of equivalence when analyzed on logarithmic scale.
Source: Table 14.2.3

***Reviewer comment:***

- *The study was conducted with the 10 mg dose, which is the dose proposed for marketing.*
- *The formulation used during the course of this study was the final market image tablet.*
- *The sponsor is proposing that lorcaserin can be taken without regard to meals. This is acceptable.*

*2.4.2 Drug-drug interactions*

*In-vitro* data indicate that lorcaserin is extensively metabolized in the liver. The main circulatory metabolite (lorcaserin sulfamate, M1) and the main urinary metabolite (N-carbamoyl lorcaserin, M5) are inactive metabolites. Lorcaserin is metabolized by multiple CYP P450 enzymes (1A1, 1A2, 2A6, 2B6, 2C19, 2D6, 2E1, 3A4), UGT enzymes (1A9, 2B7, 2B15, 2B17), and SULT enzymes (1A1, 1A2, 2A1, 1E1).

The sponsor evaluated the drug-drug interaction potential *in-vitro* and *in-vivo*. Lorcaserin is a competitive inhibitor of CYP2D6. Lorcaserin did not induce CYP1A2 but demonstrated a concentration dependent induction for CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5. However, the potential of induction is considered low at the therapeutic concentrations. Lorcaserin sulfamate has low potential for drug-drug interactions due to induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4. Based on the *in-vitro* [I]/Ki results of 0.14, the sponsor conducted two *in-vivo* studies (APD356-008 and APD356-012) to evaluate the effect of lorcaserin as a competitive inhibitor of CYP2D6. In the normal metabolizer population, the rate of exposure of dextromethorphan was approximately 76% higher when dextromethorphan was administered concomitantly with lorcaserin. The 90% confidence interval of the geometric mean ratios ranges from 146.7 to 212.5%. The extent of

exposure ($AUC_{inf}$) was 106% higher when dextromethorphan was administered concomitantly with lorcaserin. The 90% confidence interval of the geometric mean ratios ranges from 174.4 to 244% (Table 14).

**Table 14** Analysis of Pharmacokinetic Parameters of dextromethorphan when dextromethorphan was administered alone or when dextromethorphan was administered concomitantly with lorcaserin (Normal metabolizer population)

| | Geometric Means | | | |
|---|---|---|---|---|
| Parameter | Lorcaserin + Dextromethorphan (Day 10) | Dextromethorphan Alone (Day 1) | % Ratio of Geometric Means | 90% CI for Ratio of Geometric Means |
| $C_{max}$ (ng/mL) | 6.937 | 3.928 | 176.60 | (146.73 - 212.55 ) |
| $AUC_{0-t}$ (ng*hr/mL) | 68.274 | 33.365 | 204.63 | (172.73 - 242.41 ) |
| $AUC_{0-inf}$ (ng*hr/mL) | 70.564 | 34.201 | 206.32 | (174.39 - 244.10 ) |

***Reviewer comment:***

- *Based on the in-vivo DDI data, lorcaserin is a moderate inhibitor of CYP 2D6 mediated metabolism.*
- *A cautionary statement should be included in the label for patients concomitantly taking CYP 2D6 substrates with lorcaserin.*

*2.4.3 Are there any other questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?*

Lorcaserin is a chiral molecule with one chiral center. Two diastereomeric structures are possible. (b) (4) The sponsor evaluated intra-conversion during the stability testing and in in-vivo blood samples. During stability testing the sponsor noted that there is no change and minimal variability in enantiomeric purity results over the duration of the stability storage period evaluated to date. Results ranged from (b) (4) for samples stored at the long-term and accelerated conditions.

For in-vivo evaluation, two-hour (apparent Tmax) and twelve-hour plasma samples from the food effect study (APD356-015) were assayed for lorcaserin and the (S)-enantiomer (AR226175). AR226175 concentrations in all samples were below the limit of quantitation (BLQ; <0.500 ng/mL). Based on this data there appears to be no significant interconversion from the (R) to the (S)-enantiomer

## *2.5. GENERAL BIOPHARMACEUTICS*

*2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?*

The sponsor provided solubility, permeability and dissolution data supports the BCS-Class 1 classification for lorcaserin HCl.

The sponsor determined the solubility of Lorcaserin HCl at 37°C ± 1°C hydrochlorid acid buffer, pH 1.2 and phosphate buffer, pH 7.6 in triplicate for each pH. Since Lorcaserin is a monobasic molecule with a high $pK_a$ of 9.53, the sponsor did not determine the solubility at pH = pKa, pH = pKa +1, pH = pKa-1, and at pH = 1 and 7.5 but only at pH 1 and 7.5. Lorcaserin shows a solubility of > 400 mg/mL and can be considered highly soluble.

Based on Caco-2 permeability data and data obtained form the mass balance study APD356-006, lorcaserin can be classified as a highly permeable compound. The dissolution conditions for the tested lorcaserin

HCl-products were determined based on experimentation using various pH media, USP <711> Apparatus 1 and 2, and varied agitation speeds. All three formulations (capsule, clinical tablet and final market image tablet) met the definition of a rapidly dissolving dosage form with greater than (b) (4) released in 30 minutes. Furthermore, these formulations were demonstrated to be equivalent with greater than (b) (4) released in 15 minutes, and thus requiring no f2 calculation. Overall, lorcaserin is a BCS class 1 (see BCS class review in section 5.1)

*2.5.2 What data support or do not support a waiver of in vivo BE data?*
The sponsor requested a waiver of *in-vivo* bioavailability studies based on the BCS classification of lorcaserin. The formulations used in the 2 Phase 3 studies were a capsule and tablet formulation. The to-be-marketed tablet formulation has the same composition as the tablet used in the Phase 3 clinical trial, except for the difference in color. The Biopharmaceutics review concluded that:

Although the link between the capsule and tablet formulations is not necessarily established by the BCS approach (BCS based biowaiver is only applicable for the formulations with pharmaceutical equivalence), the difference of bioavailability between tablets and capsules is not expected and the biowaiver can be granted based on the following considerations.
a. The dissolutions between tablets and capsules in multiple media are similar.
b. The tablet formulation has been used in two of the three Phase III clinical trials.

For details see the Biopharmaceutics review by Dr. John Duan, DARRT date 08/05/2010.

***2.6 ANALYTICAL SECTION***
*2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?*

The active moiety is lorcaserin. Lorcaserin was (b) (4) The extracted samples were analyzed by an HPLC equipped with an AB/MDS Sciex API 4000 mass spectrometer. Positive ions were monitored for lorcaserin in the multiple reaction monitoring (MRM) mode.

*2.6.2 Which metabolites have been selected for analysis and why?*

The main circulatory metabolite $HSO_3$-lorcaserin and a minor metabolite formed by CYP 2D6 (7-OH lorcaserin) were analyzed. The 7-OH metabolite was only present in some subjects in the mass balance study. In the renal impairment study, the main urinary metabolite (N-carbamoyl glucuronide) was also assessed in plasma. Plasma samples from the mass balance study were also used to identify the metabolic profile of lorcaserin.

*2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?*
Total drug concentrations for all moieties were measured. The sponsor did not provide a rational why total plasma concentrations were measured.

*2.6.4 Was bioanalytical method validation acceptable?*
Yes, the bioanalytical method validation was acceptable. Details of the method validation are outlined below.

## Lorcaserin, 7-OH lorcaserin, and HSO3- lorcaserin 6

The validation titled "Validation of an LC-MS/MS method for the determination of lorcaserin 7-OH lorcaserin, and HSO3- lorcaserin in human plasma (heparin)" was conducted at (b) (4)

An aliquot of human plasma (heparin) containing each analyte and internal standard was (b) (4) resulting in one set of extracts for lorcaserin and 7-OH lorcaserin and one set of extracts for $HSO_3$-lorcaserin. The extracted samples were analyzed by an HPLC equipped with an AB/MDS Sciex API 4000 mass spectrometer. Positive ions were monitored for lorcaserin and 7-OH lorcaserin in the multiple reaction monitoring (MRM) mode. Negative ions were monitored for $HSO_3$-lorcaserin in the multiple reaction monitoring (MRM) mode.

No significant interference at the analyte or internal standard retention times was observed from endogenous components in any of the 8 human plasma (heparin) lots (for lorcaserin and 7-OH lorcaserin) or 10 human plasma (heparin) lots (for $HSO_3$-lorcaserin) screened. Long term stability at -20°C was 324 days (for 7-OH lorcaserin and $HSO_3$-lorcaserin) or 265 days (for lorcaserin). Samples were stable over 6 freeze thaw cycles. For a summary of the QC validation results please refer to Table 15. Long term stability was demonstrated for 160 days fro samples stored at -20°C. Samples were stable over 6 freeze thaw cycles. Long term stability was demonstrated for 160 days for samples stored at -20°C. Samples were sable over 6 freeze thaw cycles. For a summary of the QC validation results please refer to Table 15.

## N-carbamoyl glucuronide

An aliquot of human plasma (heparin) containing the analyte and internal standard was (b) (4) The extracted samples were analyzed by an HPLC equipped with an AB MDS Sciex API 4000 or 5000 mass spectrometer. Negative ions were monitored in the multiple reaction monitoring (MRM) mode. Quantitation was determined using a weighted linear regression analysis (1/concentration2) of peak area ratios of the analyte and internal standard. Long term stability was demonstrated for 160 days fro samples stored at -20°C. Samples were stable over 6 freeze thaw cycles. For a summary of the QC validation results please refer to Table 15.

**Table 15** Results of Quality Control from the bioanalytical method validation

| | Calibration | | Quality control (between batch) | | |
|---|---|---|---|---|---|
| Analyte / Parameter | Curve range (ng/mL) | LLOQ (ng/mL) | %CV | %CV | %Bias |
| lorcaserin | 0.500-100 | 0.500 | 1.8% to 5.9% | 3.7% to 8.0% | 0.0% to -2.8% |
| $HSO_3$-lorcaserin (M1) | 1.00-100 | 1.00 | 2.9% to 8.1% | 4.4% to 11.4% | 0.7% to 8.0% |
| 7-OH-lorcaserin (M2) | 0.500-100 | 0.500 | 2.4% to 6.1% | 5.6% to 12.1% | 0.8% to 7.0% |
| N-carbamoyl glucuronide (M5) | 5.00-1000 | 5.00 | 1.2% to 6.0% | 6.3% to 9.7% | -3.8% to -1.3% |

**Dextromethorphan, Dextrorphan**

The method validation study titled: "Determination of Dextromethorphan and Dextrorphan in Human Plasma Samples from APD356 012 by HPLC with MS/MS Detection" was conducted by [redacted]. The dextromethorphan and dextrorphan and the internal standards were extracted from samples by [redacted]. After evaporation under nitrogen, the residue was reconstituted and analyzed using liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS). Samples were originally analyzed singly. At a minimum, each batch included a calibration curve, a matrix blank, a control zero (matrix blank containing internal standard), a reagent blank, and duplicate quality control (QC) samples at three concentrations within the calibration range. The samples were interspersed with calibration standards and QC samples within the batch. Dilution QC samples were also included in batches where samples were diluted prior to analysis. Stability of QC samples after storage in a freezer set to maintain -10 to -30ºC for 63 days was established.

**Table 16** Results of Quality Control from the bioanalytical method validation

| | | Calibration | | Quality control (between batch) | |
|---|---|---|---|---|---|
| Analyte / Parameter | Curve range (ng/mL) | LLOQ (ng/mL) | %CV | %CV | %Bias |
| Dextromethorphan | 0.100-10.0 | 0.100 | 2.4% to 5.3% | 2.7% to 5.9% | -1.2% to 9.0% |
| Dextrophan | 0.300-300 | 0.300 | 2.2% to 4.9% | 2.4% to 4.9% | -3.3% to 6.0% |

## 3. Preliminary Labeling Recommendations

Labeling statements to be removed are shown in ~~red strikethrough~~ and suggested labeling to be included is shown in underline blue font. The following main labeling recommendations based on this submission should be considered during labeling negotiations:

7 **DRUG INTERACTIONS**

(b) (4)

5 page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

**4. Pharmacometric review**

# OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

| | |
|---|---|
| **Application Number** | NDA 22529 |
| **Submission Number (Date)** | December 18, 2009 |
| **Compound** | Lorcaserin HCl hemihydrate |
| **Clinical Division** | DMEP |
| **Primary PM Reviewer** | Immo Zdrojewski, Ph.D. |
| **Secondary PM Reviewer** | Nitin Mehrotra, Ph.D. |

## 1. Summary of findings

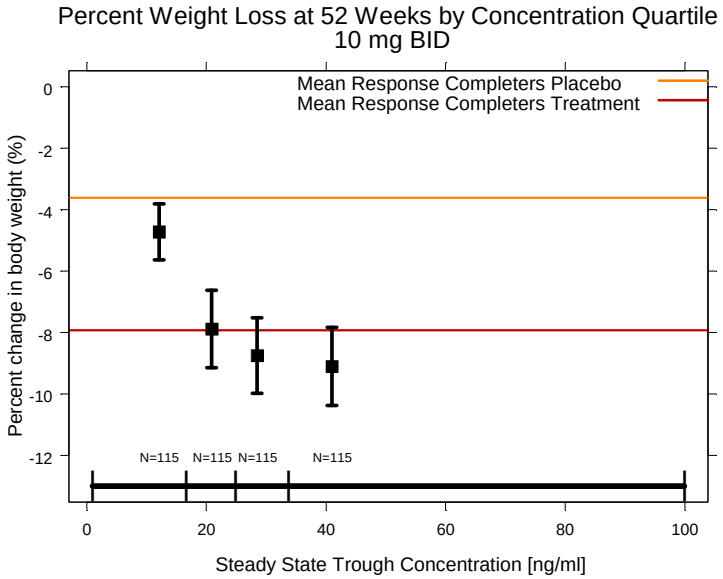
### 1.1 Key questions

#### 1.1.1 Is there evidence of exposure-response for efficacy?

Yes, there is evidence of exposure response for efficacy.

The exposure response relationship was evaluated in the subjects randomized to 10 mg BID during the Phase 3 trials (last observation carried forward population). There were 520 (16.2%) subjects out of 3198 receiving the BID dose in both Phase 3 clinical trials that had exposure measurements. Figure 15 demonstrates the exposure response relationship. Subjects demonstrated increasing weight loss from baseline after 52 weeks with increasing exposures.

**Figure 15** Percent weight loss at 52 weeks by concentration quartile in the PK subpopulation during the Phase 3 trials [a].




[a]The vertical black bars represent the mean with 95% confidence interval. The exposure range in each trough quartile is denoted by the horizontal black line along with the number of subjects in each quartile. Exposures are demonstrated as black squares at the median exposure of each quartile. The mean response demonstrated here is less than the mean response in the PK subpopulation, since the PK subpopulation was mainly composed of completers (subjects taking drug for 52 weeks and having a 52 week weight measurement)

### 1.1.2 Is dose adjustment required based on body weight?

No, dose adjustment is not required based on body weight. However, population PK analysis demonstrated that body weight is the most significant covariate affecting clearance. This implies that exposures decreased with increase in body weight (Figure 18). Therefore, subjects with higher baseline body weight might potentially benefit from a higher dose to match their exposures to the exposures observed in lower body weight quartiles, in order to maximize efficacy. However, this was a weak correlation (Figure 16), and only 41% of the subjects in the lowest concentration quartile belonged to the highest body weight quartile (109.9 to 153.8 kg). The sponsor is proposing a fixed dose of 10 mg BID in patients of all weight categories based on the results obtained during the phase 2 dose finding study. However, population pharmacokinetic analysis demonstrated that weight is a covariate on clearance and clearance tended to increase with body weight.

**Figure 16** Exposures (steady state trough levels) observed in the PK subpopulation by body weight

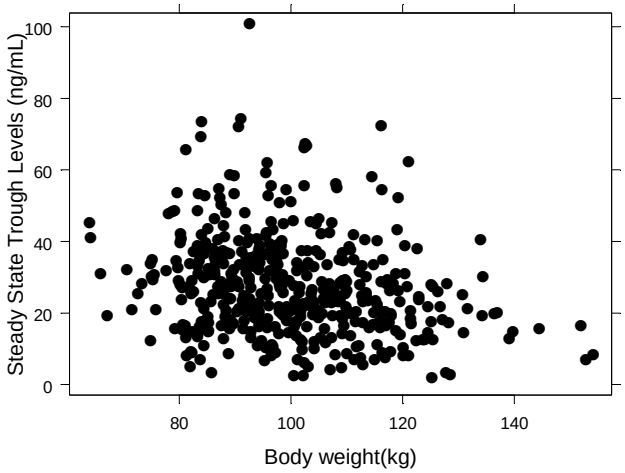
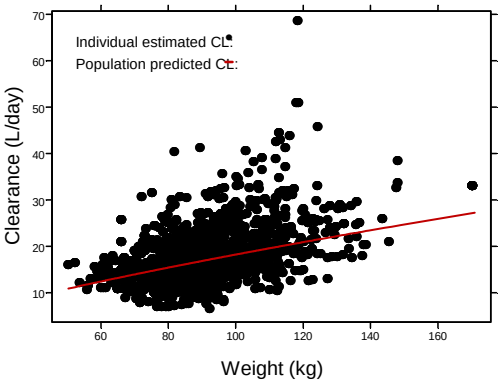
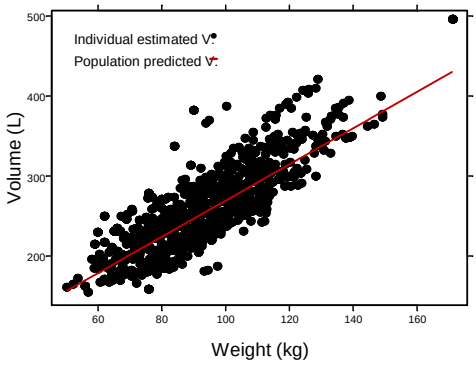



**Figure 17** Effect of weight on clearance over the observed weight range

Clearance

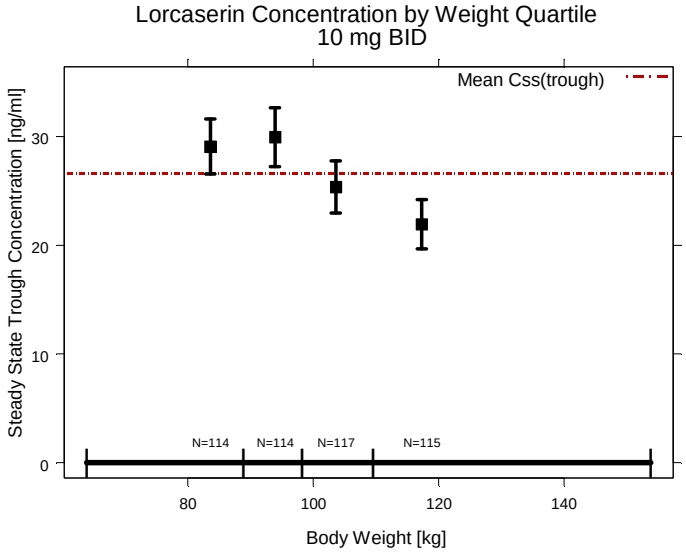



Volume



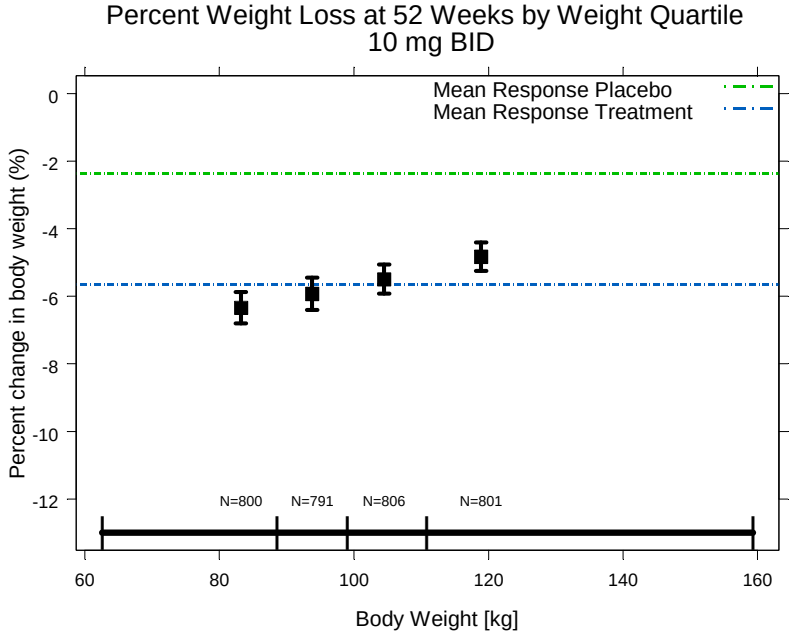

The fact that subject with higher body weight have lower exposures is illustrated in Figure 18. Subjects in the highest weight category have observed steady state trough concentration below the mean trough concentration and concentrations tended to decrease with increasing body weight.

**Figure 18** Mean ± SD steady state trough concentration in the PK subpopulation by weight quartile




Furthermore, as demonstrated in question 1.1.1 above, there is an exposure-response relationship for efficacy and percent weight loss from baseline tended to decrease with increasing body weight (Figure 19) and body weight is the most important covariate affecting clearance.

**Figure 19** Percent weight loss at 52 weeks by body weight quartile in the LOCF population during the Phase 3 trials[a]




[a] The vertical black bars represent the mean with 95% confidence interval. The body weight range in each weight quartile is denoted by the horizontal black line along with the number of subjects in each quartile. Percent weight loss is demonstrated as black squares at the median body weight of each quartile.

However, a weak correlation was observed between the lorcaserin exposure and the body weight in Phase 3 trials. Additionally, only 41% of the subjects in the lowest concentration quartile (**Figure 15**) belong to the highest body weight quartile (109.9 to 153.8 kg). Therefore, this reviewer was unable to identify a patient population that would benefit from a higher dose of lorcaserin to obtain additional efficacy.
Higher exposures, however, pose safety concerns based on pre-clinical findings, which demonstrated lorcaserin to be a potential human carcinogen with an unidentified safety margin in one pre-clinical species, and identified the uncertainty about the $EC_{50}$ at other potential off target serotonin receptor subtypes. Furthermore, one patient receiving a single dose of 40 mg, which is 4 times the proposed clinical dose demonstrated severe side effects around the $t_{max}$ of lorcaserin, exhibiting euphoria, feeling of drunkenness and other related adverse events (Please see the Pharmacology/Toxicology Review from Dr. Fred Alavi for more detailed information). In conclusion, since this reviewer was unable to identify the specific population that would benefit from an increased dose and higher lorcaserin concentrations can pose several safety concerns, this reviewer does not recommend dose adjustment based on body weight.

**1.1.3 Is the proposed dosing regimen supported by the exposure-response relationship for safety, for :**

- **Nervous system and psychiatric disorders,**
- **Valvulopathy,**

During the review of most frequent adverse events, this reviewer observed a trend in the increase in adverse events with increasing dose for nervous system disorders and psychiatric disorders Table 17.

**Table 17** Summary of Most Frequent Adverse Events (≥1% of patients in any group) Considered to be Possibly or Probably Related to Study Drug in Pooled Phase 3 Studies: Safety Population.

| System Organ Class<br>Preferred Term | Pooled Placebo (N=3185) | Pooled Lorcaserin 10 mg BID (N=3195) | Lorcaserin 10 mg QD (N=801) | Any Lorcaserin Dose (N=3996) |
|---|---|---|---|---|
| Number of Patients Reporting AEs | 799 (25.1) | 1186 (37.1) | 267 (33.3) | 1453 (36.4) |
| Gastrointestinal Disorders | | | | |
| Nausea | 85 (2.7) | 152 (4.8) | 28 (3.5) | 180 (4.5) |
| Dry mouth | 64 (2.0) | 144 (4.5) | 25 (3.1) | 169 (4.2) |
| Constipation | 61 (1.9) | 90 (2.8) | 18 (2.2) | 108 (2.7) |
| Diarrhoea | 50 (1.6) | 78 (2.4) | 11 (1.4) | 89 (2.2) |
| Vomiting | 16 (0.5) | 33 (1.0) | 7 (0.9) | 40 (1.0) |
| General Disorders And Administration Site Conditions | | | | |
| Fatigue | 45 (1.4) | 127 (4.0) | 23 (2.9) | 150 (3.8) |
| Metabolism And Nutrition Disorders | | | | |
| Decreased appetite | 27 (0.8) | 37 (1.2) | 21 (2.6) | 58 (1.5) |
| Nervous System Disorders | | | | |
| Headache | 171 (5.4) | 329 (10.3) | 83 (10.4) | 412 (10.3) |
| Dizziness | 64 (2.0) | 189 (5.9) | 29 (3.6) | 218 (5.5) |
| Somnolence | 16 (0.5) | 38 (1.2) | 5 (0.6) | 43 (1.1) |
| Psychiatric Disorders | | | | |
| Insomnia | 42 (1.3) | 32 (1.0) | 8 (1.0) | 40 (1.0) |

A dose response relationship was evaluated for FDA defined valvulopathy. There were 31 (2.06%) events in the placebo group for the completer population for the pooled Phase 3 trials. This compares to 9 (2.0%) FDA defined valvulopathy events in the10 mg QD dose group in APD356-009 trial and 40 (2.29%) in the completer population for the pooled Phase 3 trials for the 10 mg BID dose. Based on

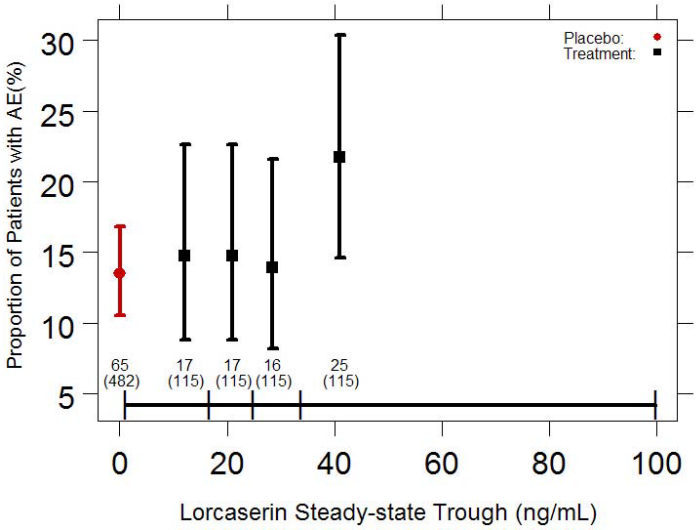
this dose response data, this reviewer evaluated whether there is an exposure-response relationship for these safety events.

Overall, the results from the exposure-response evaluation for safety are inconclusive, because:

- The number of preferred term adverse events in the population randomized to PK sampling was low, which did not allow for evaluation of exposure response relationship on the adverse event preferred term level
- Exposure-response relationship analysis for safety on the system organ class (SOC) level is confounded by the variety of preferred term events included in the SOC.

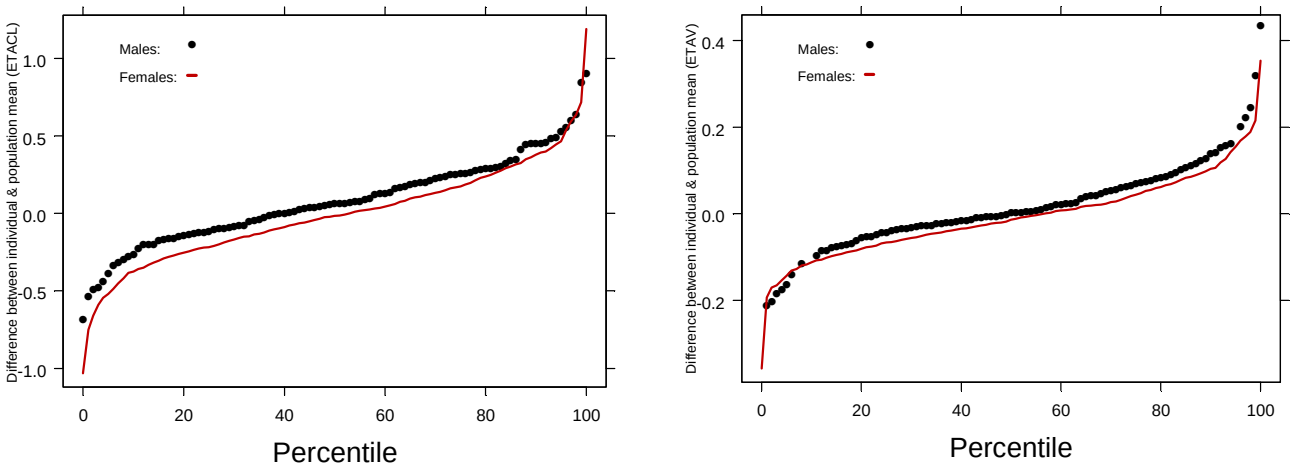
This reviewer was unable to determine an exposure response relation for safety for these adverse events. Evaluation of the exposure-response relationship for the all System Organ Class (SOC) classification and Nervous system disorders and Psychiatric disorder in particular were evaluated. The SOC is a more general term and comprises of all adverse events related to psychiatric disorders.
The adverse events included in the SOC are coded as preferred terms. There was no significant exposure-response relationship for safety for any single preferred terms within this SOC. This is most likely because event rates in each preferred term were low and PK data is limited. When evaluating the more general adverse event category SOC Psychiatric disorder, the exposure-response relationship demonstrated a slight trend of higher AEs with higher exposures. The proportion of patients experiencing psychiatric disorders (all grade) were slightly higher in the fourth quartile compared to first three concentration quartiles (Figure 20). Furthermore, the AEs in the first three concentration quartiles overlap with placebo. This relationship however includes all adverse events coded as preferred terms in the psychiatric disorders category and might not be associated with single specific events. Hence, this relationship is not conclusive and should be evaluated with caution.

**Figure 20** Proportion of patients with adverse events (SOC Psychiatric Disorders) by observed steady state trough concentration quartile




**1.1.4 Is there an effect of age, race, or gender on PK of lorcaserin?**
Figure 21 illustrates the difference between individual & population mean clearance (ETACL) (Figure 21, panel A) and volume (Figure 21, panel B) for lorcaserin for each percentile for males and females. Overlap of the black circles (males) and red line (females) means that the difference between individual and population mean clearance or volume between males and females are not different. Thus, there is no effect of gender of lorcaserin PK.

**Figure 21** Plot for difference between individual and population predicted clearance (ETA CL, panel A) and volume (ETA V, panel B) for males and females showing no difference between individual & population mean clearance or volume for all percentiles.




There was no significant effect of age or race on the pharmacokinetics of lorcaserin (**Figure 27** and **Figure 29**).

### 1.2 Recommendations

The application is acceptable from a Clinical Pharmacology perspective, provided that the sponsor and the Agency come to a mutually satisfactory agreement regarding the language in the PI.

### 1.3 Label statements

See section 3 of the Clinical Pharmacology review.

## 2. Pertinent Regulatory background

The sponsor, Arena Pharmaceuticals Inc., submitted a 505 (b)(1) new drug application (NDA 22-529) seeking marketing approval for a 10 mg BID dose of lorcaserin hydrochloride immediate release tablets. Lorcaserin, according to the sponsor, is a selective serotonin 2C ($5\text{-HT}_{2C}$) receptor agonist.

The sponsor is seeking the indication for weight management, including weight loss and maintenance of weight loss, and usage in conjunction with a reduced-calorie diet and a program of regular exercise. The intended target population is 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).

During the clinical program, the sponsor conducted two phase 2 studies, APD356-003 and APD356-004 with a total duration of 28 days and 3 month respectively. Study APD356-003 assessed doses of 1 mg, 5 mg, and 15 mg given once daily, and placebo. Study APD356-004 evaluated doses of 10 mg and 15 mg given once daily, 10 mg given twice daily, and placebo. Additionally, two phase 3 safety and efficacy studies APD356-009 and APD356-011 were

conducted. An additional third phase 3 study in overweight and obese patients with type 2 diabetes mellitus is still ongoing.

Study APD356-009 evaluated doses of 10 mg BID and placebo. The total duration of the study was 104 weeks. The efficacy for weight loss and weight maintenance were evaluated. For the efficacy for weight loss, the weight loss in the 10 mg BID dosing group was compared to placebo at week 52. Efficacy for weight maintenance was assessed during the second year of the trial: at Week 52, patients assigned to lorcaserin were re-randomized 2:1 to remain on lorcaserin or to switch to placebo; all patients on placebo remained on placebo. Safety assessments included echocardiograms (for FDA-defined valvulopathy assessment) at screening, Week 24, Week 52, Week 76, and Week 104. In a subset of patients, PK samples were obtained at week 12 visit (pre-dose and 2 hours post dose).

Study APD356-011 evaluated doses of 10 mg QD and 10 mg BID compared to placebo; the total duration of the study was 52 weeks. Safety assessments included echocardiograms at baseline, Week 24 and Week 52 prolactin samples were collected at baseline and at week 4, 12, 24, and 52 (pre dose, and 2 h post dose sample). PK samples were collected in a subset of patients at weeks 12, 24 and 52 (pre-dose, 1.5 to 2.5 h, and 3.5 to 6 h post-dose)

Studies APD356-009 and APD356-011 evaluated the following co-primary endpoints:

- 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

In each phase 3 study and in the analysis of the pooled phase 3 datasets, a significantly greater proportion of patients taking lorcaserin 10 mg BID lost 5% or more of their baseline body weight as compared to patients taking placebo. More than 35% of patients assigned to lorcaserin BID and QD achieved the 5% weight loss benchmark; the proportion of patients achieving this benchmark in the lorcaserin BID group was more than twice the proportion in the placebo group, and less than twice in the lorcaserin QD group. At the Week 52 endpoint, patients assigned to placebo lost on average 2.5% of their baseline body weight in the pooled analysis, as compared to 5.83% in the lorcaserin 10 mg BID group.

Arena Pharmaceuticals Inc. proposes a 10 mg dose given twice daily without regards to food. While there is no proposed dose adjustment in mild renal impaired patients, use with caution is recommended in moderate renal impaired patients, and lorcaserin should not be used in patients with severe renal impairment and ESRD. No dose adjustment is proposed based on hepatic impairment (HI) for mild and moderate HI. Additionally, the sponsor proposes no dose adjustments based on other covariates (body weight, age, gender, and race).
During the IND stage of lorcaserin, the sponsor submitted the PopPK analysis plan for review to the agency, and the Agency found it acceptable. (DARRTS date: 05/27/2009).

3. **Results of sponsor's analysis**
The sponsor analyses are summarized below.

**3.1 Population pharmacokinetic analysis:**
The sponsor evaluated the effect of each covariate (BW, IBW, BMI, Age, Sex, and Race) on the PK parameters CL/F and V/F and recording the OFV value and assessing the precision of model parameters of each scenario. The effect of time, lorcaserin dose, ALT, Bilirubin, ICR, and CRCL

on CL/F were also tested. Additionally differences in Ka and bioavailability (F1) between formulations and studies were also tested, as was the effect of dose on Ka.
The following summarizes their results of this analysis and the salient factors that influenced the kinetics.

**Population pharmacokinetic analysis: Lorcaserin**
The final PK model for the population PK analysis of lorcaserin was a one-compartment model, with IIV estimated for CL/F, V/F, and Ka, with a proportional error model for residual variability and covariance between CL/F and V/F. The model included a power relationship between body weight and CL/F and a linear relationship between body weight and V/F.
The final model estimates of the population pharmacokinetics parameters are presented in Table 18.

**Table 18** Final Model Estimates of Population Pharmacokinetic Parameters of Lorcaserin in Healthy Volunteers and Obese/Overweight Patients after Single and Multiple Oral Doses of Lorcaserin

| Parameter | Estimate [95% CI] | %RSE [(b)] |
|---|---|---|
| $CL/F = \Theta_{CL} \cdot (BW/92.5)^{0.75}$ | | |
| $\Theta_{CL}$ (L/h) | 17.2 [16.7 – 17.7] | 1.34 |
| $V/F = \Theta_V + \Theta_{V,BW} \cdot (BW/92.5)$ | | |
| $\Theta_V$ (L) | 43.0 [12.2 – 73.8] | 36.5 |
| $\Theta_{V,BW}$ (L) | 209 [175 – 243] | 8.23 |
| $Ka=\Theta_{Ka}$ | | |
| $\Theta_{Ka}$ ($h^{-1}$) | 1.45 [1.29 – 1.61] | 5.57 |
| Inter-subject variability in CL/F (%CV) [(a)] | 32.2 | 7.36 |
| Inter-subject variability in V/F (%CV) [(a)] | 16.6 | 15.5 |
| Inter-subject variability in Ka (%CV) [(a)] | 40.4 | 26.9 |
| Co-variance in CL/F and V/F | 0.389 | 29.7 |
| Proportional residual variability in lorcaserin concentrations in healthy subjects and patients (%CV) [(a)] | 26.3 | 5.49 |

(a) The %CV for both inter-subject/patient and proportional residual variability is an approximation taken as the square root of the variance x 100. The approximation is due to the expansion of the exponential function only to first-order.
(b) RSE was calculated as the s.e. divided by the parameter estimate x 100.

**Lorcaserin covariate effects:**
There were eight significant effects identified by the univariate analysis to be carried forward to the multivariate analysis, these are presented in rank order in Table 19. In the univariate analysis there were several other effects that resulted in a significant decrease in OFV (>6.63 per df). For CL/F and V/F there were also significant decreases produced for the effects of BMI. However, BMI is closely related to BW and the effect of BW on both CL/F and V/F resulted in a greater decrease in OFV than BMI. Subsequently only the effect of BW on CL/F and BW on V/F was carried forward to the

multivariate analysis. Power models for the effect of BW, IBW, and BMI on CL/F were run both estimating the power factor and also with the power factor set to 0.75.

**Table 19** Significant Effects Highlighted by the Univariate PK Analysis for Lorcaserin for Forward Selection

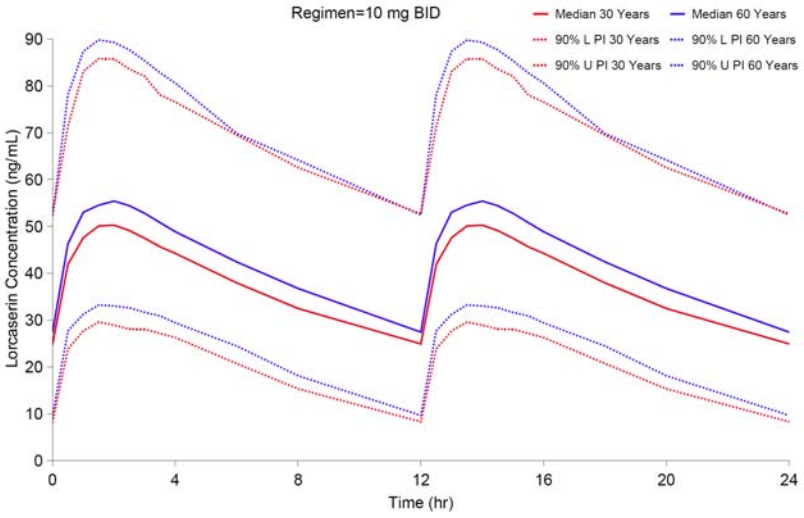
| Effect | ΔOFV | df | ΔIIV (%) | ΔResidual Var (%) |
|---|---|---|---|---|
| Power relationship of BW on CL/F with power=0.75 | -76.779 | 1 | -4.1 | -0.1 |
| Linear relationship with intercept of BW on V/F | -75.489 | 1 | -5.5 | 0.0 |
| Linear relationship with intercept of $CR_{CL}$ on CL/F | -37.696 | 1 | -1.8 | -0.1 |
| Linear relationship with intercept of Age on CL/F | -24.115 | 1 | -0.6 | 0.0 |
| Power relationship of ALT on CL/F | -14.628 | 1 | -0.3 | -0.1 |
| Sex on CL/F | -13.678 | 1 | -0.7 | 0.0 |
| Bioavailability (F1) of formulation 4 (Study APD356-011) relative to other three formulations | -9.018 | 1 | NA[a] | 0.0 |
| Linear relationship of Age on V/F | -7.601 | 1 | -0.2 | 0.0 |

a Not applicable, IIV was not estimated for F1

The results of the multivariate analysis indicated that CL/F decreased with age. The effect of age on CL/F was responsible for a small but significant increase (> 10.84 points) in OFV upon its removal. However, the effect of age on CL/F resulted in only a very small improvement in IIV for CL/F (32.2% to 31.8%).

Simulations showed that there was less than a 10% increase in lorcaserin concentrations following a doubling of age. From 250 simulations median and 90% PI lorcaserin concentrations were very similar for a population of median weight of 92.5 kg but aged 30 and 60 years (Figure 22). Therefore, the sponsor concluded that the effect of age on CL/F not to be clinically significant and consequently as the effect was dropped from the final PK model for lorcaserin.

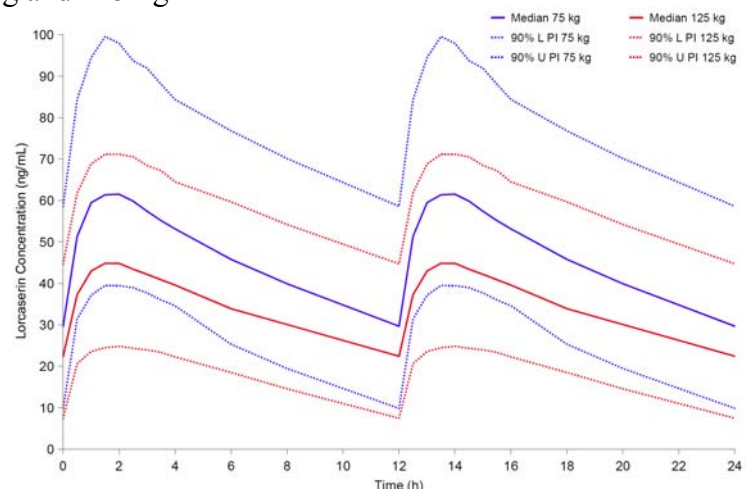
**Figure 22** Simulated (N=250) Median and 90% PI following Administration of 10 mg Lorcaserin BID to a Population with a Median Age 30 Years and 60 Years




Additionally, the sponsor assessed the implication of the body weight effect on both CL/F and V/F. A series of simulations were performed following both QD and BID dosing regimens to typical subjects of different weights using the final PK model. The sponsor simulated median and 90% PI following 10 mg lorcaserin BID to subjects weighing either 75 kg or 125 mg (Figure 23). The 75 and 125 kg body weights were chosen since a the majority of subjects used in the population PK analysis from studies

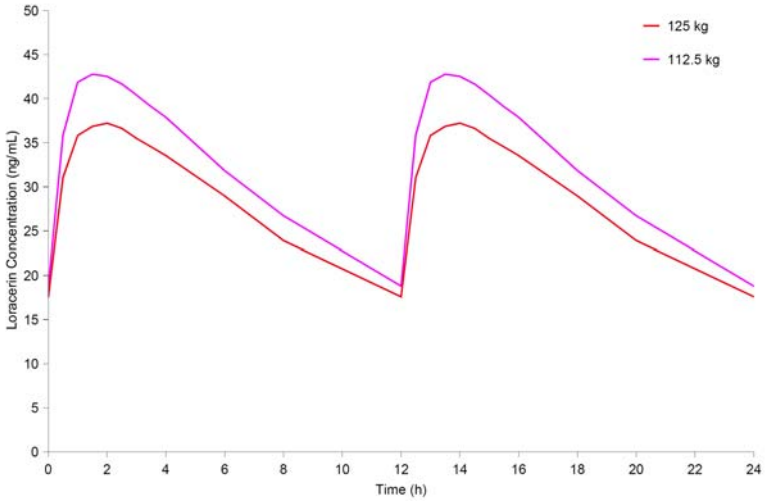
APD356-009 and APD356-011 were between 75 and 125 kg and would represent the extreme differences in body weight.

**Figure 23** Steady-State Simulated Lorcaserin Concentration-Time Profiles Following BID Administration of 10 mg Lorcaserin to a Patient Population with a Median Body Weight of 75 kg and 125 kg




During the 2 Phase 3 trial, 22.6% of subjects lost more than 10% of their body weight. Since lorcaserin is indicated for the management of weight loss, the sponsor evaluated the difference in exposure in subjects loosing 10% of their body weight. To investigate this, a simulation using the final PK model was performed for a single subject receiving 10 mg lorcaserin BID weighing 125 kg who then lost 10% of their body weight.

**Figure 24** Steady-State Simulated Lorcaserin Concentration-Time Profiles Following BID Administration of 10 mg Lorcaserin to a Patient with a Body Weight of 125 kg and to the same Patient but having lost 10% of Body Weight (12.5 kg)




The steady-state lorcaserin concentration-time profiles presented in Figure 24 indicate that following loss of 10% of body weight a subject receiving BID 10 mg lorcaserin would see slightly increased exposure to lorcaserin when following the same regimen as prior to weight loss. The increase in exposure appears to be approximately 10% and the simulation indicates that the dose and dosing regimen of lorcaserin would not require adjustment following the reduction in body weight.

The sponsor concluded that, based on the population pharmacokinetic results, a 50% increase or decrease in the predicted AUCss,24hr value was well within the maximum and minimum observed AUCss,24h values which is consistent with the moderate inter-individual variability of apparent oral clearance (32.2%).

From the eight significant effects identified by the univariate analysis to be carried forward to the multivariate analysis, only body weight on the apparent volume of distribution and on apparent clearance as statistically significant covariate is included in the final model. Including body weight on volume and clearance is physiologically plausible, however the results indicate, that the predicted AUCss,24hr decreased from that of patients of median weight (92.5 kg) by on average 21% following BID dosing, in patients weighing 125 kg. Conversely, patients weighing 75 kg had an AUCss,24hr that increased by 18% following BID dosing in comparison to subjects of median weight (92.5 kg).

## 3.2 Exposure Response Models for Effectiveness and Safety

The sponsor conducted and exposure-response analysis for the primary and co-primary endpoints and also evaluated the exposure-response relationship with the occurrence of FDA defined valvulopathy. Additionally, exploratory parameters total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, diastolic and systolic blood pressure, fasting insulin, and HOMA-IR vs. lorcaserin steady state 24-hour exposure were assessed. The following sections describe the results of each exposure-response modeling analysis. The sponsor conducted simulations to evaluate the effect of weight and age on the exposure of lorcaserin.

***Exposure-Efficacy Response Analysis: % weight loss from baseline***

Mean ± standard deviation individual predicted %weight loss at Week 52 from the FINAL model was 3.72% ± 5.52% for placebo, 6.58% ± 6.06% for 10 mg QD and 8.23% ± 6.26% for 10mg BID lorcaserin administration. The observed weight loss during the Phase 3 trial was approximately -2.2% to -2.8% for the placebo group and -5.8% for the 10 mg BID dose. Maximum %weight loss for placebo, lorcaserin 10 mg QD and lorcaserin 10 mg BID was predicted to be achieved by about week 32.

***Exposure-Efficacy Response Analysis: probability of >5% weight loss***

The categorical PK/PD model for weight loss ≥ 5% for median creatinine clearance predicted a 25% probability of a successful placebo response. At median lorcaserin exposure, approximately 41% of the patients on QD administration and 57% of the patients on BID administration will achieve weight loss ≥ 5%.

***Exposure-Efficacy Response Analysis: probability of >10% weight loss***

The categorical PK/PD model for weight loss ≥ 10% predicted a 6% probability of a successful placebo response. At median lorcaserin exposure, approximately 13% of the patients on 10 mg QD administration and 26% of the patients on 10 mg BID administration will achieve weight loss ≥ 10%.

***Exploratory Exposure-Safety Response Analysis: occurrence of FDA defined valvulopathy***

Exploratory plots of occurrence of FDA-defined valvulopathy versus lorcaserin AUCss,24hr exposure at weeks 24 and 52 showed no exposure response relationship. The occurrence of FDA-defined valvulopathy in the lorcaserin treated subjects was similar to placebo.

***Exploratory Exposure-Response Analysis: clinical chemistry parameters***

There was no apparent relationship between total cholesterol, HDL cholesterol, LDL cholesterol, fasting insulin, triglycerides, diastolic and systolic blood pressure, and HOMA-IR.

### 3.3 Sponsor's Conclusions

Using data from 2 phase 1 studies, and two phase 3 studies the population pharmacokinetic and the exposure-response analysis for efficacy and safety led to the following conclusion:

- Differences in exposure due to differences in body weight across and within patients do not warrant dose and/or dosing regimen adjustment.
- Maximum %weight loss for placebo, lorcaserin 10 mg QD and lorcaserin 10 mg BID was predicted to be achieved by about week 32.
- Mean ± standard deviation individual predicted %weight loss at Week 52 from the final model was 3.72% ± 5.52% for placebo and 8.23% ± 6.26% for 10mg BID lorcaserin.
- The categorical PK/PD model for weight loss ≥ 5% for median creatinine clearance predicted a 25% probability of a successful placebo response. At median lorcaserin exposure, approximately 57% of the patients on BID administration will achieve weight loss ≥ 5%.
- The categorical PK/PD model for weight loss ≥ 10% predicted a 6% probability of a successful placebo response. At median lorcaserin exposure, approximately 26% of the patients on 10 mg BID administration will achieve weight loss ≥ 10%.
- Exploratory plots of occurrence of FDA-defined valvulopathy versus lorcaserin AUCss,24hr exposure at weeks 24 and 52 showed no exposure response relationship. The occurrence of FDA-defined valvulopathy in the lorcaserin treated subjects was similar to placebo.
- There was no apparent relationship between total cholesterol, HDL cholesterol, LDL cholesterol, fasting insulin, triglycerides, diastolic and systolic blood pressure and HOMA-IR lorcaserin exposure

***Reviewer comment on sponsor's analysis:***

- *In this submission, the sponsor included labeling statements relevant to intrinsic and extrinsic factors that might potentially influence the pharmacokinetics and the dosing of lorcaserin or the lack thereof. The population PK analysis was conducted to evaluate the accuracy of these statements and to evaluate whether other additional statements should be included in the label.*
- *The sponsor also included exposure-efficacy analysis for all co-primary endpoints to evaluate if the drug exposure supports drug efficacy, and exposure safety response analysis to evaluate if the safety response with for FDA defined valvulopathy is acceptable. Exposure-response analysis for efficacy was conducted for both continuous and categorical variable. The approach for the PK/PD analysis seems acceptable, however this reviewer did not review the PK/PD model in detail since exposure-response analysis for efficacy was performed using observed steady state trough concentrations.*

## 4. Reviewer's Analysis

### 4.1 Objectives

The objectives of the reviewer's analysis are:

1. To determine whether dose adjustment is needed based on body weight.
2. To determine the major intrinsic factors (age, gender, race, body weight, creatinine clearance, BMI) that influence lorcaserin pharmacokinetics
3. To evaluate if proposed dosing regimen is supported by the exposure-response relationship for efficacy and safety

### 4.2 Methods

For conducting the exposure-efficacy analysis, the data was pooled from study 009 and 011. Observed steady state trough concentrations and percent change in body weight from baseline at week 52 were the variables utilized in the analysis. Exposure (trough concentrations) data were divided into quartiles. Similarly for exposure safety analysis, data was pooled from study 009 and 011. Exposures were divided into quartiles and proportion of patients experiencing relevant adverse events (all grade) were plotted

against exposure quartiles to explore if there was a trend of increasing adverse events with increasing exposures.

4.2.1 Datasets

Data sets used are summarized in Table 20.

**Table 20 Datasets Used During Analysis**

| Purpose of dataset | Name of dataset | Link to EDR |
|---|---|---|
| PK analysis dataset | apdpk.xpt | \\Cdsesub1\EVSPROD\NDA022529\\0000\m5\datasets\0604-005\analysis\apdpk.xpt |
| Vital sign datasets | Vs1.xpt<br>Vs2.xpt<br>Vs3.xpt | \\Cdsesub1\EVSPROD\NDA022529\\0000\m5\datasets\iss-ise\analysis\vs1.xpt<br>\\Cdsesub1\EVSPROD\NDA022529\\0000\m5\datasets\iss-ise\analysis\vs2.xpt<br>\\Cdsesub1\EVSPROD\NDA022529\\0000\m5\datasets\iss-ise\analysis\vs3.xpt |
| PK datasets | d-pktest.xpt<br>pk.xpt | \\Cdsesub1\EVSPROD\NDA022529\\0004\m5\datasets\apd356-009\analysis\d-pktest.xpt<br>\\Cdsesub1\EVSPROD\NDA022529\\0000\m5\datasets\apd356-011\analysis\pk.xpt |
| AE datasets | d_ae.xpt<br>ae.xpt | \\m5\datasets\apd356-009\analysis\d-ae.xpt<br>\\m5\datasets\apd356-011\analysis\ae.xpt |
| Echocardio-gram datasets | echo1.xpt<br>echo2.xpt | \ \m5\datasets\iss-ise\analysis\echo.xpt<br>\\m5\datasets\iss-ise\analysis\echo2.xpt |

4.2.2 **Software**

NONMEM VI was used to review the sponsor's pharmacokinetic analysis. S-plus was used to for all linear regressions and plots of the exposure response relationships for efficacy and safety.

### 4.3 Results:

#### 4.3.1 Is dose adjustment required based on body weight?

No, dose adjustment is not required based on body weight. The sponsor is proposing a fixed dose of 10 mg BID in patients of all weight categories based on the results obtained during the phase 2 dose finding study. However, population pharmacokinetic analysis demonstrated that weight is a covariate on clearance and clearance tended to increase with body weight resulting in lower exposures in heavier patients.

**I**nclusion of weight (Figure 17) on the estimate of clearance and volume reduced the objective function by 224.543 and the BSV was reduced from 36.2 to 32.2 and 22.6 to 16.6 for clearance and volume, respectively.

The fact that subject with higher body weight have lower exposures is illustrated in Figure 18. Subjects in the highest weight category have observed steady state trough concentration below the mean trough concentration and concentrations tended to decrease with increasing body weight.

Furthermore, as demonstrated in question 1.1.1 above, there is an exposure-response relationship for efficacy and percent weight loss from baseline tended to decrease with increasing body weight. However, even though the trough concentration observed in the PK subpopulation for completers in the Phase 3 trials indicated that subjects with higher body weight have lower steady state trough concentrations, there was significant body weight overlap in all four concentration quartiles. However,

this was a weak correlation, and only 41% of the subjects in the lowest concentration quartile belonged to the highest body weight quartile (109.9 to 153.8 kg). Therefore, this reviewer was unable to identify a patient population that would benefit from a higher dose of lorcaserin to obtain additional efficacy. Additionally there are significant pre-clinical safety concerns with respect to drug accumulation in the brain and development of cancers in pre-clinical species. Since this reviewer was unable to identify this population and lower lorcaserin concentrations do not pose a safety, this reviewer does not recommend dose adjustment based on body weight.

**4.3.2 Is the proposed dosing regimen supported by the exposure-response relationship for safety, for:**

- **Nervous system and psychiatric disorders,**
- **Prolactin levels,**
- **Valvulopathy,**
- **Pulmonary hypertension?**

Overall, the results from the exposure-response evaluation for safety are inconclusive, because:

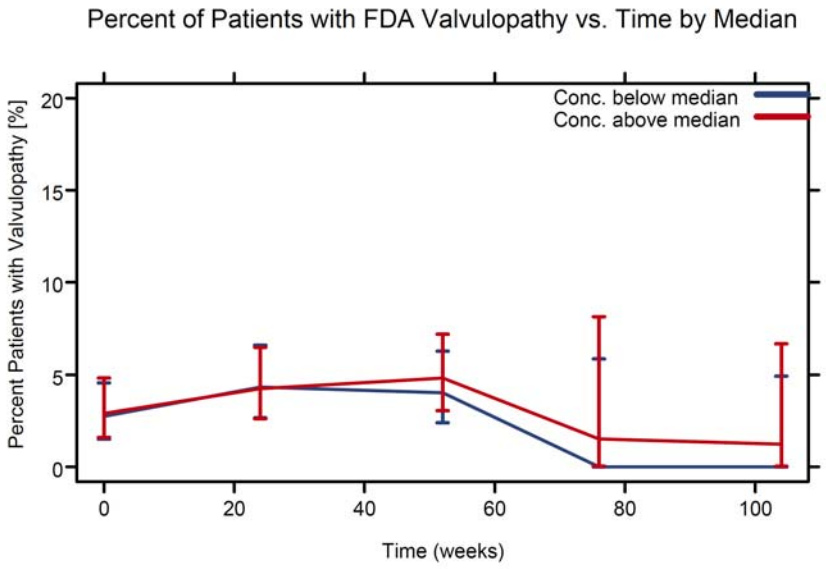
- The number of preferred term adverse events in the population randomized to PK sampling was low, which did not allow for evaluation of exposure response relationship on the adverse event preferred term level
- Exposure-response relationship analysis for safety on the system organ class (SOC) level is confounded by the variety of preferred term events included in the SOC.

Serotonergic agents that are active at the 5-$HT_{2B}$ receptor can cause a characteristic thickening of heart valves (especially mitrial and aortic) that results in valvular regurgitation. Since this phenomenon was observed in prior weight management drug such as fenfluramin and dexfenfluramin the sponsor performed evaluation of cardiac valvular function during their phase 3 trials and incidence of valvulopathy was one of the parameters evaluated for exposure-response for safety.

Overall, the event rate of valvulopathy, psychiatric disorders, and pulmonary arterial hypertension in the PK subpopulation, where the relationship to study drug was not unrelated, was low. Thus, this reviewer was unable to determine an exposure response relation for safety for these adverse events.

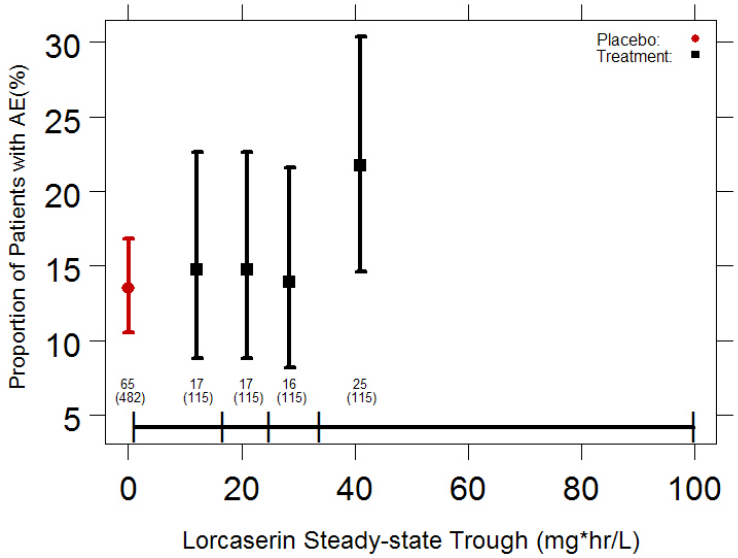
There were not enough events in the PK population subset to evaluate the exposure-response relationship for safety for psychiatric disorders, valvulopathy, and pulmonary hypertension. For FDA defined valvulopathy, only 14 events were recorded in the subset of patients that had PK samples taken (Figure 25). Thus, because of few events, the steady state trough concentrations were divided into two groups (below median and above median trough concentration) and percent of patients with FDA defined valvulopathy was plotted against time for the two groups.

**Figure 25** Limited PK data to evaluate the exposure-response relationship for valvulopathy (N=14 patients with FDA defined valvulaopathy in the PK subset)




There were also a limited number of events in the preferred term category for psychiatric disorders, and psychiatric disorders. On the system organ class level (SOC) there was no significant relationship between exposure and response for nervous system disorders. Evaluation of the exposure-response relationship for the SOC Psychiatric disorders demonstrated a shallow but significant slope for this SOC (Figure 26). However, this finding should be regarded with caution, since it comprises a variety of preferred adverse event terms, and no single preferred term showed a significant number of events for exposure response analysis.

**Figure 26** Proportion of patients with adverse events (SOC Psychiatric Disorders) by observed steady state trough concentration quartile



**4.3.3. Are the labeling claims made for the effect of age, race, gender and body weight on PK of lorcaserin based on population PK adequate?**

Yes, the sponsor's claims are acceptable.

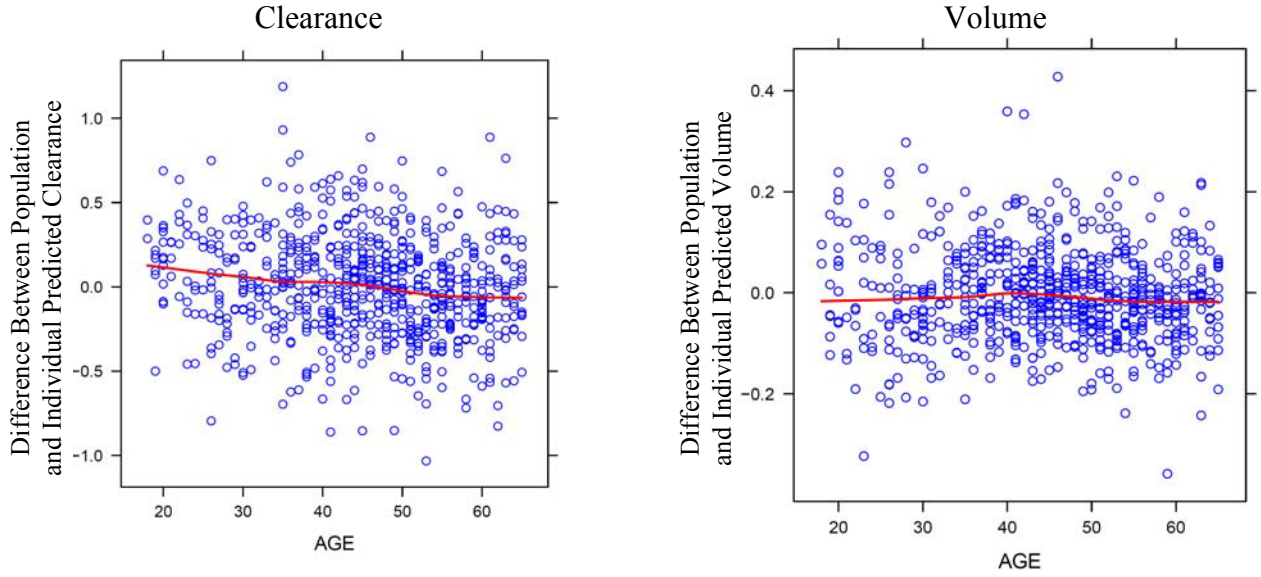
Gender:
Figure 20 illustrates the difference between individual & population mean clearance (ETACL) Figure 20, panel A) and volume (Figure 20, panel B) for lorcaserin for each percentile for males and females. Overlap of the black circles (males) and red line (females) means that the difference between individual and population mean clearance or volume between males and females are not different. Thus, there is no effect of gender of lorcaserin PK.

Weight:

- Inclusion of weight (Figure 17) on the estimate of clearance and volume reduced the objective function by 224.543 and the BSV was reduced from 36.2 to 32.2 and 22.6 to 16.6 for clearance and volume, respectively.

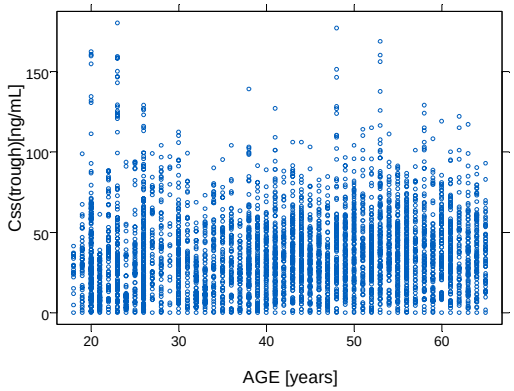
Age:
As Figure 27 demonstrates, there is no effect of age on the difference between individual & population mean clearance or Volume before or after adjusting for body weight.

**Figure 27** Difference between individual & population mean clearance ( left)) or Volume (right) by age after adjusting for body weight (Final Model)



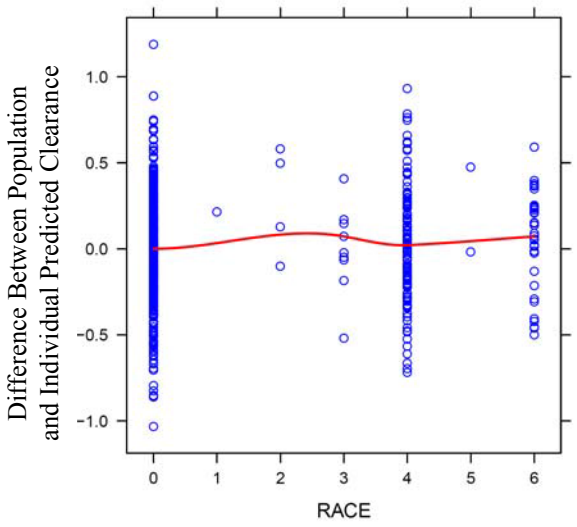
Furthermore, observed steady state trough concentrations were not correlated with age (Figure 28).

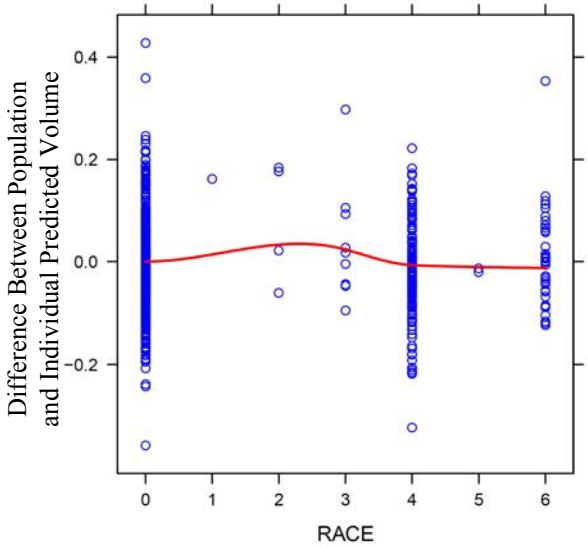
**Figure 28** Observed steady state trough concentrations in phase 3 trials by age




Race:
As Figure 29 demonstrates, there is no effect of race (Caucasians, African Americans, Hispanic/Latinos) on the difference between individual & population mean clearance or Volume before or after adjusting for body weight.

**Figure 29** Difference between individual & population mean clearance or Volume by race after adjusting for body weight. Final model




0= Caucasian, 1= Afro-Caribbean, 2=Asian, 3=Other, 5= American Indian or Alaskan Native,4=African American, 6=Hispanic/Latino

**Listing of Analysis Codes and Output Files**

| File name | Description | Location in \\cdsnas\pharmacometrics\Reviews\ Ongoing PM Reviews\ |
|---|---|---|
| Plot12-10.ssc | Exposure-Response plot (% change in body weight by steady state trough concentration) | **\Lorcaserin_NDA22529_S000_IZ\PPK Analyses\Graphs Group1** |
| Plot41.ssc | Clearance and Volume vs. weight plots | **\Lorcaserin_NDA22529_S000_IZ\PPK Analyses\Graphs Group1** |
| Plot12-12.ssc | Steady state trough concentrations vs. Weight | **\Lorcaserin_NDA22529_S000_IZ\PPK Analyses\Graphs Group1** |
| Plot21-6.ssc | Proportion of subjects with psychiatric disorders adverse event vs. steady state trough concentration quartile | **\Lorcaserin_NDA22529_S000_IZ\PPK Analyses\Graphs Group1** |
| Plot41_1.ssc | Clearance by gender percentile plot | **\Lorcaserin_NDA22529_S000_IZ\PPK Analyses\Graphs Group1** |
| Plot41_2.ssc | Volume by gender percentile plot | **\Lorcaserin_NDA22529_S000_IZ\PPK Analyses\Graphs Group1** |
| Plot21-7.ssc | FDA defined valvulopathy vs. time by median concentration | **\Lorcaserin_NDA22529_S000_IZ\PPK Analyses\Graphs Group1** |
| Run1.lst | Base PK model output | **\Lorcaserin_NDA22529_S000_IZ\PPK Analyses\Sponsor Model\Base Model** |
| Run1.ctl | Base PK model control stream | **\Lorcaserin_NDA22529_S000_IZ\PPK Analyses\Sponsor Model\Base Model** |
| Run2.lst | Final PK model output file | **\Lorcaserin_NDA22529_S000_IZ\PPK Analyses\Sponsor Model\Final Model** |
| Run2.ctl | Final PK model control stream | **\Lorcaserin_NDA22529_S000_IZ\PPK Analyses\Sponsor Model\Final Model** |

**5. Individual Study Reviews**

# 5.1. INDIVIDUAL STUDY REVIEWS (IN-VIVO)

## *5.1.1 Mass Balance Study: APD356-006*

The study was a mass balance study titled: "An Open-Label, Single-Dose, Mass-Balance Study to Assess the Disposition of 14C-Labeled APD356 in Healthy Male Subjects." The primary objective was to assess the mass balance of lorcaserin following a single oral dose of $^{14}$C-labeled lorcaserin. The study had three secondary objectives as listed below:

1) to assess the pharmacokinetics of lorcaserin and 2 known metabolites (7-OH lorcaserin and HS03-lorcaserin) in plasma
2) to assess to what extent lorcaserin enters red blood cells
3) to screen for, and identify for profiling, potential lorcaserin metabolites previously unidentified in humans in selected plasma, urine, and fecal samples

**STUDY DESIGN**

The mass balance study was an open-label, single-dose, mass balance study which enrolled 6 healthy male subjects in the age range of 19 to 55 years. Subjects with a Body Mass Index (BMI) of ≥ 18.5 but ≤ 30 (kg/m$^2$) were enrolled. Subjects received a 10 mg oral dose of lorcaserin Hemihydrate containing 100 μCi $^{14}$C-Lorcaserin, administered under fasting conditions. The capsule formulation was used in this study.

**SAMPLE COLLECTION**

- Blood samples were collected at pre dose and at 10, 20, 30, 45 min, and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hours post dose
- Urine samples were collected predose (Hour -2 - 0), and during the 0 - 2, 2 - 4, 4 - 8, 8 - 12, 12 - 24, 24 - 36, 36 - 48, 48 - 60, 60 - 72, 72 - 84, 84 - 96, 96 - 120, 120 - 144, 144 - 168, 168 - 192, 192 - 216, and 216 - 240 postdose intervals.
- Feces were collected predose (within 24 hours prior to dosing) and during the 0 - 24, 24 - 48, 48 - 72, 72 - 96, 96 - 120, 120 - 144, 144 - 168, 168 - 192, 192 - 216, and 216 - 240 postdose intervals.

**CHANGES IN THE CONDUCT OF THE STUDY**

According to the protocol, urine volume was to be measured at the end of each urine collection interval. However, the sponsors decided that the total weight, rather than the total volume, was to be recorded, reasoning that this would more accurately quantify the amount of urine produced during each collection interval.
The calculation of renal clearance (CLr) was to be assessed using the equation CLr = Amu/plasma AUC(0-t). Instead, CLr was calculated as Amt/plasma AUC(0-t), where Amt was the amount of drug excreted in urine up to the time of the last measurable plasma concentration (Ct).

***Reviewer comment:***
*This is acceptable.*

## PROTOCOL VIOLATIONS

On Day 11, at approximately 08:11, Subject 3 did not urinate into a urine collection jug and it is estimated that the volume not collected would have been approximately 30 mL or 29.6 g. At the predose collection interval on Day 1 of Period 1, Subject 6 was only able to provide approximately 35.4 mL of urine rather than the 40 ml required by the protocol.

## RESULTS

**Demographics:**
All 6 subjects completed the study. All 6 subjects participating in the study were male. Regarding race, 5 subjects were Caucasian, and 1 was Black. The mean age for all subjects was 28.0 years (range 20.0 - 45.0 years), the mean weight was 69.7 kg (range 58.5 - 79.8 kg), and the mean height was 170.2 cm (range 160.0 - 180.0 cm). Mean BMI was 24.03 kg/m2 (range 21.47 - 26.57 kg/m2).

**Pharmacokinetics:**
The PK parameters for radioactive [$^{14}$C]-lorcaserin in plasma and whole blood for mean Cmax, AUC0-t, and AUC0-inf for plasma were 92%, 95%, and 78% higher than whole blood, respectively. Plasma PK parameters, computed from the individual plasma concentrations of lorcaserin and of its 2 known metabolites (7-OH lorcaserin and HSO3-lorcaserin), are summarized in Table 21, however, the 7-OH lorcaserin metabolite was detectable in only 2 of the 6 subjects.

**Table 21** Summary of the Pharmacokinetic Parameters of Plasma lorcaserin, Plasma 7-OH lorcaserin, and Plasma HSO3-lorcaserin

| | Plasma APD356 | Plasma 7-OH APD356 | Plasma $HSO_3$-APD356 |
|---|---|---|---|
| **Pharmacokinetic Parameters** | **Mean ± SD (N)** | **Mean ± SD (N)** | **Mean ± SD (N)** |
| $C_{max}$ (ng/mL) | 46.0 ± 12.8 | 0.313 ± 0.487 | 45.1 ± 13.2 |
| | (6) | (6) | (6) |
| $T_{max}$ (hr) | 2.34 ± 0.983 | 1.76 ± 0.353 | 3.34 ± 0.816 |
| | (6) | (2) | (6) |
| $AUC_{(0-t)}$ (ng*hr/mL) | 679.6 ± 190.5 | 1.243 ± 2.141 | 2501 ± 1199 |
| | (6) | (6) | (6) |
| $AUC_{(0-inf)}$ (ng*hr/mL) | 692.3 ± 192.0 | 10.13 ± . | 2607 ± 1277 |
| | (6) | (1) | (6) |
| $K_{el}$ (1/hr) | 0.0641 ± 0.0117 | 0.112 ± . | 0.0175 ± 0.00386 |
| | (6) | (1) | (6) |
| $T_{1/2}$ (hr) | 11.1 ± 1.91 | 6.21 ± . | 41.3 ± 10.0 |
| | (6) | (1) | (6) |

. = Value missing or not reportable
Treatment = 1 x 10 mg [$^{14}$C]-APD356 Containing 100 µCi of Total Radioactivity

A mean $^{14}$C recovery of 94.5% was achieved in 6 subjects by the end of the study period. Mean recovery from urine was 92.3% and mean recovery from feces was 2.2%. Subject 5 exhibited detectable plasma total radioactivity at 240 hours postdose.

## ANALYTICAL METHOD:

The concentrations of lorcaserin, 7-OH lorcaserin, and HSO3-lorcaserin in Human Plasma (Heparin) were determined using high performance liquid chromatography with mass spectrometric detection. Study samples were analyzed without exceeding long-term, short-term, freeze-thaw stability, or post-preparative stability. Results of the quality control of this bioanalytical report are represented in Table 22.

**Table 22** Results of Quality Control from the bioanalytical method

| | Calibration | | Quality control (between batch) | | |
|---|---|---|---|---|---|
| Analyte / Parameter | Curve range (ng/mL) | LLOQ (ng/mL) | %CV | %CV | %Bias |
| lorcaserin | 05-100 | | 2.5% to 6.9% | 3.4% to 5.0% | -4.1% to 0.7 % |
| 7-OH lorcaserin | 05-100 | | 2.6% to 8.5% | 4.1% to 6.7% | -2.0% to 6.0% |
| $HSO_3$-lorcaserin | 1-100 | | 0.7% to 8.1% | 3.5% to 4.8% | -4.0% to -2.0% |

A set of 8 non-zero calibration standards, ranging from 0.5 ng/mL to 100 ng/mL for lorcaserin and 7-OH lorcaserin were used, also a set of 8 non-zero calibration standards, ranging from 1 ng/mL to 100 ng/mL for $HSO_3$-lorcaserin, were used. QC samples at 3 different concentrations: 1.5 ng/mL, 15 ng/mL, and 75 ng/mL for lorcaserin and 7-OH lorcaserin and 3 ng/mL, 15 ng/mL, and 75 ng/mL for $HSO_3$-lorcaserin were used.

## CONCLUSIONS

The majority of a single radioactively labeled dose of lorcaserin was recovered in urine (92.3%) and feces (2.2%).
An in-vitro study (PDR-06-012) to identify for profiling, potential lorcaserin metabolites previously unidentified in humans in selected plasma was conducted in conjunction with this study.

**TITLE:** "*In Vivo Metabolism of [$^{14}$C] APD356 in Humans*."

**OBJECTIVE:** The objective of this study was identification and quantitation of the circulatory and urinary metabolites of [$^{14}$C]lorcaserin

**EXPERIMENT METHODS:** Aliquots of plasma from 6 human subjects were pooled (0.3-72 hr) proportionally to time intervals to obtain a single sample representative of the entire time range (e.g. $AUC_{0-72h}$). Urine samples were pooled for individual subjects. As a complimentary experiment to the mass spectral analysis for the identification of the glucuronides, potential glucuronide containing metabolites were incubated in the presence of β-glucuronidase. Additionally, phase I oxidative metabolites of lorcaserin were incubated in microsomes (human, monkey mouse and rat liver microsomes) in the presence of UDGPA and alamethicin. Samples were analyzed using a LC/MS/MS system with a β-ram radioactivity detector.

**RESULTS:** This study identified 10 metabolites. These ten metabolites accounted for more than 90% of radioactivity excreted in urine, whereas the three un-identified metabolites accounted for less than 10% of radioactivity excreted in urine. M5 (N-carbamoyl glucuronide) was found to the major metabolite in urine, representing approximately 36% of the total dose. While M1 (lorcaserin sulfamate) was the major metabolite in plasma ( approximately 36% of radioactivity in plasma), it was only a minor metabolite in urine, representing approximately 3% of dose. In addition to M5 (N-carbamoyl glucuronide), only one urinary metabolite, M8 (1-carboxyl glucuronide) was excreted in urine greater than 10% of dose.

**CONCLUSIONS:** Lorcaserin is metabolized to 10 identified and 3 unidentified metabolites. The ten identified metabolites make up 90% of the radioactivity in urine. The majority of a single radioactively labeled dose of lorcaserin was recovered in urine (92.3%) and feces (2.2%).

***Reviewer comment:*** *The study is acceptable.*

### *5.1.2 Maximum Tolerated Dose – Single dose study: APD356-001A*

The Maximum tolerated dose (single dose) study was titled: "A Single-Dose Study to Assess the Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of APD356 in Healthy Volunteers" The primary objective was o define the maximum tolerated dose (MTD) of lorcaserin following a single oral dose. The secondary objective of the study was to determine the PK characteristics of lorcaserin and two potential metabolites (M1 and M2)* following a single oral dose and to determine the appropriate dose to be used in Parts B and C.

**STUDY DESIGN**

This study was a randomized, double-blind, placebo-controlled, single ascending dose study, which enrolled 45 healthy male and female volunteers in the age range of 18 to 60 years. Doses of 10, 20, 40 mg of lorcaserin were administered. Subject with a BMI between 23-32 $kg/m^2$ were enrolled in the study. The washout period between the treatments was at least 7 days depending on the review of PK data.

**SAMPLE COLLECTION**

Blood and urine samples were collected and samples were analyzed for lorcaserin and its primary metabolite M1.

- Blood samples: pre-dose then at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 hours post-dose
- Urine: at time intervals of 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, 48- 72, 72-96, 96-120 hours post-dose

**RESULTS**

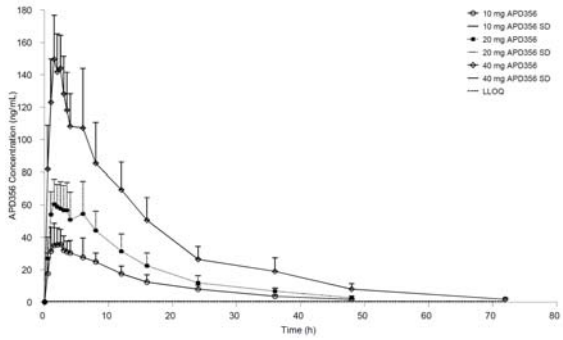
Changes in the conduct of the study:
There were no quantifiable plasma concentrations of the M1 metabolite in this study. Subsequently the sponsor and the CRO agreed that the M2 metabolite will not be determined in plasma and urine.

***Reviewer comment:***
*In this study (Part A, B, and C) M1 was assigned to be 7-OH lorcaserin and M2 to be $HSO_3$-lorcaserin. In all other studies M1 was assigned to be $HSO_3$-lorcaserin and M2 was assigned to be 7-OH lorcaserin. There were no quantifiable concentrations for M1 and M2 was not measured. The sponsor measured $HSO_3$-lorcaserin concentrations and samples from the 40 mg dose level had measurable concentrations.

Pharmacokinetics:
All subjects completed the study therefore, the pharmacokinetic dataset comprised all subjects that received a single dose of lorcaserin. A summary of the pharmacokinetic parameters is illustrated in
Mean (+SD) plasma concentration-time profiles for APD and $HSO_3$-APD (after 40 mg dose) are illustrated in Figure 30.

**Figure 30** *Mean (+SD) Plasma Concentration-Time Profiles of lorcaserin (panel A, ng/mL) and $HSO_3$-lorcaserin (panel B, ng/mL) After Administration of Single Oral Doses of lorcaserin to Healthy Male and Female Subjects*

A




B

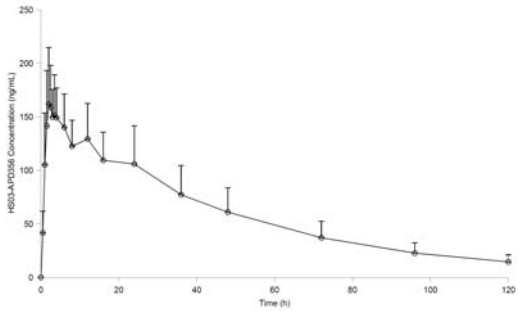



**Table 23** Summary of lorcaserin Pharmacokinetic Parameters at 10 mg, 20 mg, and 40 mg dose

| Parameter | Summary Statistic | Dose APD356 | | |
|---|---|---|---|---|
| | | 10 mg | 20 mg | 40 mg |
| Number of subjects dosed | | 12 | 12 | 6 |
| $C_{max}$ (ng/mL) | n | 12 | 12 | 6 |
| | Mean | 40.158 | 69.352 | 159.793 |
| | SD | 10.8604 | 15.3325 | 24.7077 |
| | Range | 27.01 – 57.67 | 45.82 – 92.76 | 112.28 – 180.16 |
| | Male Mean[1] | 37.505 | 61.853 | 153.295 |
| | Female Mean[2] | 42.810 | 76.850 | 172.790 |
| $t_{max}$ (h) | n | 12 | 12 | 6 |
| | Median | 2.000 | 2.250 | 1.750 |
| | Range | 1.00 – 6.10 | 1.00 – 6.00 | 1.50 – 2.50 |
| | Male Median[1] | 2.000 | 1.750 | 1.750 |
| | Female Median[2] | 2.000 | 3.000 | 1.750 |
| $AUC_{0\text{-}120}$ (ng.h/mL) | n | 12 | 12 | 6 |
| | Mean | 587.58 | 1001.62 | 2309.82 |
| | SD | 160.038 | 282.630 | 473.124 |
| | Range | 397.4 – 875.8 | 634.8 – 1439.9 | 1402.4 – 2737.1 |
| | Male Mean[1] | 526.22 | 837.23 | 2303.50 |
| | Female Mean[2] | 648.95 | 1166.02 | 2322.45 |
| $AUC_{last}$ (ng.h/mL) | n | 12 | 12 | 6 |
| | Mean | 572.92 | 982.04 | 2291.43 |
| | SD | 161.926 | 288.301 | 478.696 |
| | Range | 389.5 – 865.0 | 600.5 – 1427.7 | 1374.6 – 2728.6 |
| | Male Mean[1] | 512.03 | 810.02 | 2285.08 |
| | Female Mean[2] | 633.80 | 1154.12 | 2304.10 |
| $AUC_{inf}$ (ng.h/mL) | n | 12 | 12 | 6 |
| | Mean | 588.23 | 1001.96 | 2311.08 |
| | SD | 160.536 | 282.614 | 473.437 |
| | Range | 397.5 – 876.5 | 635.8 – 1440.4 | 1403.1 – 2739.3 |
| | Male Mean[1] | 526.78 | 837.43 | 2304.60 |
| | Female Mean[2] | 649.65 | 1166.50 | 2324.05 |
| $t_{½z}$ (h) | n | 12 | 12 | 6 |
| | Mean | 11.199 | 10.157 | 10.943 |
| | SD | 1.6426 | 1.2505 | 1.8837 |
| | Range | 8.30 – 13.46 | 8.16 – 11.52 | 8.20 – 12.84 |
| | Male Mean[1] | 10.705 | 9.957 | 10.240 |
| | Female Mean[2] | 11.693 | 10.360 | 12.355 |

***Reviewer comment:***

*Even though the $C_{max}$ and AUC appear to increase with dose and roughly doubling with dose, strict dose-proportionality could not be established.*

## ADVERSE EVENTS

There were a total of 97 adverse events recorded in 33 subjects, all of which were treatment emergent, with 83 being reported following active treatment and 14 following administration of placebo. Of the treatment-emergent AEs 82 were classified as mild in severity, 12 as moderate and three as severe. Following single administration of 40 mg there were two AE with severe intensity in one subject. The two severe intensity events were reports of disorientation and hallucinations and were both recorded in the same subjects who also had the moderate intensity events of crying, euphoric mood, feeling drunk, tremor and vomiting.

As a result of the dosing of the third cohort with a single dose of 40 mg lorcaserin not being well tolerated (especially in one female subject) further dose escalation was not performed. Instead, two further cohorts were assigned to repeat the previously satisfactorily tolerated lower doses of 10 mg and 20 mg lorcaserin but this time using female subjects. In total 5 cohorts of subjects were dosed with lorcaserin, two with 10 mg, two with 20 mg and one cohort with 40 mg, the planned sixth cohort was not required.

## ANALYTICAL METHOD

Lorcaserin:

The analytical procedure involved extraction of lorcaserin and 7-Hydroxylorcaserin from human plasma by a protein precipitation method using formic acid in acetonitrile. The human plasma samples were analyzed using a validated HPLC method with MS/MS detection.

$HSO_3$-lorcaserin:

An aliquot of human plasma (heparin) containing each analyte and internal standard was (b) (4) The extracted samples were analyzed by an HPLC equipped with an AB/MDS Sciex API 4000 mass spectrometer. Negative ions were monitored for $HSO_3$-lorcaserin in the multiple reaction monitoring (MRM) mode. A set of 8 non-zero calibration standards, ranging from 1 ng/mL to 100 ng/mL and QC samples at 3 different concentrations: 3 ng/mL, 15 ng/mL, and 75 ng/mL were prepared.

| | Calibration | | | Quality control (between batch) | |
|---|---|---|---|---|---|
| Analyte / Parameter | Curve range (ng/mL) | LLOQ (ng/mL) | %CV | %CV | %Bias |
| Lorcaserin | 0.5-99.53 | 0.5 | <16% at LLOQ | <15% | <14% |
| $HSO_3$-lorcaserin | 1 to 10 ng/mL | 1 | 2.1% to 9.1% | 4.3% to 11% | -0.7% to 10.7% |

## CONCLUSIONS

Lorcaserin was well tolerated up to doses of 20 mg. Doses of 40 mg were not well tolerated especially in females. This is illustrated by the adverse events recorded at the 40 mg dose level where male subjects showed mild adverse events and female subjects (particularly Subject 25) showed moderate and severe intensity events. Even though the $C_{max}$ and AUC appear to increase with dose and roughly doubling with dose, strict dose-proportionality could not be established.

### *5.1.3 Maximum Tolerated Dose – Multiple dose study: APD356-002*

The Maximum tolerated dose (multiple dose) study was titled:" A Multiple-Dose Study to Assess the Safety, Tolerability, and Steady State Pharmacokinetics of APD356 in Healthy Volunteers." The primary objective was to define the MTD of lorcaserin following multiple oral doses. The secondary objective of the study was to determine the steady state PK characteristics of lorcaserin and 2 potential metabolites, HSO3-lorcaserin (M1) and 7-OH-lorcaserin (M2), in plasma and urine.

**STUDY DESIGN**

This study was a double-blind, placebo-controlled, randomized, parallel dose-escalated group study, which enrolled 27 healthy male and female volunteers (Subjects were enrolled into 1 of 3 cohorts, each containing 9 subjects (6 active and 3 placebo)). Subjects were ages 18-60 years old and had a BMI ≥25 $kg/m^2$. Doses of 3, 10, 20 mg were administered daily for 14 days. In this study the capsule formulation was used.

**SAMPLE COLLECTION**

Blood and urine samples were collected and blood samples were analyzed for lorcaserin and its primary metabolite M1 and M2 ($HSO_3$-lorcaserin and 7-OH-lorcaserin).Urine samples were analyzed for lorcaserin and M2.

Blood samples:

- predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, and 24 hours postdose on Day 1 and Day 14
- Blood samples were also obtained at predose and 2 hours postdose on Days 3, 5, 7, 9, 11, and 13 as well as at the nominal dosing time (± 5 minutes) on Days 17, 19, and 21.

Urine:

- intervals of 0 - 2, 2 - 4, 4 - 6, 6 - 8, 8 - 12, and 12 - 24 hours postdose on Day 1 and Day 14.
- Urine samples were also obtained via 24-hour urine collection on Days 3, 5, 7, 9, 11, 13, 16, 18, and 20.

**PROTOCOL VIOLATIONS**

All of the protocol deviations were PD related and did not affect the PK outcome of the study.

**RESULTS**

Over all 27 subjects who received at least one dose of treatment were included in the safety analysis. 18 subjects who completed lorcaserin treatment were included in the PK analysis since 9 subjects received placebo treatment. Lorcaserin was well tolerated up to 20 mg. Mean plasma PK parameters for lorcaserin are illustrated in Table 24. Accumulation of the 10 mg QD dose was approximately 35%. The estimated accumulation for a proposed marketed dose of 10 mg BID dose based on a 11 h half-life is approximately 70%.

**Table 24** Arithmetic Mean (SD) Pharmacokinetic Parameters for lorcaserin in Plasma

| Pharmacokinetic Parameters | Treatment A 3 mg Daily for 14 Days | Treatment B 10 mg Daily for 14 Days | Treatment C 20 mg Daily for 14 Days |
|---|---|---|---|
| **Day 1** | | | |
| $T_{max}$ (hr)* | 2.000 (2.00 – 3.00) | 1.500 (1.50 – 2.50) | 1.750 (1.00 – 2.50) |
| $C_{max}$ (ng/mL) | 11.16 (3.842) | 39.07 (11.144) | 83.77 (16.584) |
| $AUC_{(0-t)}$ (ng·hr/mL) | 132.1 (47.46) | 436.1 (130.01) | 878.7 (206.85) |
| $AUC_{(0-\tau)}$ (ng·hr/mL) | 132.3 (47.56) | 436.6 (130.19) | 879.9 (207.23) |
| $AUC_{(0-inf)}$ (ng·hr/mL) | 172.0 (69.08) | 516.9 (159.41) | 1086.2 (299.03) |
| $T_{½z}$ (hr) | 11.381 (1.9918) | 8.866 (1.8053) | 9.546 (2.8174) |
| **Day 14** | | | |
| $T_{max}$ (hr)* | 1.750 (1.00 – 2.50) | 2.500 (1.50 – 3.00) | 2.000 (1.00 – 3.50) |
| $C_{max}$ (ng/mL) | 13.70 (4.192) | 50.85 (15.745) | 85.02 (33.622) |
| $C_{min}$ (ng/mL) | 2.604 (1.8236) | 9.297 (4.7587) | 12.694 (14.0964) |
| $C_{avg}$ (ng/mL) | 7.17 (2.578) | 24.74 (8.500) | 37.47 (18.925) |
| $AUC_{(0-t)}$ (ng·hr/mL) | 172.2 (61.86) | 593.8 (204.01) | 899.2 (454.20) |
| $AUC_{(0-\tau)}$ (ng·hr/mL) | 172.2 (61.86) | 593.8 (204.01) | 899.2 (454.20) |
| $T_{½z}$ (hr) | 10.229 (2.8697) | 10.281 (2.4270) | 11.264 (3.7134) |
| Cl/F (L/hr) | 19.81 (8.600) | 18.07 (4.352) | 26.07 (9.675) |
| AI | 1.327 (0.2578) | 1.358 (0.1808) | 1.051 (0.4561) |
| $C_{max}$ Ratio | 1.2739 (0.32255) | 1.3121 (0.20441) | 1.0695 (0.48292) |

* Median (range) presented

$AUC_{0-t}$ and $C_{max}$ on day 1 and 14, and $AUC_{0-inf}$ on day 1 showed dose proportionality between 3 mg and 20 mg of lorcaserin. Steady state levels were reach on day 3.

The primary circulatory metabolite lorcaserin sulfamate (M1) accumulated approximately 2.6-fold in the 10 mg QD dosing group based on the observed data. The estimated accumulation for BID dosing is approximately 6-fold based on a observed half-life of 47 hours. Mean PK parameters for M1 are shown in Table 25.

**Table 25** Arithmetic Mean (SD) Pharmacokinetic Parameters for M1 in Plasma

| Pharmacokinetic Parameters | Treatment A 3 mg Daily for 14 Days | Treatment B 10 mg Daily for 14 Days | Treatment C 20 mg Daily for 14 Days |
|---|---|---|---|
| **Day 1** | | | |
| $T_{max}$ (hr)* | 2.750 (2.50 – 4.00) | 2.250 (2.00 – 6.00) | 3.000 (2.00 – 3.50) |
| $C_{max}$ (ng/mL) | 9.29 (2.648) | 50.07 (16.125) | 138.97 (104.215) |
| $AUC_{(0-t)}$ (ng·hr/mL) | 160.8 (46.66) | 823.5 (306.74) | 2382.3 (1991.20) |
| $AUC_{(0-\tau)}$ (ng·hr/mL) | 161.2 (46.82) | 825.7 (307.70) | 2388.9 (1997.09) |
| $AUC_{(0-inf)}$ (ng·hr/mL) | 506.5 (238.77) | 1857.1 (726.85) | 6257.5 (5901.47) |
| $T_{½z}$ (hr) | 44.59 (15.275) | 32.37 (4.120) | 33.27 (9.681) |
| **Day 14** | | | |
| $T_{max}$ (hr)* | 3.250 (2.00 – 4.00) | 3.250 (2.03 – 8.00) | 2.500 (1.50 – 6.00) |
| $C_{max}$ (ng/mL) | 23.00 (9.649) | 120.45 (59.176) | 293.22 (373.532) |
| $C_{min}$ (ng/mL) | 14.50 (7.790) | 68.52 (36.214) | 166.63 (212.488) |
| $C_{avg}$ (ng/mL) | 18.35 (8.002) | 90.61 (44.212) | 229.94 (290.751) |
| $AUC_{(0-t)}$ (ng·hr/mL) | 440.3 (192.09) | 2174.7 (1061.08) | 5518.6 (6978.02) |
| $AUC_{(0-\tau)}$ (ng·hr/mL) | 474.2 (193.62) | 2599.5 (1404.41) | 5518.6 (6978.02) |
| $T_{½z}$ (hr) | 52.36 (18.345) | 46.78 (0.406) | 47.23 (12.043) |
| AI | 2.698 (0.6117) | 2.596 (0.4685) | 2.075 (0.9402) |
| $C_{max}$ Ratio | 2.432 (0.4574) | 2.368 (0.6121) | 1.875 (0.9842) |

* Median (Min-Max)

Plasma concentrations for 7-OH lorcaserin (M2) were below LLOQ for a significant number of subjects in each treatment arm. Where possible, PK parameters for M2 in plasma were calculated and are shown in Table 26.

**Table 26** Arithmetic Mean (SD) Pharmacokinetic Parameters for M2 in Plasma

| Pharmacokinetic Parameters | Treatment A 3 mg Daily for 14 Days | Treatment B 10 mg Daily for 14 Days | Treatment C 20 mg Daily for 14 Days |
|---|---|---|---|
| **Day 1** | | | |
| $T_{max}$ (hr)* | 2.500 (2.00 – 3.00) | 1.500 (1.50 – 3.50) | 2.000 (1.00 – 3.50) |
| $C_{max}$ (ng/mL) | 0.2617 (0.42962) | 0.7845 (0.55161) | 1.0563 (0.52878) |
| $AUC_{(0-t)}$ (ng·hr/mL) | 0.2307 (0.39687) | 1.7263 (1.84814) | 5.6974 (5.81067) |
| $AUC_{(0-\tau)}$ (ng·hr/mL) | . | 3.317 (2.4661) | 9.216 (6.7669) |
| $AUC_{(0-inf)}$ (ng·hr/mL) | . | . | . |
| $T_{½z}$ (hr) | . | . | . |
| **Day 14** | | | |
| $T_{max}$ (hr)* | 1.750 (1.00 – 2.50) | 3.750 (3.50 – 6.00) | 1.500 (1.00 – 4.00) |
| $C_{max}$ (ng/mL) | 1.2033 (1.55775) | 0.6623 (0.56142) | 0.7183 (0.39759) |
| $C_{min}$ (ng/mL) | 0.000 (0.0000) | 0.000 (0.0000) | 0.000 (0.0000) |
| $C_{avg}$ (ng/mL) | 0.23750 (0.289553) | 0.18577 (0.170134) | 0.11949 (0.072738) |
| $AUC_{(0-t)}$ (ng·hr/mL) | 3.0683 (5.06672) | 2.1573 (3.04127) | 1.9645 (1.76219) |
| $AUC_{(0-\tau)}$ (ng·hr/mL) | . | . | . |
| $T_{½z}$ (hr) | . | . | . |
| AI | . | 1.6368 (1.22328) | 0.4693 (0.27714) |
| $C_{max}$ Ratio | . | 0.8047 (0.48332) | 0.7328 (0.40928) |

* Median (Min-Max)

## ANALYTICAL METHOD

Concentrations of 7-OH lorcaserin, lorcaserin, and $HSO_3$-lorcaserin in human plasma (heparin) were determined using high performance liquid chromatography with mass spectrometric detection. A set of 8 non-zero calibration standards, ranging from 0.5 ng/mL to 100 ng/mL for 7-OH lorcaserin and lorcaserin, and 1 ng/mL to 100 ng/mL for $HSO_3$-lorcaserin, were prepared and subsequently stored at a nominal temperature of -20°C. QC samples at 4 different concentrations: 1.5 ng/mL, 15 ng/mL, 75 ng/mL, and 500 ng/mL for 7-OH lorcaserin and lorcaserin and 3 ng/mL, 15 ng/mL, 75 ng/mL, and 500 ng/mL for $HSO_3$-lorcaserin were prepared and also subsequently stored at a nominal temperature of -20°C.

**Table 27** Results of Quality Control from the bioanalytical method

| | Calibration | | | Quality control (between batch) | |
|---|---|---|---|---|---|
| Analyte / Parameter | Curve range (ng/mL) | LLOQ (ng/mL) | %CV | %CV | %Bias |
| lorcaserin | 0.5-100 | 0.5 | 3.2% to 8.8% | 4.9% to 6.3% | 0.9% to 6.5% |
| 7-OH lorcaserin | 0.5-100 | 0.5 | 3.4% to 8.5% | 7.3% to 7.9% | 2.7% to 3.3% |
| $HSO_3$-lorcaserin | 1-100 | 1 | 2.8% to 6.1% | 2.0% to 10.3% | -1.3%to 1.5% |

### *5.1.4 Pharmacokinetics in Renal Impaired Patients: APD356-016*

The renal impairment study was titled: "A Phase 1, Open-Label, Single-Dose Study of the Pharmacokinetic Properties of Lorcaserin in Subjects with Renal Impairment." The objective of this study was to assess the pharmacokinetic properties of lorcaserin in subjects with mild, moderate or severe renal impairment as compared to subjects with normal renal function and to evaluate the extent to which lorcaserin is cleared from the blood by hemodialysis.

**STUDY DESIGN**

The renal impairment study was a Phase 1, open-label, single-dose, parallel group study. The study enrolled 40 subjects (detailed demographics see Table 30) with an age range between 19 to 79 years and a BMI of 27 to 45 kg/m$^2$. Renal function was assessed by Cockgroft-Gault creatinine clearance estimation (Table 28). Group assignment was based on calculation of CrCl based on ideal and actual body weight. The difference in classification using actual and ideal body weight are illustrated in Table 29. Subjects in group 1-4 (normal renal function to severe renal impairment) received a dose of 10 mg lorcaserin. Subjects in group 5 (end stage renal disease) received 2 doses of 10 mg each of lorcaserin separated by 7 days. Subjects had the option to consume a small snack 2 hours prior to dosing (groups 1-4) and subjects in-group 5 were given a low fat meal during the dialysis day at least 2 hours prior to dosing.

***Reviewer comment:***
*Food had no impact on the pharmacokinetics of lorcaserin. The food options given during the conduct of this study are acceptable.*

**Table 28** Cockgroft-Gault Creatinine Clearance Levels to Assess Renal Function

| Group | Description | Estimated Creatinine Clearance (mL/min) |
|---|---|---|
| 1 | Normal renal function | > 80 mL/min |
| 2 | Mild renal impairment | 51-80 mL/min |
| 3 | Moderate renal impairment | 31-50 mL/min |
| 4 | Severe renal impairment not receiving dialysis | 5-30 mL/min |
| 5 | End stage renal disease requiring hemodialysis | ESRD |

**Table 29** Group Assignments Based on Calculated Creatinine Clearance

| | Calculation based on Ideal Body Weight | | Calculation based on Actual Body Weight | |
|---|---|---|---|---|
| Mean ± sd | Creatinine Clearance (mL/min) | Number of Subjects in Group | Creatinine Clearance (mL/min) | Number of Subjects in Group |
| 1 | 105.2 ± 12.3 | 8 | 128.0 ± 24 | 13 |
| 2 | 64.7 ± 8.9 | 8 | 62.8 ± 6.7 | 10 |
| 3 | 38.8 ± 4.6 | 8 | 38.3 5.9 | 8 |
| 4 | 22.7 ± 5.8 | 8 | 9.7 | 1 |
| 5 | 9.9 ± 3.8 | 8 | 15.2 ± 6.9 | 8 |

**Table 30** Summary of Subject Demographics by Group

| Demographics | Normal (N=8) | Mild (N=8) | Moderate (N=8) | Severe (N=8) | ESRD (N=8) | Total (N=40) |
|---|---|---|---|---|---|---|
| **Age (years)** | | | | | | |
| Mean (SD) | 28.6 (9.86) | 58.9 (14.42) | 65.4 (10.82) | 56.6 (14.28) | 47.6 (6.16) | 51.4 (16.90) |
| Min-Max | 19 - 45 | 35 - 78 | 42 - 75 | 36 - 75 | 39 - 57 | 19 - 78 |
| **Race n (%)** | | | | | | |
| White or Caucasian | 3 (37.5%) | 4 (50.0%) | 6 (75.0%) | 6 (75.0%) | 0 (0.0%) | 19 (47.5%) |
| Black or African American | 3 (37.5%) | 3 (37.5%) | 2 (25.0%) | 2 (25.0%) | 7 (87.5%) | 17 (42.5%) |
| Asian | 0 (0.0%) | 1 (12.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.5%) |
| Hispanic or Latino | 2 (25.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (12.5%) | 3 (7.5%) |
| **Gender n (%)** | | | | | | |
| Male | 7 (87.5%) | 5 (62.5%) | 7 (87.5%) | 5 (62.5%) | 7 (87.5%) | 31 (77.5%) |
| Female | 1 (12.5%) | 3 (37.5%) | 1 (12.5%) | 3 (37.5%) | 1 (12.5%) | 9 (22.5%) |
| **Weight (kg)** | | | | | | |
| Mean (SD) | 93.0 (14.11) | 87.4 (9.05) | 100.6 (17.61) | 98.9 (17.26) | 109.0 (13.78) | 97.8 (15.75) |
| Min-Max | 75 - 115 | 76 - 102 | 75 - 126 | 71 - 123 | 91 - 127 | 71 - 127 |
| **Height (cm)** | | | | | | |
| Mean (SD) | 173.3 (6.47) | 167.8 (5.31) | 173.9 (12.70) | 170.0 (9.60) | 176.5 (4.90) | 172.3 (8.48) |
| Min-Max | 161 - 183 | 162 - 176 | 160 - 191 | 161 - 191 | 170 - 183 | 160 - 191 |
| **BMI ($kg/m^2$)** | | | | | | |
| Mean (SD) | 30.9 (3.07) | 31.1 (3.62) | 33.3 (4.77) | 34.3 (5.69) | 35.0 (4.29) | 32.9 (4.48) |
| Min-Max | 28.2 - 36.6 | 26.3 - 36.9 | 27.7 - 41.5 | 27.3 - 45.0 | 28.9 - 41.9 | 26.3 - 45.0 |
| **Cockroft-Gault Creatinine** | | | | | | |
| Mean (SD) | 105.2 (12.40) | 64.7 (8.84) | 38.9 (4.76) | 22.7 (5.78) | NA | 57.9 (32.66) |
| **Diabetic Subjects** | | | | | | |
| Diet Controlled | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (13.0%) | 1 (13.0%) | 2 (5.00%) |
| Insulin (N%) | 0 (0.00%) | 0 (0.00%) | 1 (13.0%) | 2 (25.0%) | 2 (25.0%) | 5 (12.5%) |
| Oral Agents (N%) | 0 (0.00%) | 2 (25.0%) | 2 (25.0%) | 0 (0.00%) | 0 (0.00%) | 4 (10.0%) |

## SAMPLE COLLECTION

**Groups 1-4:**
Blood and urine samples for pharmacokinetic assessment of lorcaserin and metabolites, M1 ($HSO_3$-sulfamate) and M5 (N-carbamoyl glucuronide), were planned for the following timepoints:

- Blood samples: pre-dose (-15 min) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, and 120 hours post-dose
- Urine samples: pre-dose (-15 min) and at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-48, 48-72, 72-96, and 96-120 hours post-dose

**Group 5:**
10 mg of Lorcaserin were administered on day 1 no sooner than 1 hour after hemodialysis and on day 8 no sooner than 1 hour prior to hemodialysis. A detailed schematic of drug administration and sampling for group 5 is illustrated in Table 31. Blood samples were collected as follows:

- Non-dialysis phase: pre-dose (-15 min) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours post-dose for measurement of lorcaserin, M1 and M5.

- Dialysis phase: pre-dose (-15 min) and at 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours post-dose for measurement of lorcaserin, M1 and M5. The 2, 3, 4, and 5 hour timepoints, blood samples were to be collected at both the dialysis inflow ("arterial side") and outflow ("venous side") sites. At all other timepoints, blood collection was by simple venipuncture.
- Urine: not collected

**Table 31** Drug administration and drug sampling for group 5 during non-dialysis and dialysis phase

| | Check-in | Non-dialysis Phase | | | | Washout/Out-patient | Dialysis Phase | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | -1 | 1 | 2 | 3 | 4 | 5-7* | 8 | 9 | 10 | 11 |
| **Lorcaserin Dose** | | X | | | | | X | | | |
| **Dialysis** | | X | | | X | X | X | | | X |
| **PK sampling** | | X ——— | | | X | | X ——— | | | X |

*Check-in for Dialysis Phase was the evening of Day 7 (at least 10 hours before dosing on Day 8).

**Lorcaserin:**

The 90% confidence intervals for Cmax, AUC0-t and AUC0-inf were outside the defined "no effect" boundaries (0.700 to 1.43 for Cmax and 0.800 to 1.25 for AUC) the renal impairment groups, with the exception of Cmax for the mild impairment group which was within the "no effect" boundary. The geometric mean ratios of lorcaserin and 90% confidence intervals are shown in Table 32.

**Table 32** Geometric Mean Ratios of Lorcaserin Plasma Pharmacokinetic Parameters

| Pharmacokinetic Parameters | Geometric Mean Ratios of LSM (90% Confidence Intervals) of Lorcaserin Relative to Normal Renal Function Group (n=8 per Group) | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| $C_{max}$ | 0.991 (0.764, 1.29) | 0.697 (0.537, 0.904) | 0.686 (0.529, 0.891) |
| $AUC_{0-t}$ | 1.31 (1.01, 1.69) | 1.02 (0.791, 1.32) | 0.933 (0.723, 1.20) |
| $AUC_{0-inf}$ | 1.30 (1.01, 1.67) | 1.03 (0.806, 1.32) | 0.931 (0.727, 1.19) |

***Reviewer comment:***

*The sponsor did not provide geometric mean ratios for plasma concentrations of lorcaserin in end stage renal diseases patients compared to patients with normal renal function. These results are provided in Table 33 as results of the reviewer's analysis.*

**Table 33** Geometric Mean Ratios of Lorcaserin Plasma Pharmacokinetic Parameters (patients with end stage renal disease with and without dialysis)

| Pharmacokinetic Parameters | Geometric Mean Ratios of LSM (90% Confidence Intervals) of Lorcaserin Relative to Normal Renal Function Group (n=8 per Group) | |
|---|---|---|
| | ESRD (no dialysis) | ESRD (dialysis) |
| $C_{max}$ | 0.692 (0.51, 0.92) | 0.74 (0.55, 0.99) |
| $AUC_{0-t}$ | 1.21 (0.91, 1.60) | 1.10 (083, 1.47) |
| $AUC_{0-inf}$ | 1.64 (1.23, 2.19) | 1.32 (0.97, 1.79) |

**Table 34** Mean Lorcaserin Plasma and Urine Pharmacokinetic Parameters after a 10 mg Dose of Lorcaserin·HCl

| PK Parameters[a] | Mean Pharmacokinetic Parameters for Lorcaserin (n = 8 per Group) | | | | | |
|---|---|---|---|---|---|---|
| | Normal | Mild | Moderate | Severe | ESRD (Period 1)[b] | ESRD (Period 2)[b] |
| | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| $AUC_{0-t}$ (µg·hr/mL) | 0.482 (0.101) | 0.623 (0.088) | 0.515 (0.190) | 0.469 (0.172) | 0.618 (0.242) | 0.561 (0.217) |
| $AUC_{0-48}$ (µg·hr/mL) | 0.477 (0.094) | 0.594 (0.073) | 0.476 (0.163) | 0.423 (0.150) | 0.505 (0.194) | 0.472 (0.173) |
| $AUC_{0-inf}$ (µg·hr/mL) | 0.501 (0.104) | 0.644 (0.089) | 0.538 (0.190) | 0.486 (0.179) | 0.916 (0.460) | 0.710 (0.317) |
| $\%AUC_{0-inf}$ Extrapolated | 3.81 (1.57) | 3.36 (0.87) | 4.92 (2.68) | 3.59 (1.01) | 28.4 (15.3) | 19.2 (8.5) |
| $C_{max}$ (ng/mL) | 37.0 (8.7) | 36.3 (8.0) | 26.2 (8.3) | 26.4 (11.7) | 27.2 (12.7) | 28.3 (10.1) |
| $t_{max}$ (hr)[a] | 2.00 (1.00-3.00) | 4.50 (1.00-8.00) | 2.50 (2.00-3.00) | 3.00 (1.00-4.00) | 2.00 (1.00-6.00) | 2.65 (2.10-5.20) |
| Cl/F (L/hr) | 17.5 (3.4) | 13.3 (1.8) | 17.7 (6.6) | 19.7 (8.0) | 11.5 (5.7) | 14.1 (6.2) |
| $Cl_R$/F (L/hr) | 0.392 (0.202) | 0.533 (0.322) | 0.667 (0.228) | 0.657 (0.373) | NA | NA |
| $Cl_{NR}$/F (L/hr) | 17.1 (3.3) | 12.8 (1.6) | 17.0 (6.5) | 19.0 (7.8) | NA | NA |
| Vz/F (L) | 276 (53) | 248 (40) | 399 (132) | 401 (103) | 672 (355) | 646 (308) |
| $MRT_{inf}$ (hr) | 14.8 (2.2) | 18.0 (3.0) | 21.1 (2.8) | 21.7 (5.7) | 59.5 (27.9) | 42.6 (12.4) |
| $Ae_{0-120}$ (µg) | 185 (78) | 326 (156) | 327 (100) | 280 (140) | NA | NA |
| $fe_{0-120}$ | 0.0220 (0.0092) | 0.0386 (0.0185) | 0.0387 (0.0118) | 0.0332 (0.0166) | NA | NA |
| $t_{1/2z}$ (hr) | 11.0 (1.4) | 13.0 (1.9) | 15.9 (2.1) | 15.0 (3.6) | 43.8 (18.1) | 32.7 (8.8) |

a Median (minimum – maximum)
b Lorcaserin administered after hemodialysis in Period 1; lorcaserin administered ~1 hour before dialysis in Period 2.
NA: Not applicable

## <u>$HSO_3$-sulfamate metabolite (M1):</u>

A summary of the pharmacokinetic parameters of lorcaserin sulfamate in patients with varying degree of renal impairment is illustrated in Table 35.

**Table 35** Mean M1 Plasma and Urine Pharmacokinetic Parameters after a 10 mg Oral Dose of Lorcaserin·HCl

| Pharmacokinetic Parameters | Mean Pharmacokinetic Parameters for M1 (n = 8 per Group) | | | | | |
|---|---|---|---|---|---|---|
| | Normal | Mild | Moderate | Severe | ESRD (Period 1) | ESRD (Period 2) |
| | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| $AUC_{0-t}$ (µg·hr/mL) | 1.27 (0.50) | 1.94 (0.24) | 2.24 (1.08) | 7.85 (11.38) | 3.65 (1.02) | 8.77 (3.61) |
| $AUC_{0-inf}$ (µg·hr/mL) | 1.41 (0.56) | 2.31 (0.26) | 3.32 (1.56) | 23.6 (31.8) | ND | ND |
| % AUC Extrapolated | 10.1 (2.8) | 16.0 (5.3) | 30.3 (12.1) | 63.3 (16.5) | ND | ND |
| $C_{max}$ (ng/mL) | 33.6 (12.9) | 43.5 (10.9) | 34.1 (18.4) | 103 (178) | 67.6 (22.4) | 155 (59) |
| $MRT_{inf}$ (hr) | 50.0 (8.9) | 65.0 (11.4) | 105 (43) | 319 (165) | ND | ND |
| $t_{max}$ (hr)[a] | 2.50 (2.00-4.00) | 4.00 (3.00-16.0) | 4.00 (2.00-16.0) | 15.0 (4.00-48.0) | 72.0 (48.0-72.0) | 5.20 (4.20-5.20) |
| $t_{1/2z}$ (hr) | 36.2 (5.9) | 45.5 (10.0) | 70.8 (29.1) | 220 (114) | ND | ND |
| Ae (µg) | 216 (95) | 252 (102) | 233 (126) | 399 (839) | NA | NA |
| $fe_{0-120}$ | 0.0182 (0.0080) | 0.0212 (0.0085) | 0.0196 (0.0106) | 0.0335 (0.0705) | NA | NA |

***Reviewer comment:***

*The sponsor did not provide an analysis of the geometric mean ratios for the M1 metabolite.* Table 36*illustrates the geometric mean ratio of plasma lorcaserin sulfamate concentrations compared to patients with normal renal function. These results were obtained as part of the reviewer's analysis.*

**Table 36** Geometric Mean Ratios of Lorcaserin sulfamate Plasma Pharmacokinetic Parameters

| Pharmacokinetic Parameters | Geometric Mean Ratios of LSM (90% Confidence Intervals) of $HSO_3$-Lorcaserin Relative to Normal Renal Function Group (n=8 per Group) | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| $C_{max}$ | 1.33 (0.84, 2.10) | 0.97 (0.61, 1.53) | 1.71 (1.08, 2.71) |
| $AUC_{0-t}$ | 1.61 (1.07, 2.42) | 1.72 (1.15, 2.59) | 4.13 (2.75, 6.19) |
| $AUC_{0-inf}$ | 1.73 (1.06, 2.83) | 2.27 (1.39, 3.71) | 10.5 (6.47, 17.3) |

| Pharmacokinetic Parameters | Geometric Mean Ratios of LSM (90% Confidence Intervals) of $HSO_3$-Lorcaserin Relative to Normal Renal Function Group (n=8 per Group) | |
|---|---|---|
| | ESRD (no dialysis) | ESRD (dialysis) |
| $C_{max}$ | 1.99 (1.26, 3.15) | 4.50 (3.15, 6.44) |
| $AUC_{0-t}$ | 2.93 (1.95, 4.39) | 6.71 (4.58, 9.82) |
| $AUC_{0-inf}$ | NC | 75.6 (41.0, 139) |

NC: not calculated

**N-carbamoyl metabolite (M5):**

A summary of the pharmacokinetic parameters of lorcaserin sulfamate in plasma and urine, in patients with varying degree of renal impairment is illustrated in Table 37.

**Table 37** Mean ±SD Plasma and Urine pharmacokinetic parameters of N-carbamoyl lorcaserin after a 10 mg dose of lorcaserin in patients with varying degree of renal impairment.

| Pharmacokinetic Parameters | Mean Pharmacokinetic Parameters for M5 (n = 8 per Group) | | | | | |
|---|---|---|---|---|---|---|
| | Normal | Mild | Moderate | Severe | ESRD (Period 1) | ESRD (Period 2) |
| | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| $AUC_{0-t}$ (µg·hr/mL) | 0.345 (0.111) | 0.482 (0.136) | 0.944 (0.343) | 2.29 (1.70) | 9.53 (4.94) | 8.24 (4.02) |
| $AUC_{0-inf}$ (µg·hr/mL) | 0.475 (0.155) | 0.583 (0.146) | 1.10 (0.31) | 2.47 (1.72) | 11.2 (5.6) | 11.9 (6.0) |
| % AUC Extrapolated | 26.3 (51.6) | 17.7 (5.1) | 15.6 (10.7) | 8.46 (5.01) | 14.7 (7.3) | 26.9 (15.4) |
| $C_{max}$ (ng/mL) | 70.5 (22.3) | 62.4 (10.7) | 96.4 (23.7) | 153 (57) | 300 (139) | 231 (93) |
| $MRT_{inf}$ (hr) | 14.6 (10.9) | 13.5 (3.0) | 18.5 (4.6) | 20.0 (7.5) | 38.6 (9.5) | 59.1 (27.5) |
| $t_{max}$ (hr)[a] | 1.00 (1.00-2.00) | 2.00 (1.00-3.00) | 2.00 (1.00-3.00) | 2.50 (2.00-4.00) | 3.00 (2.00-6.00) | 3.10 (2.10-6.00) |

| Pharmacokinetic Parameters | Mean Pharmacokinetic Parameters for M5 (n = 8 per Group) | | | | | |
|---|---|---|---|---|---|---|
| | Normal | Mild | Moderate | Severe | ESRD (Period 1) | ESRD (Period 2) |
| | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| $t_{1/2z}$ (hr) | 12.2 (9.3) | 10.7 (2.6) | 15.4 (4.8) | 14.9 (5.5) | 25.7 (7.2) | 40.5 (20.2) |
| Ae (µg) | 8540 (1722) | 7160 (1375) | 8000 (1975) | 6300 (1249) | NA | NA |
| $fe_{0-120}$ | 0.476 (0.096) | 0.399 (0.077) | 0.446 (0.110) | 0.351 (0.070) | NA | NA |

***Reviewer comment:***
*The sponsor did not provide an analysis of the geometric mean ratios for the M5 metabolite. Table 38 illustrates the geometric mean ratio of plasma N-carbamoyl lorcaserin concentrations compared to patients with normal renal function. These results were obtained as part of the reviewer's analysis.*

**Table 38** Geometric Mean Ratios of N-carbamoyl Lorcaserin Plasma Pharmacokinetic Parameters

| Pharmacokinetic Parameters | Geometric Mean Ratios of LSM (90% Confidence Intervals) of N-carbamoyl glucuronide Relative to Normal Renal Function Group (n=8 per Group) | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| $C_{max}$ | 0.91 (0.68, 1.21) | 1.39 (1.04, 1.85) | 2.14 (1.61, 2.85) |
| $AUC_{0-t}$ | 1.45 (0.99, 2.13) | 2.74 (1.87, 4.02) | 5.96 (4.07, 8.74) |
| $AUC_{0-inf}$ | 1.37 (0.95, 1.98) | 2.51 (1.74, 3.62) | 5.07 (3.51, 7.31) |

| Pharmacokinetic Parameters | Geometric Mean Ratios of LSM (90% Confidence Intervals) of N-carbamoyl glucuronide Relative to Normal Renal Function Group (n=8 per Group) | |
|---|---|---|
| | ESRD (no dialysis) | ESRD (dialysis) |
| $C_{max}$ | 4.03 (3.03, 5.36) | 3.21 (2.33, 4.41) |
| $AUC_{0-t}$ | 26.2 (17.9, 38.5) | 23.0 (15.3, 34.4) |
| $AUC_{0-inf}$ | 24.2 (16.8, 35.0) | 25.0 (16.1, 39.0) |

## ANALYTICAL METHOD

Concentrations of Lorcaserin and $HSO_3$-lorcaserin in human plasma (heparin) were determined using high performance liquid chromatography (HPLC) with mass spectrometric detection. A set of 8 non-zero calibration standards, ranging from 0.500 ng/mL to 100 ng/mL for Lorcaserin and 1.00 ng/mL to 100 ng/mL for $HSO_3$-lorcaserin, were prepared. QC samples at 4 different concentrations: 1.50 ng/mL, 15.0 ng/mL, 75.0 ng/mL, and 500 ng/mL for lorcaserin and 3.00 ng/mL, 15.0 ng/mL, 75.0 ng/mL, and 500 ng/mL for $HSO_3$-lorcaserin were prepared.
Concentrations of Lorcaserin-beta-carbamoyl-glucuronide in human plasma (heparin) were determined using high performance liquid chromatography (HPLC) with mass spectrometric detection. A set of 8 non-zero calibration standards, ranging from 5.00 ng/mL to 1000 ng/mL was prepared. QC samples at 3 different concentrations: 15.0 ng/mL, 400 ng/mL and 800 ng/mL were prepared.

**Table 39** Results of Quality Control from the bioanalytical method

| | Calibration | | | Quality control (between batch) | |
|---|---|---|---|---|---|
| Analyte / Parameter | Curve range (ng/mL) | LLOQ (ng/mL) | %CV | %CV | %Bias |
| lorcaserin | 0.5-100 | 0.5 | 3.0% to 5.3% | 4.5% to 8.2% | -2.6% to 9.4% |
| $HSO_3$-lorcaserin (M1) | 1.00-100 | 1.00 | 2.4% to 6.8% | 3.7% to 6.3% | -1.0% to 3.8% |
| N-carbamoyl-glucuronide | 5.00-1000 | 5.00 | 3.9% to 6.5% | 5.4% to 7.5% | -4.0% to 1.9% |

## CONCLUSIONS

- AUC and $C_{max}$ of lorcaserin were not meaningfully affected by renal function.
- Lorcaserin sulfamate (M1) increased approximately 1.7-fold and N-carbamoyl-lorcaserin (M5) increased approximately 2.8-fold in patients with moderate renal impairment.
- Metabolites M1 and M5 increased by approximately 4-fold and 6-fold, respectively in patients with severe renal impairment, and increased 3-fold and 26-fold, respectively in patients with end-stage renal disease.
- Lorcaserin and M1 were not removed from the circulation by hemodialysis, and M5 was only modestly extracted (18%).
- Based on the exposure changes of M1 and M5 in moderate and severe renal impairment, and end stage renal disease, we agree with the sponsor's proposal that lorcaserin should be used with caution in patients with moderate renal impairment, and should not be used in patients with severe renal impairment or end-stage renal disease.

### *5.1.5 Pharmacokinetics in Hepatic Impaired Patients: APD356-017*

This hepatic impairment study was titled: "An Open Label, Single Dose Study of the Pharmacokinetic Properties of Lorcaserin in Subjects with Hepatic Impairment." The objective of this study was to evaluate the pharmacokinetic properties of lorcaserin in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function.

**STUDY DESIGN**

The hepatic impairment study was a multi-site, open-label, parallel-group study, which enrolled 24 subjects (detailed demographics see Table 30), with an age range between 18 to 75 years and a BMI of 27-45 $kg/m^2$. The hepatic function of the subjects was assessed using the Child-Pugh classification system with the parameters as illustrated in Table 28. Subjects received a 10 mg dose of lorcaserin after 10 hour fast.

**Table 40** The Modified Child-Pugh Classification System to Assess Liver Function

| Points Scored for Observed Findings | | | |
|---|---|---|---|
| **Parameter** | **1** | **2** | **3** |
| Encephalopathy grade[a] | none | 1 or 2 | 3 or 4 |
| Ascites | absent | slight | Moderate (tense) |
| Serum bilirubin, mg/dL | < 2 | 2 to 3 | > 3 |
| Serum albumin, g/dL | > 3.5 | 2.8 to 3.5 | < 2.8 |
| Prothrombin time, sec prolonged<br>*or*<br>INR[b] | < 4<br><br>< 1.7 | 4 to 6<br><br>1.7-2.3 | > 6<br><br>> 2.3 |

a Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

b INR, International normalized ratio

**Table 41** Summary of Subject Demographics by Group

| Demographics | Normal (N=8) | Mild (N=8) | Moderate (N=8) | Total (N=24) |
|---|---|---|---|---|
| Age (years) | | | | |
| Mean (SD) | 40.0 (16.48) | 47.8 (12.21) | 49.9 (5.36) | 45.9 (12.47) |
| Min-Max | 20 - 59 | 33 - 74 | 39 - 55 | 20 - 74 |
| Gender n (%) | | | | |
| Male | 7 (87.5%) | 3 (37.5%) | 7 (87.5%) | 17 (70.8%) |
| Female | 1 (12.5%) | 5 (62.5%) | 1 (12.5%) | 7 (29.2%) |
| Race n (%) | | | | |
| White or Caucasian | 5 (62.5%) | 7 (87.5%) | 5 (62.5%) | 17 (70.8%) |
| Black or African American | 1 (12.5%) | 1 (12.5%) | 2 (25.0%) | 4 (16.7%) |
| Hispanic or Latino | 2 (25.0%) | 0 (0.0%) | 1 (12.5%) | 3 (12.5%) |
| Weight (kg) at Screening | | | | |
| Mean (SD) | 97.3 (8.49) | 92.0 (18.48) | 94.0 (11.46) | 94.4 (13.07) |
| Min-Max | 84 - 107 | 75 - 123 | 75 - 115 | 75 - 123 |
| Height (cm) | | | | |
| Mean (SD) | 174.7 (5.41) | 166.3 (6.87) | 173.8 (9.61) | 171.6 (8.13) |
| Min-Max | 168 - 183 | 158 - 175 | 158 - 189 | 158 - 189 |
| BMI ($kg/m^2$) | | | | |
| Mean (SD) | 31.8 (1.56) | 33.2 (5.59) | 31.1 (2.22) | 32.0 (3.54) |
| Min-Max | 29.3 - 33.9 | 27.8 - 44.5 | 27.9 - 34.7 | 27.8 - 44.5 |

## SAMPLE COLLECTION

Blood and urine samples for pharmacokinetic assessment of lorcaserin and metabolite M1 ($HSO_3$-sulfamate) were planned for the following timepoints:

- Blood samples: pre-dose (-15 min), and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, and 120 hr post-dose
- Urine samples: pre-dose and at 0-4, 4-8, 8-24, 24- 48, 48-72, 72-96, and 96-120 hr post-dose

## PROTOCOL VIOLATIONS:

Six protocol violations occurred. Four were missed exit pregnancy test that were subsequently performed. The two other protocol violations included vital signs and one subject not collecting urine during the 8-24 hour period. Overall, these protocol violations are unlikely to affect the outcome of the study.

## RESULTS

A total of 24 subjects completed the study and were included in the PK and safety analyses.

**Lorcaserin:**

The 90% confidence intervals for Cmax, AUC0-t, and AUC0-inf were outside the defined "no effect" boundaries (0.800 to 1.25 for AUC and Cmax) for mild and moderate impairment groups. Total exposure was increased approximately 25% and 30% in subjects with mild and moderate renal impairment respectively. $C_{max}$ was approx. 8% and 15% decreased in subjects with mild and moderate hepatic impairment respectively. The geometric mean ratios of lorcaserin and 90% confidence intervals are shown in Table 7.

**Table 42** Mean Lorcaserin Plasma and Urine Pharmacokinetic Parameters after a 10 mg Dose of Lorcaserin·HCl

| Pharmacokinetic Parameters [a] | Group 1: Normal Hepatic Function | | Group 2: Mild Hepatic Impairment | | Group 3: Moderate Hepatic Impairment | |
|---|---|---|---|---|---|---|
| N | 8 | | 8 | | 8 | |
| | Mean | SD | Mean | SD | Mean | SD |
| $AUC_{0-t}$ (µg·h/mL) | 0.545 | 0.088 | 0.699 | 0.205 | 0.725 | 0.171 |
| $AUC_{0-48}$ (µg·h/mL) | 0.530 | 0.070 | 0.620 | 0.138 | 0.630 | 0.145 |
| $AUC_{0-inf}$ (µg·h/mL) | 0.566 | 0.087 | 0.719 | 0.208 | 0.751 | 0.170 |
| $\%AUC_{0-inf}$ Extrapolated | 3.92 | 1.31 | 2.96 | 1.06 | 3.61 | 1.71 |
| $C_{max}$ (ng/mL) | 35.8 | 5.7 | 33.0 | 5.3 | 31.7 | 9.5 |
| Cl/F (L/h) | 15.2 | 2.0 | 12.6 | 3.6 | 11.9 | 3.5 |
| $Cl_R$/F (L/h) | 0.397 | 0.211 | 0.382 | 0.183 | 0.751 | 0.612 |
| $Cl_{NR}$/F (L/h) | 14.8 | 1.9 | 12.6 | 3.6 | 11.2 | 3.1 |
| $V_z$/F (L) | 264 | 24 | 292 | 41 | 329 | 144 |
| $MRT_{last}$ (h) | 14.3 | 2.1 | 20.0 | 5.5 | 22.5 | 6.2 |
| $Ae_{0-120}$ (µg) | 218 | 102 | 268 | 124 | 518 | 336 |
| $fe_{0-120}$ | 0.0259 | 0.0121 | 0.0317 | 0.0147 | 0.0613 | 0.0398 |
| $t_{max}$ (h)[b] | 2.00 | 1.00 - 4.00 | 4.00 | 1.00 - 6.00 | 3.00 | 1.00 - 8.00 |
| $t_{1/2z}$ (h) | 12.2 | 1.5 | 16.9 | 4.1 | 19.4 | 6.9 |

a Source: Table 14.2.1.2
b Median (minimum – maximum)

Table 43 Geometric Mean Ratios of LSM (90% Confidence Intervals) of Lorcaserin Relative to Normal Hepatic Function Group (n=8 per Group)

| Pharmacokinetic Parameters[a] | Group 2: Mild Hepatic Impairment | Group 3: Moderate Hepatic Impairment |
|---|---|---|
| $AUC_{0-t}$ | 1.25 (1.01, 1.54) | 1.31 (1.06, 1.61) |
| $AUC_{0-inf}$ | 1.24 (1.01, 1.52) | 1.30 (1.06, 1.60) |
| $C_{max}$ | 0.922 (0.763, 1.11) | 0.857 (0.710, 1.04) |

**$HSO_3$-sulfamate metabolite (M1):**

The mean pharmacokinetic parameters for plasma and urine lorcaserin are illustrated in Table 44. The 90% confidence intervals for Cmax, AUC0-t, and AUC0-inf were outside the defined "no effect" boundaries (0.800 to 1.25 for AUC and Cmax) for mild and moderate impairment groups. Total exposure was increased approximately 34% and 42% in subjects with mild and moderate renal impairment respectively. $C_{max}$ was approx. 43% and 23% increased in subjects with mild and moderate hepatic impairment respectively. The geometric mean ratios of lorcaserin and 90% confidence intervals are shown in Table 45

**Table 44** Mean M1 Plasma and Urine Pharmacokinetic Parameters after a 10 mg Oral Dose of Lorcaserin·HCl

| Pharmacokinetic Parameters [a] | Group 1: Normal Hepatic Function | | Group 2: Mild Hepatic Impairment | | Group 3: Moderate Hepatic Impairment | |
|---|---|---|---|---|---|---|
| n | 8 | | 8 | | 8 | |
| | Mean | SD | Mean | SD | Mean | SD |
| $AUC_{0-t}$ (µg·h/mL) | 1.36 | 0.42 | 1.77 | 0.31 | 2.01 | 0.89 |
| $AUC_{0-inf}$ (µg·h/mL) | 1.63 | 0.48 | 2.05 | 0.39 | 2.23 | 0.97 |
| % AUC Extrapolated | 16.3 | 5.9 | 13.5 | 3.2 | 10.8 | 4.2 |
| $C_{max}$ (ng/mL) | 29.0 | 12.4 | 39.6 | 6.6 | 36.7 | 18.1 |
| $MRT_{last}$ (h) | 41.2 | 3.5 | 41.0 | 3.2 | 41.7 | 3.6 |
| $Ae_{0-120}$ (µg) | 192 | 91 | 261 | 23 | 397 | 176 |
| $t_{max}$ (h)[b] | 2.00 | 2.00 – 4.00 | 3.50 | 2.00 - 4.00 | 4.00 | 3.00 - 8.00 |
| $t_{1/2z}$ (h) | 46.6 | 9.0 | 40.9 | 5.3 | 34.6 | 6.0 |

a Source Table 14.2.2.2
b Median (minimum – maximum)

***Reviewer comment:***

*The sponsor did not provide an analysis of the geometric mean ratios for the M1 metabolite. Table 45 illustrates the geometric mean ratio of plasma lorcaserin sulfamate concentrations compared to patients with normal hepatic function. These results were obtained as part of the reviewer's analysis.*

**Table 45** Geometric Mean Ratios of LSM (90% Confidence Intervals) of $HSO_3$-sulfamate metabolite (M1) Relative to Normal Hepatic Function Group (n=8 per Group)

| Pharmacokinetic Parameters[a] | Group 2: Mild Hepatic Impairment | Group 3: Moderate Hepatic Impairment |
|---|---|---|
| $AUC_{0-t}$ | 1.34 (1.00-1.79) | 1.42 (1.06-1.89) |
| $AUC_{0-inf}$ | 1.31 (0.98-1.74) | 1.34 (1.00-1.78) |
| $C_{max}$ | 1.47 (1.04-2.07) | 1.23 (0.88-1.73) |

## ANALYTICAL METHOD

Concentrations of Lorcaserin and $HSO_3$-lorcaserin in human plasma (heparin) were determined using high performance liquid chromatography (HPLC) with mass spectrometric detection. A set of 8 non-zero calibration standards, ranging from 0.500 ng/mL to 100 ng/mL for Lorcaserin and 1.00 ng/mL to 100 ng/mL for $HSO_3$-lorcaserin, were prepared. QC samples at 4 different concentrations: 1.50 ng/mL, 15.0 ng/mL, 75.0 ng/mL, and 500 ng/mL for lorcaserin and 3.00 ng/mL, 15.0 ng/mL, 75.0 ng/mL, and 500 ng/mL for $HSO_3$-lorcaserin were prepared.

**Table 46** Results of Quality Control from the bioanalytical method

| | Calibration | | | Quality control (between batch) | |
|---|---|---|---|---|---|
| Analyte / Parameter | Curve range (ng/mL) | LLOQ (ng/mL) | %CV | %CV | %Bias |
| lorcaserin | 0.5-100 | 0.5 | 1.6% to 8.2% | 3.2% to 4.9% | -2.1% to 7.3% |
| $HSO_3$-lorcaserin (M1) | 1.00-100 | 1.00 | -2.8% to 2.6% | -2.0% to 1.6% | 2.1% to 8.4% |

## CONCLUSIONS

- The final population PK model estimates a between subject variability in clearance of 32.2% Based on this estimate and since clearance is correlated to AUC, a increase of 30% in AUC is acceptable.
- We agree with the sponsor's proposal of no dose adjustment in patients with mild or moderate hepatic impairment.
- The sponsor did not evaluate the effect of severe hepatic impairment on the pharmacokinetics of lorcaserin. A statement should be added to the labeling language that lorcaserin should not be used in patients with severe hepatic impairment since there is no data available in this patient population.

### *5.1.6 PK in Elderly vs. Adults Study: APD356-018*

This pharmacokinetic study was titled: "An Open-Label, Single-Dose Study of the Pharmacokinetic Properties of Lorcaserin in Obese or Overweight Elderly Subjects." the primary objective was to compare the single-dose pharmacokinetic (PK) parameters of lorcaserin in the obese or overweight Elderly (>65) to those obtained from the obese or overweight Adult (18-65). The secondary objective was to assess the safety and tolerability of a single oral dose of lorcaserin in obese or overweight Elderly (>65) and obese or overweight Adult (18-65) subjects.

**STUDY DESIGN**

This pharmacokinetic study was a phase 1, single-dose, open-label, parallel-group study. The study enrolled 12 adults in the age range of 18 to 65 years with a BMI of 27 to 45 $kg/m^2$ inclusive with no more than ¼ of subjects with a BMI < 30 $kg/m^2$ and 12 Elderly subjects older than 65 years, with a BMI of 27 to 45 $kg/m^2$, inclusive with no more than ¼ of the subjects with a BMI < 30 $kg/m^2$. Subjects received a 10 mg dose of lorcaserin under fasting conditions. The formulation used in this study was the final market image tablet. Tobacco users were allowed in the study; however, tobacco use was restricted in order to minimize interference with scheduled study procedures.

**SAMPLE COLLECTION**

Blood samples were collected at pre –dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, and 120 hours post-dose

**PROTOCOL VIOLATIONS**

The sponsor did not specify in the SAP how to impute sampling time deviations, especially, at which cut-off time the actual sampling time point will be used. The sponsor used the actual timepoints throughout the dataset for this deviation. These protocol deviations are unlikely to have an impact on the outcome of the study.

**RESULTS**

Demographics:
A total of 24 subjects were enrolled in the study, 12 in the Adult group and 12 in the Elderly group. Demographic data and baseline characteristics were summarized and tabulated by study period and are presented in Table 47.

**Table 47** Demographic and Baseline Characteristics (Safety Population and PK Population)

| | Adult (N=12) | Elderly (N=12) | Total (N=24) |
|---|---|---|---|
| Age (years) | - | - | - |
| Mean (SD) | 36.4 (8.97) | 68.2 (3.04) | 52.3 (17.49) |
| Min - Max | 21-55 | 65-74 | 21-74 |
| Gender n(%) | | | |
| Male | 6 (50%) | 9 (75%) | 15 (62.5%) |
| Female | 6 (50%) | 3 (25%) | 9 (37.5%) |
| Race n(%) | - | - | - |
| Asian | 0 | 1 (8.3%) | 1 (4.2%) |
| Black | 8 (66.7%) | 1 (8.3%) | 9 (37.5%) |
| North American Indian or Alaska Native | 1 (8.3%) | 0 | 1 (4.2%) |
| Caucasian | 3 (25%) | 10 (83.3%) | 13 (54.2%) |
| Weight (kg) at Screening | - | - | - |
| Mean (SD) | 98.53 (12.134) | 100.25 (17.955) | 99.39 (15.012) |
| Min - Max | 72.0-112.0 | 73.6-129.7 | 72.0-129.7 |
| Height (cm) at Screening | - | - | - |
| Mean (SD) | 171.13 (10.321) | 171.59 (8.150) | 171.36 (9.098) |
| Min - Max | 152.0-185.0 | 73.6-129.7 | 72.0-129.7 |
| BMI ($kg/m^2$) | - | - | - |
| Mean (SD) | 33.72 (3.870) | 33.89 (4.339) | 33.80 (4.022) |
| Min - Max | 28.9-40.2 | 27.0-41.8 | 27.0-41.8 |

Pharmacokinetic parameters following administration of a single dose of lorcaserin (10 mg) in adult or elderly subjects are summarized in Table 48.

**Table 48** Summary of Pharmacokinetic Parameters of Lorcaserin (Adult and Elderly subjects) - PK Population

| Parameter | Adult N=12 | | Elderly N=12 | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| $C_{max}$ (ng/mL) | 33.94 | 8.051 | 27.95 | 5.069 |
| $AUC_{0-t}$ (ng·h/mL) | 463.44 | 134.905 | 451.91 | 110.895 |
| $AUC_{0-inf}$ (ng·h/mL) | 481.93 | 138.952 | 467.93 | 113.531 |
| $AUC_{0-120}$ (ng·h/mL) | 476.95 | 137.483 | 462.67 | 111.559 |
| $t_{max}$ (h) | 2.00 | 0.603 | 2.504 | 1.245 |
| $\lambda_z$ (1/h) | 0.067 | 0.014 | 0.057 | 0.012 |
| $t_{1/2z}$ (h) | 10.686 | 2.169 | 12.927 | 4.022 |
| MRT (h) | 14.77 | 2.821 | 17.34 | 3.413 |
| CL/F (L/h) | 19.32 | 8.015 | 19.22 | 5.882 |
| Vz/F (L) | 281.98 | 68.811 | 344.18 | 89.303 |

The 90% confidence intervals when comparing adult and to elderly subjects with respect to lorcaserin $AUC_t$, and $AUC_\infty$ regimens were contained within the equivalence range of 0.80 to 1.25. $C_{max}$ was approximately 17% lower in elderly subjects compared to adult subjects. The 90% confidence interval of the geometric mean ratio with regards to $C_{max}$ was 71-97% (Table 49).

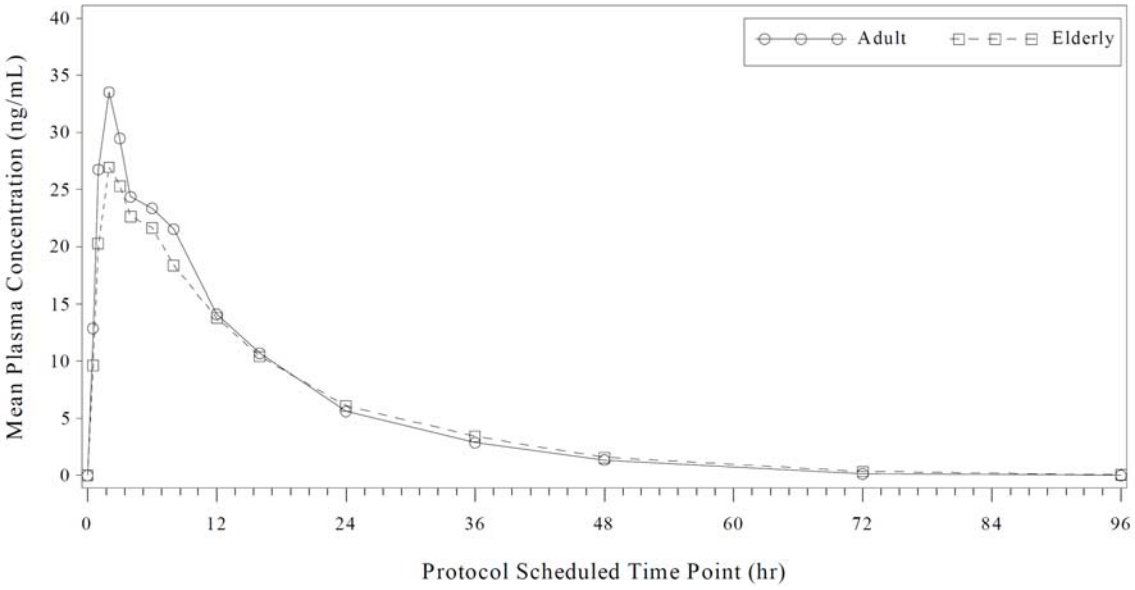
**Table 49** Analysis of Pharmacokinetic Parameters of Lorcaserin-PK Population

| Parameter | Geometric Mean | | Geometric Mean Ratio (Elderly/Adult) | |
|---|---|---|---|---|
| | Adult | Elderly | Ratio | 90%CI |
| $C_{max}$ (ng/mL) | 33.0 | 27.5 | 0.83 | 0.71-0.97 |
| $AUC_{0-t}$ (ng.hr/mL) | 442.8 | 437.8 | 0.99 | 0.80-1.22* |
| $AUC_{0-inf}$ (ng.hr/mL) | 460.7 | 453.5 | 0.98 | 0.80-1.22* |

*Note: Denotes 90% confidence interval fell within the recommended 0.80-1.25 limits of equivalence when analyzed on logarithmic scale

Mean plasma concentrations of lorcaserin over time are displayed by treatment period (Adults and Elderly) are displayed in Figure 31.

**Figure 31** Mean Plasma Concentration (ng/mL) of Lorcaserin over Time by Group – PK Population




## SPONSOR'S CONCLUSIONS

The mean apparent volume of distribution was approximately 1.2 fold higher for the elderly group compared to the adult group. This may explain the slight difference observed in Cmax for the elderly group compared to the adult group Both gender distribution and ethnic distribution differed between the Adult and Elderly groups, with a higher proportion of men (75% vs. 50%) and Caucasians (83% vs. 25%) in the Elderly group than in the Adult group. As presented in Table 5, mean Cmax was slightly higher in Adult and Elderly women (36.7 ± 8.5 ng/mL and 30.9 ± 3.6 ng/mL respectively) than in Adult and Elderly men (31.2 ± 7.2 ng/mL and 26.5 ng/mL respectively). Mean Cmax in Adult Caucasians was 32.1 ± 1.9 ng/mL, and 34.6 ± 9.9 ng/mL in Adult African Americans. These data suggest that the higher proportion of males in the elderly group could have contributed to the lower Cmax in this group, but the ethnic imbalance did not.

***Reviewer comment:***

- *Gender differences were not observed in the population PK analysis.*

- *No significant age effect was observed in the population PK analysis.*

## CONCLUSIONS

Since lower $C_{max}$ concentrations do not pose a safety concern, the AUC did not change significantly, and the population pharmacokinetic analysis did not reveal any significant effect of age on the pharmacokinetics, we agree with the sponsor's conclusion that no dose adjustment is necessary based on the patients age.

## ANALYTICAL METHOD

Plasma samples were [redacted] (b) (4) The extracted samples were analyzed by an HPLC equipped with an AB/MDS Sciex API 4000 mass spectrometer. Positive ions were monitored for lorcaserin in the multiple reaction monitoring (MRM) mode. A set of 8 non-zero calibration standards, ranging from 0.500 ng/mL to 100 ng/mL, and QC samples at 4 different concentrations: 1.50 ng/mL, 15.0 ng/mL, and 75.0 ng/mL were prepared.

| | | Calibration | | Quality control (between batch) | |
|---|---|---|---|---|---|
| Analyte / Parameter | Curve range (ng/mL) | LLOQ (ng/mL) | %CV | %CV | %Bias |
| Lorcaserin | 0.500-100 | 0.500 | -5.6% to 9.0% | 4.9% to 7.8% | 4.1% to 6.0% |

### *5.1.7 Food Effect Study: APD356-015*

The food effect study was titled: "An Open Label, Single Dose, Cross-over Study to Assess the Pharmacokinetic Properties of Lorcaserin in the Fed and Fasted State." The primary objective of this study was to evaluate the pharmacokinetic properties of a single oral dose of lorcaserin in the fed versus fasted state

## STUDY DESIGN

The food effect study was a single site, open-label, two-period crossover study, which enrolled 12 overweight or obese men or women, age range between 18 to 65 years and a BMI 27-45 kg/m$^2$. Lorcaserin was given as a 10 mg dose and the final market image tablet formulation was used during the conduct of this study. Washout between the doses was 7 ± 1 day. Under fed conditions subject were given a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800–1000 calories) meal. This meal contained approximately 150, 250, and 500–600 calories from protein, carbohydrate, and fat, respectively.

## SAMPLE COLLECTION

Blood samples were collected at pre –dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hr post-dose.

## RESULTS

Demographics
A total of 12 subjects were enrolled in the study. Demographic data and baseline characteristics were summarized and tabulated by study period and are presented in Table 50.

**Table 50** Demographic and Baseline Characteristics (Safety Population and PK Population)

| | Fed Period N=12 | Fasted Period N=12 | Total N=12 |
|---|---|---|---|
| Age (years) | | | |
| Mean (SD) | 40.03 (6.80) | 40.03 (6.80) | 40.03 (6.80) |
| Min - Max | 29-53 | 29-53 | 29-53 |
| Gender n(%) | | | |
| Male | 6 (50%) | 6 (50%) | 6 (50%) |
| Female | 6 (50%) | 6 (50%) | 6 (50%) |
| Race n(%) | | | |
| Black | 5 (41.7%) | 5 (41.7%) | 5 (41.7%) |
| Hispanic or Latino | 1 (8.3%) | 1 (8.3%) | 1 (8.3%) |
| Caucasian | 4 (33.3%) | 4 (33.3%) | 4 (33.3%) |
| Weight (kg) at Screening | | | |
| Mean (SD) | 94.2 (10.96) | 94.2 (10.96) | 94.2 (10.96) |
| Min - Max | 82-115 | 82-115 | 82-115 |
| Height (cm) at Screening | | | |
| Mean (SD) | 168.1 (10.46) | 168.1 (10.46) | 168.1 (10.46) |
| Min - Max | 152-182 | 152-182 | 152-182 |
| BMI (kg/m$^2$) | | | |
| Mean (SD) | 33.3 (2.24) | 33.3 (2.24) | 33.3 (2.24) |
| Min - Max | 31-38 | 31-38 | 31-38 |

Pharmacokinetic parameters following administration of a single dose of lorcaserin (10 mg) with and without food are summarized in Table 51.

**Table 51** Summary of Pharmacokinetic Parameters of Lorcaserin by Group - PK Population

| Parameter | Fed Period N=12 | | Fasted Period N=12 | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| $C_{max}$ (ng/mL) | 33.53 | 7.982 | 30.63 | 6.146 |
| $AUC_{0-t}$ (ng·h/mL) | 447.88 | 73.112 | 433.27 | 94.064 |
| $AUC_{0-inf}$ (ng·h/mL) | 462.34 | 74.343 | 449.85 | 95.084 |
| $AUC_{0-96}$ (ng·h/mL) | 458.20 | 73.306 | 444.13 | 94.296 |
| $t_{max}$(h) | 3.335 | 1.230 | 2.167 | 0.389 |
| $\lambda_z$ (1/h) | 0.065 | 0.013 | 0.065 | 0.014 |
| $t_{1/2z}$ (h) | 11.113 | 2.698 | 11.142 | 2.417 |
| MRT (h) | 15.35 | 2.948 | 15.37 | 2.663 |
| CL/F (L/h) | 18.62 | 3.153 | 19.56 | 4.631 |
| Vz/F (L) | 296.42 | 80.883 | 307.36 | 74.807 |

The 90% confidence intervals for comparing non-fasting and fasting regimens with respect to lorcaserin $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ regimens were contained within the equivalence range of 0.80 to 1.25.

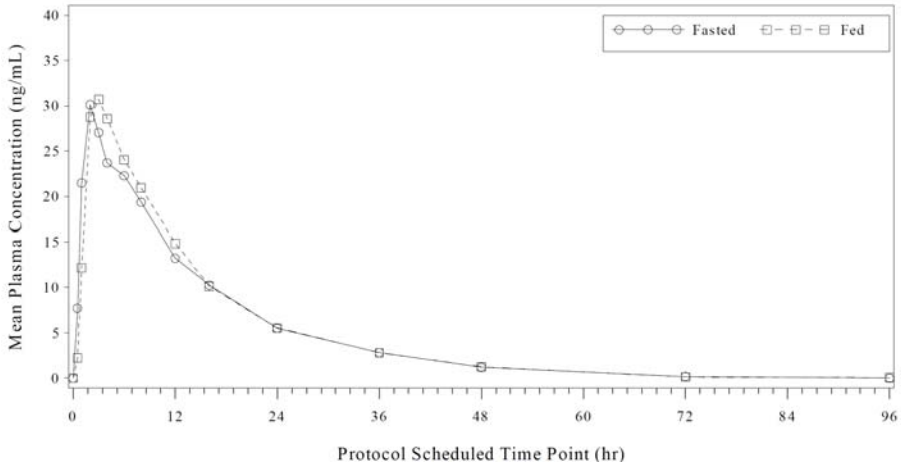
**Table 52** Analysis of Pharmacokinetic Parameters of Lorcaserin-PK Population

| Parameter | Geometric Mean | | Geometric Mean Ratio (Fed/Fasted Periods) | |
|---|---|---|---|---|
| | Fed Period | Fasted Period | Ratio | 90%CI |
| $C_{max}$ (ng/mL) | 32.7 | 30.1 | 1.086 | 0.995, 1.186* |
| $AUC_{0-t}$ (ng.hr/mL) | 442.4 | 423.3 | 1.045 | 0.976, 1.119* |
| $AUC_{0-inf}$ (ng.hr/mL) | 456.8 | 440.0 | 1.038 | 0.974, 1.107* |

Note: *Denotes 90% confidence interval fell within the recommended 0.80-1.25 limits of equivalence when analyzed on logarithmic scale.
Source: Table 14.2.3

Mean plasma concentrations of lorcaserin over time are displayed by treatment period (Fed or Fasted) are displayed in Figure 32.

**Figure 32** Mean Plasma Concentration (ng/mL) of Lorcaserin over Time by Group – PK Population




## CONCLUSIONS

Lorcaserin tables can be given without regard to meals.

## ANALYTICAL METHOD

Plasma samples were [redacted] (b) (4) resulting in one set of extracts for Lorcaserin and 7-OH Lorcaserin and one set of extracts for $HSO_3$-lorcaserin. The extracted samples were analyzed by an HPLC equipped with an AB/MDS Sciex API 4000 mass spectrometer. Positive ions were monitored for Lorcaserin and 7-OH Lorcaserin in the multiple reaction monitoring (MRM) mode. Negative ions were monitored for $HSO_3$- Lorcaserin in the multiple reaction monitoring (MRM) mode. A set of 8 non-zero calibration standards, ranging from 0.500 ng/mL to 100 ng/mL, and QC samples at 4 different concentrations: 1.50 ng/mL, 15.0 ng/mL, 75.0 ng/mL, and 500 ng/mL were prepared.

| | | Calibration | | Quality control (between batch) | |
|---|---|---|---|---|---|
| Analyte / Parameter | Curve range (ng/mL) | LLOQ (ng/mL) | %CV | %CV | %Bias |
| Lorcaserin | 0.500-100 | 0.500 | 3.5% to 8.1% | 5.4% to 7.3% | 0.0% to 6.0% |

### *5.1.8 Dextromethorphan DDI Study: APD356-012*

The in-vivo drug-drug interaction study was titled: "Drug-Interaction Study Evaluating the Effects of Lorcaserin on Dextromethorphan in Healthy Adult Volunteers under Fasting Conditions". The primary objective of this study was to determine the impact of multiple doses of lorcaserin, a potential CYP2D6 inhibitor, on the plasma levels of a single 60 mg dose of dextromethorphan (CYP2D6 substrate) in healthy volunteers. The secondary objectives were to evaluate the safety and tolerability of multiple doses of lorcaserin and to evaluate the pharmacokinetic properties of lorcaserin when administered orally at a 10 mg BID dose. This study was a repeat study since the DDI study (APD356-008) with similar design was not conducted with the final market image formulation and since twelve subjects elected to withdraw consent prior to receiving the second dose of Lorcaserin out of 24 subjects enrolled in the previous study.

**STUDY DESIGN**

This DDI study was an open-label, single- and multiple-dose, randomized, 1-sequence DDI study, which enrolled 24 non-smoking men or women in the age range of 19 to 55 years. Subjects weighted at least 52 kg for males and 45 kg for females and within 20% of their ideal weights. Lorcaserin was administered as the clinical tablet formulation (10 mg). The clinical tablet formulation differs from the final market formulation only by color. Dextromethorphan (60 mg) was administered as Robitussin® Cough Long-Acting; 15 mg/5 mL. The difference between the long acting and regular Robitussin formulation is the purely based on differences in dosing (20 mg q2h to q4h for regular and 30 mg q6h to q8h for long acting). Dextromethorphan was given as a single 60 mg dose on Day 1 followed by a 7-day washout period. Lorcaserin was then given twice a day (10 mg BID) for 4 consecutive days (Days 8 - 11). Dextromethorphan was given as a single dose of 60 mg on Day 10 and sampled out to 48 hours. The study was conducted under fasting conditions.

**SAMPLE COLLECTION:**

Dextromethorphan:

- On Days 1 and 10, blood samples were taken before the dextromethorphan dose, and at the following times thereafter: 0.5, 1, 1.333, 1.667, 2, 2.333, 2.667, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 12, 16, 24, 36, and 48 hours postdose

Lorcaserin:

- Blood samples (2 mL) were collected on Day 8 prior to the evening lorcaserin dose, and on Days 9 and 10 before the morning and evening lorcaserin doses

**PROTOCOL VIOLATIONS:**

- There were 18 sampling time deviations during this study.

***Reviewer comment:***

- *The sponsor did not specify in the SAP how to impute sampling time deviations, especially, at which cut-off time the actual sampling time point will be used. The sponsor included the planned and actual timepoints throughout the dataset. It is unclear whether the sponsor used actual or planned timepoint for the analysis. This however only represents ~ 4% of the samples. These protocol deviations are unlikely to have an impact on the outcome of the study.*

## RESULTS

Demographics

A total of 24 subjects were enrolled in the study. 23 subjects completed the study. One subject withdrew consent from the study on Day 9 in association with an AE of moderate headache. Demographic data and baseline characteristics were summarized and tabulated by study period and are presented in Table 53. Subject 7 and Subject 22 were identified as poor metabolizers and were excluded from the summary statistics and the statistical comparisons.

**Table 53** Demographic and Baseline Characteristics

| Trait | | Total |
|---|---|---|
| Gender | Female | 12 |
| | Male | 12 |
| Race | Asian | 2 |
| | Black | 3 |
| | Caucasian | 18 |
| | Hispanic | 1 |
| Age (years) | Mean | 35 |
| | SD | 12 |
| | Minimum | 21 |
| | Median | 34 |
| | Maximum | 51 |
| | N | 24 |
| Weight (kg) | Mean | 73.9 |
| | SD | 10.4 |
| | Minimum | 50.8 |
| | Median | 74.4 |
| | Maximum | 92.1 |
| | N | 24.0 |
| Height (cm) | Mean | 170.0 |
| | SD | 10.1 |
| | Minimum | 150.0 |
| | Median | 170.0 |
| | Maximum | 191.0 |
| | N | 24.0 |

Pharmacokinetic parameters for dextromethorphan without or with coadministration of lorcaserin are summarized in Table 54.

**Table 54** Arithmetic Mean (SD) Pharmacokinetic Parameters for Dextromethorphan after Dosing of Dextromethorphan alone or in Combination with Lorcaserin (Normal Metabolizer Population)

| | Dextromethorphan Alone (Day 1) | Lorcaserin + Dextromethorphan (Day 10) |
|---|---|---|
| **Pharmacokinetic Parameters** | **Mean ± SD (N)** | **Mean ± SD (N)** |
| $C_{max}$ (ng/mL) | 6.43 ± 7.77 | 9.15 ± 8.92 |
| | (22) | (21) |
| $t_{max}$ (hr) | 2.17 (1.00, 3.50) | 3.00 (1.67, 4.53) |
| | (22) | (21) |
| $AUC_{0-t}$ (ng*hr/mL) | 69.97 ± 141.8 | 109.0 ± 175.7 |
| | (22) | (21) |
| $AUC_{0-inf}$ (ng*hr/mL) | 77.40 ± 172.2 | 122.4 ± 227.4 |
| | (22) | (21) |
| $t_{1/2}$ (hr) | 8.44 ± 2.76 | 9.61 ± 3.20 |
| | (22) | (21) |
| $K_{el}$ (1/hr) | 0.0874 ± 0.0194 | 0.0768 ± 0.0166 |
| | (22) | (21) |
| AUCR | 0.976 ± 0.0352 | 0.968 ± 0.0447 |
| | (22) | (21) |
| MR | 0.516 ± 0.595 | NC |
| | (22) | NC |

$t_{max}$ is presented as Median (Minimum, Maximum)
Subjects 7 and 22 were identified as poor metabolizers and were excluded from summary statistics.
Source: Table 14.2.8 and Table 14.2.9
NC: Not calculated

In the normal metabolizer population, the rate of exposure was approx. 76% higher when dextromethorphan was administered concomitantly with lorcaserin. The 90% confidence interval of the geometric mean ratios range from 146.7 to 212.5%. The extent of exposure ($AUC_{inf}$) was 106% higher when dextromethorphan was administered concomitantly with lorcaserin. The 90% confidence interval of the geometric mean ratios range from 174.4 to 244%.

**Table 55** Analysis of Pharmacokinetic Parameters of dextromethorphan when dextromethorphan was administered alone or when dextromethorphan was administered concomitantly with lorcaserin (Normal metabolizer population)

| | Geometric Means | | | |
|---|---|---|---|---|
| **Parameter** | **Lorcaserin + Dextromethorphan (Day 10)** | **Dextromethorphan Alone (Day 1)** | **% Ratio of Geometric Means** | **90% CI for Ratio of Geometric Means** |
| $C_{max}$ (ng/mL) | 6.937 | 3.928 | 176.60 | (146.73 - 212.55 ) |
| $AUC_{0-t}$ (ng*hr/mL) | 68.274 | 33.365 | 204.63 | (172.73 - 242.41 ) |
| $AUC_{0-inf}$ (ng*hr/mL) | 70.564 | 34.201 | 206.32 | (174.39 - 244.10 ) |

Pharmacokinetic parameters for dextrorphan without or with coadministration of lorcaserin are summarized in Table 56.

**Table 56** Arithmetic Mean (SD) Pharmacokinetic Parameters for Dextromethorphan after Dosing of Dextromethorphan alone or in Combination with Lorcaserin (Normal Metabolizer Population)

| | Dextromethorphan Alone (Day 1) | Lorcaserin + Dextromethorphan (Day 10) |
|---|---|---|
| **Pharmacokinetic Parameters** | **Mean ± SD (N)** | **Mean ± SD (N)** |
| $C_{max}$ (ng/mL) | 11.7 ± 5.21 | 10.8 ± 4.76 |
| | (22) | (21) |
| $t_{max}$ (hr) | 1.67 (1.00, 2.67) | 2.00 (1.33, 4.00) |
| | (22) | (21) |
| $AUC_{0-t}$ (ng*hr/mL) | 59.62 ± 26.24 | 62.39 ± 22.95 |
| | (22) | (21) |
| $AUC_{0-inf}$ (ng*hr/mL) | 62.86 ± 27.98 | 66.06 ± 24.82 |
| | (22) | (21) |
| $t_{1/2}$ (hr) | 5.00 ± 5.68 | 5.09 ± 4.59 |
| | (22) | (21) |
| $K_{el}$ (1/hr) | 0.200 ± 0.0668 | 0.171 ± 0.0502 |
| | (22) | (21) |
| AUCR | 0.945 ± 0.0393 | 0.945 ± 0.0343 |
| | (22) | (21) |

In the normal metabolizer population, the rate and extent of exposure of dextrorphan was similar when dextromethorphan was administered concomitantly with lorcaserin.

**Table 57** Analysis of Pharmacokinetic Parameters of dextrorphan when dextromethorphan was administered alone or when dextromethorphan was administered concomitantly with lorcaserin (Normal metabolizer population)

| | Geometric Means | | | |
|---|---|---|---|---|
| **Parameter** | **Lorcaserin + Dextromethorphan (Day 10)** | **Dextromethorphan Alone (Day 1)** | **% Ratio of Geometric Means** | **90% CI for Ratio of Geometric Means** |
| $C_{max}$ (ng/mL) | 10.038 | 10.579 | 94.88 | ( 85.02 - 105.90 ) |
| $AUC_{0-t}$ (ng*hr/mL) | 59.122 | 53.890 | 109.71 | ( 98.61 - 122.06 ) |
| $AUC_{0-inf}$ (ng*hr/mL) | 62.514 | 57.079 | 109.52 | ( 98.59 - 121.67 ) |

## ANALYTICAL METHOD

Lorcaserin:

Plasma samples were [redacted](b) (4). The extracted samples were analyzed by an HPLC equipped with an [redacted](b) (4) mass spectrometer. Positive ions were monitored for lorcaserin in the multiple reaction monitoring (MRM) mode. A set of 8 non-zero calibration standards, ranging from 0.500 ng/mL to 100 ng/mL, and QC samples at 3 different concentrations: 1.50 ng/mL, 15.0 ng/mL, 75.0 ng/mL and 500ng/mL were prepared.

| Analyte / Parameter | Calibration Curve range (ng/mL) | Calibration LLOQ (ng/mL) | Quality control (between batch) %CV | Quality control (between batch) %CV | Quality control (between batch) %Bias |
|---|---|---|---|---|---|
| Lorcaserin | 0.500-100 | 0.500 | 3.9% to 9.6% | 6.7% to 9.0% | 0.5% to 4.0% |

Dextromethorphan & dextrorphan (unconjugated):

The dextromethorphan and dextrorphan and the internal standards were extracted from samples by (b) (4). After evaporation under nitrogen, the residue was reconstituted and analyzed using liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS). Procedures (SOPs) and the validated method. Samples were originally analyzed singly. At a minimum, each batch included a calibration curve, a matrix blank, a control zero (matrix blank containing internal standard), a reagent blank, and duplicate quality control (QC) samples at three concentrations within the calibration range. Calibration curves for dextromethorphan ranged from 0.0100 to 10.0 ng/mL and dextrorphan (unconjugated) ranged from 0.300 to 300 ng/mL.

| Analyte / Parameter | Calibration Curve range (ng/mL) | Calibration LLOQ (ng/mL) | Quality control (between batch) %CV | Quality control (between batch) %CV | Quality control (between batch) %Bias |
|---|---|---|---|---|---|
| Dextromethorphan | 0.0100 – 10.0 | 0.0100 | 2.4% to 5.3% | 2.7% to 5.9% | -1.2% to 9.0% |
| Dextrorphan | 0.300-300 | 0.300 | 2.2% to 4.9% | 2.4% to 4.9% | -3.3% to 6.0% |

***REVIEWER COMMENT:***

- *The study results are acceptable*

5.2 INDIVIDUAL STUDY REVIEWS (IN-VITRO)

*In-Vivo* metabolism of Lorcaserin: Study PDR-06-012

**TITLE:** "*In Vivo Metabolism of [$^{14}$C] APD356 in Humans*."

**OBJECTIVE:** The objective of this study was identification and quantitation of the circulatory and urinary metabolites of [$^{14}$C]lorcaserin

**EXPERIMENT METHODS:** Aliquots of plasma from 6 human subjects were pooled (0.3-72 hr) proportionally to time intervals to obtain a single sample representative of the entire time range (e.g. $AUC_{0\text{-}72h}$). Urine samples were pooled for individual subjects. As a complimentary experiment to the mass spectral analysis for the identification of the glucuronides, potential glucuronide containing metabolites were incubated in the presence of β-glucuronidase. Additionally, phase I oxidative metabolites of lorcaserin were incubated in microsomes (human, monkey mouse and rat liver microsomes) in the presence of UDGPA and alamethicin. Samples were analyzed using a LC/MS/MS system with a β-ram radioactivity detector.

**RESULTS:** This study identified 10 metabolites. These ten metabolites accounted for more than 90% of radioactivity excreted in urine, whereas the three un-identified metabolites accounted for less than 10% of radioactivity excreted in urine. M5 (N-carbamoyl glucuronide) was found to the major metabolite in urine, representing approximately 36% of the total dose. While M1 (lorcaserin sulfamate) was the major metabolite in plasma ( approximately 36% of radioactivity in plasma), it was only a minor metabolite in urine, representing approximately 3% of dose. In addition to M5 (N-carbamoyl glucuronide), only one urinary metabolite, M8 (I-carboxyl glucuronide) was excreted in urine greater than 10% of dose.

**CONCLUSIONS:** Lorcaserin is metabolized to 10 identified and 3 unidentified metabolites. The ten identified metabolites make up 90% of the radioactivity in urine. The majority of a single radioactively labeled dose of lorcaserin was recovered in urine (92.3%) and feces (2.2%).

***Reviewer comment:*** *The study is acceptable.*

*In-Vitro* Protein Binding Measurement: Study PDR-05-208

**TITLE:** "*In vitro* determination of plasma protein binding of lorcaserin in human, rat, mouse, monkey, rabbit and dog plasma using equilibrium dialysis."

Note: The animal data were not reviewed.

**OBJECTIVE:** To determine the fraction of protein binding *in vitro* for lorcaserin in human male and female.

**EXPERIMENT METHODS:** By using the equilibrium dialysis method, lorcaserin plasma binding fractions were measured at 0.1 μM, 1.0 μM and 10.0 μM in human male and female plasma samples.

**RESULTS:** At concentrations at 0.1 μM, 1.0 μM and 10.0 μM, the fractions of lorcaserin bound to the human male plasma are 70.1 ± 0.36, 69.3 ± 1.65, and 75.1 ± 4.55 respectively, and the fractions bound to the human female plasma are 71.3 ± 0.69, 71.2 ± 1.15, and 72.9 ± 5.54, respectively.

**CONCLUSIONS:** Lorcaserin is moderately bound to plasma protein (approximately 70%).

***Reviewer comment:*** *The results are acceptable. The sponsor also measured the binding fractions using ultrafiltration method, and the results ($f_b$~99%) after correcting for membrane binding of lorcaserin (~25%) are consistent with above results using equilibrium dialysis method.*

*In-Vitro* Partition Coefficient (Whole Blood/Plasma) Measurement: Study PDR-08-056

**TITLE:** "*In vitro* determination of human whole blood to plasma partition coefficient of lorcaserin."

**OBJECTIVE:** To determine the *in vitro* partitioning of lorcaserin between human whole blood and plasma.

**EXPERIMENT METHODS:** Lorcaserin was incubated with whole blood from a total of six male and female human donors. Whole blood to plasma partition coefficient of lorcaserin was determined at three different final concentrations (0.1, 1.0, and 10.0 μM).

**RESULTS:** At concentrations at 0.1 μM, 1.0 μM and 10.0 μM, the mean values of whole blood to plasma partition coefficient of lorcaserin from six donors were 0.63, 0.64, and 0.63, respectively. The mean values were 0.61, 0.61 and 0.62 for male donors, and 0.66, 0.66, and 0.64 for female donors, respectively.

**CONCLUSIONS:** Lorcaserin is mainly distributed to human plasma, based on the human whole blood to plasma partition coefficient is approximately 0.63. There is no gender difference in the whole blood to plasma partition coefficient.

***Reviewer comment:*** *The results are acceptable.*

Permeability and P-glycoprotein (P-gp) Interaction Potential of Lorcaserin: Study PDR-08-160

**TITLE:** "Permeability and P-glycoprotein (P-gp) interaction potential of lorcaserin."

**OBJECTIVE:** To determine the *in vitro* permeability of lorcaserin and evaluate whether lorcaserin is a substrate and/or an inhibitor of P-gp in Caco-2 monolayers.

**EXPERIMENT METHODS:** Lorcaserin permeability coefficient of the apical to basolateral side ($P_{app(A\ to\ B)}$) and permeability of the basolateral to apical side ($P_{app\ (B\ to\ A)}$) were measured at the concentrations of 1, 10, and 50 μM lorcaserin with or without the P-gp inhibitor, cyclosporin A (5 μM). The bidirectional permeability of digoxin (25 nM) across Caco-2 cell monolayers was determined without and with either cyclosporin A (5 μM) or lorcaserin (100 μM). Permeability of testosterone and mannitol were also measured as reference controls for high permeability and low permeability drugs.

| Test Compound | $P_{app(AtoB)}$[a] ($\times 10^{-6}$ cm/sec) | $P_{app(BtoA)}$[a] ($\times 10^{-6}$ cm/sec) | Efflux Ratio[b] |
|---|---|---|---|
| Lorcaserin (1 μM) | 28.1 ± 3.69 | 33.3 ± 2.07 | 1.19 |
| Lorcaserin (1 μM) + Cyclosporin A (5 μM) | 28.9 ± 2.91 | 32.6 ± 2.75 | 1.13 |
| Lorcaserin (10 μM) | 31.3 ± 2.74 | 37.3 ± 3.69 | 1.19 |
| Lorcaserin (10 μM) + Cyclosporin A (5 μM) | 31.7 ± 1.43 | 34.5 ± 3.36 | 1.09 |
| Lorcaserin (50 μM) | 34.5 ± 2.73 | 41.9 ± 2.15 | 1.21 |
| Lorcaserin (50 μM) + Cyclosporin A (5 μM) | 33.9 ± 2.04 | 35.6 ± 2.88 | 1.05 |
| **Positive Control of Inhibition** | | | |
| $^3$H-digoxin (25 nM) | 0.485 ± 0.248 | 11.9 ± 1.52 | 24.5 |
| $^3$H-digoxin (25 nM) + Cyclosporin A (5 μM) | 1.19 ± 0.244 | 2.48 ± 0.285 | 2.08 |
| $^3$H-digoxin (25 nM) + Lorcaserin (100 μM) | 0.416 ± 0.0936 | 11.4 ± 1.36 | 27.4 |
| **High & Low Permeability Reference Control** | | | |
| $^3$H-mannitol (low permeability) | 0.205 ± 0.0602 | NA[c] | NA |
| $^3$H-testosterone (high permeability) | 27.0 ± 1.31 | NA | NA |

[a] Result for each condition is presented as mean ± standard deviation of four separate experiments conducted in triplicates.

[b] Efflux ratio = $P_{app(BtoA)}/P_{app(AtoB)}$.

[c] NA: not applicable (permeability only A to B direction)

**RESULTS:**
The efflux ratios ($P_{app\ (B\ to\ A)}/P_{app(A\ to\ B)}$ of lorcaserin at three concentrations were less than 2. The efflux ratios with and without cyclosporin A are similar. Lorcaserin $P_{app(A\ to\ B)}$ was comparable to that of testosterone.

**CONCLUSIONS:** Lorcaserin is high permeable across Caco-2 cell monolayer and appear not to be a substrate or an inhibitor of P-gp.

***Reviewer comment:*** *The results are acceptable. According the paper (Volpe et al., Clinical Research and Regulatory Affairs, 2007 24(1): 39-41), over 20 model drugs were classified based on absorption fraction (fa) and permeability: for low-permeability drugs (fa 0% - 89%) the $P_{app}$ values were less than 5.0 x $10^{-6}$ cm/sec, and for high permeability drugs (fa 90% -100%), the $P_{app}$ values were greater than 14.0 x $10^{-6}$ cm/sec. Lorcaserin is high permeable across Caco-2 cell monolayer.*

Lorcaserin Oxidative Metabolism by Human Cytochrome P450 (CYP) and Flavin-Containing Monooxygenase (FMO) Enzymes: Study PDR-08-281

**TITLE:** "Identification of human CYP and FMO enzymes responsible for the oxidative metabolism of lorcaserin."

**OBJECTIVE:** To identify human CYP and FMO enzymes involved in the metabolism of lorcaserin.

**EXPERIMENT METHODS:** (1) Evaluate the range of metabolism of lorcaserin in sixteen individual human liver microsomes and a pooled sample of renal microsomes. (2) Determine the correlation coefficient of lorcaserin metabolism versus CYP activity in these liver microsomes. (3) Use of a human recombinant CYP (rCYP) and FMO (rFMO) enzymes as well as CYP- and FMO-

enzyme selective chemical inhibitors to identify the enzyme responsible for the metabolism of lorcaserin.

**RESULTS:** There were four primary oxidative metabolites formed in human liver microsomes, including N-hydroxylorcaserin, 7-hydroxylorcaserin, 5-hydroxylorcaserin and 1-hydroxylorcaserin. In human liver microsomes, the formation of 7-hydroxylorcaserin demonstrated a correlation with CYP2D6 mediated bufuralol 1'-hydroxylation ($r^2$ = 0.696-0.819). The formation of N-hydroxylorcaserin had a correlation with CYP2B6 mediated (S)-mephenytoin N-demethylation ($r^2$ = 0.674). The formation of 1-hydroxylorcaserin had a correlation with CYP3A4 mediated testosterone 6β-hydroxylation (r2 = 0.68). The 5-hydroxylorcaserin had a correlation with CYP1A2 mediated phenacetin-O-deethylation ($r^2$ = 0.531) and CYP3A4 mediated testosterone 6β-hydroxylation (r2 = 0.481). In human liver microsomes, two CYP nonspecific inhibitors including 1-aminobenotriazole (1-ABT) and N-benzylimidazole inhibited 75 -100% of formation of N-hydroxylorcaserin, 7-hydroxylorcaserin, 5-hydroxylorcaserin and 1-hydroxylorcaserin. The $IC_{50}$ of furafylline for CYP1A2 mediated 5-hydroxylorcaserin is 1.914 μM. The $IC_{50}$ of quinidine for CYP2D6 mediated 7-hydroxylorcaserin is 0.213 μM. The $IC_{50}$ of ketoconazole for CYP3A4 mediated 1-hydroxylorcaserin is 0.281 μM.
Unlike human liver microsomes, human renal microsomes produced only N-hydroxylorcaserin metabolite. Using recombinant enzymes, the study demonstrated that N-hydroxylorcaserin was formed by multiple CYP enzymes such as CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and FMO1. 7-Hydroxylorcaserin was formed by CYP2D6 and CYP3A4. 5-Hydroxylorcaserin was formed by CYP1A2, CYP2D6, and CYP3A4. 1-Hydroxylorcaserin was formed by only CYP3A4.

**CONCLUSIONS:** Lorcaserin is metabolized by multiple CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) and FMO1.

***Reviewer comment::*** *The results are acceptable. The sponsor used Simple Emax Michaelis-Menten kinetic equations to fit the data from human liver microsomes and recombinant enzymes and calculate intrinsic clearances. However, the model fits were not well for 5-hydroxylorcaserin and 1-hydroxylorcaserin formation by human liver microsomes, N-hydroxylorcaserin and 5-hydroxylorcaserin formation by rCYP1A2, N-hydroxylorcaserin formation by rCYP2B6, 5-hydroxylorcaserin and 1-hydroxylorcaserin formation by rCYP3A4.*

*Lorcaserin N-Carbamoyl Glucuronidation by Human UDP-Glucuronosyltransferases (UGT): Study PDR-08-294*

**TITLE:** "Identification of human UGT responsible for lorcaserin N-carbamoyl glucuronidation."

**OBJECTIVE:** To identify human UGT enzymes and efficient human organs responsible for lorcaserin N-carbamoyl glucuronide formation. CYP and FMO enzymes involved in the metabolism of lorcaserin.

**EXPERIMENT METHODS:** Incubations were conducted by using recombinant UGT enzymes (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGA1A10, UGT2B4, UGT2B7, UGT15, and UGT2B17) and human tissue (liver, renal, intestine, and lung) microsomal preparations. Kinetic parameters ($V_{max}$, $K_m$ and intrinsic clearance) of lorcaserin N-carbamoyl glucuronide formation were determined.

**RESULTS:**

| UGT Enzymes source | Kinetic Parameters | | |
|---|---|---|---|
| | $K_m$ (µM) | $V_{max}$ (pmol/mg protein/min) | $CL_{int}$ (µL/mg protein/min) |
| Human liver microsomes | 128.1 | 2379.2 | 18.57 |
| UGT1A9 | 518.0 | 103.3 | 0.199 |
| UGT2B7 | 93.8 | 186.4 | 1.987 |
| UGT2B15 | 51.6 | 237.4 | 4.601 |
| UGT2B17 | 254.1 | 155.3 | 0.611 |

All four human tissues (liver, kidney, intestine, and lung) catalyzed lorcaserin N-carbamoyl glucuronidation. Liver is a more efficient organ than kidney, intestine, and lung based on the metabolite formation rate (1028 pmol/mg protein/min).

**CONCLUSIONS:** Lorcaserin is metabolized by multiple UGTs (UGT1A9, UGT2B7, UGT2B15, and UGT2B17). Liver is a more efficient organ than kidney, intestine, and lung for lorcaserin N-carbamoyl glucuronidation.

***Reviewer comment:*** *The results are acceptable.*

Lorcaserin N-Sulfamate Formation by Sulfotransferase (SULT): Study PDR-06-204

**TITLE:** "Identification of human SULT involved in lorcaserin N-sulfamate formation."

**OBJECTIVE:** To identify human SULT enzymes involved in the metabolism of lorcaserin to lorcaserin N-sulfamate and compare their catalytic efficiency.

**EXPERIMENT METHODS:** Incubations were conducted by using recombinant SULT enzymes (SULT1A1, SULT1A2, SULT1A3, SULT2A1, and SULT1E1). Kinetic parameters ($V_{max}$, $K_m$ and intrinsic clearance) of lorcaserin N-sulfamate formation were determined.

**RESULTS:**

| Recombinant Human Sulfotransferase | Kinetic Constant | | |
|---|---|---|---|
| | $K_m$ (µM) | $V_{max}$ (nmol/mg/min) | $CL_{int}$ (µL/mg/min) |
| SULT1A1 | 742 | 189 | 255 |
| SULT1A2 | 5420 | 15.5 | 2.86 |
| SULT2A1 | 3210 | 62.0 | 19.3 |
| SULT1E1 | 368 | 0.682 | 1.85 |

The SULT1E1 and SULT1A2 demonstrated the lowest Km (368 µM) and the highest Km (5420 µM). The order of intrinsic clearances for recombinant SULTs is SULT1A1 > SULT2A1 > SULT2A1 > SULT1E1.

**CONCLUSIONS:** Lorcaserin is metabolized by multiple SULTs (SULT1A1, SULT1A2, SULT2A1, and SULT1E1).

***Reviewer comment:*** *The results are acceptable.*

Inhibition of Human Liver Microsomal CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 by Lorcaserin: Study PDR-07-197

**TITLE:** "Inhibition of human liver microsomal CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 by lorcaserin."

**OBJECTIVE:** To assess the inhibitory potential of lorcaserin on human liver microsomal CYP1A2, CYP2C9, CYP2C6, and CYP3A4-mediated metabolism.

**EXPERIMENT METHODS:** Incubations were conducted for each of the CYP enzymes (reactions): CYP1A2 (phenacetin O-deethylation), CYP2C9 (tolbutamide 4'-hydroxylation), CYP2C19 (S-mephenytoin 4'-hydroxylation), CYP2D6 (dextromethorphan O-demethylation) and CYP3A4 (1'-hydroxymidazolam). The incubation protein concentration was 0.5 mg/mL. Lorcaserin concentration was 0 μM to 200 μM. Substrate concentrations were close to Km of each CYP enzymes. Time-dependent inhibition of CYP2D6 was also assessed. Kinetic parameters ($IC_{50}$ and Ki) of lorcaserin on different enzymes mediated activity were determined.

**RESULTS:** Lorcaserin competitively inhibited the dextromethorphan O-demethylation in a concentration-dependent manner with an $IC_{50}$ value of 3.99 ± 0.41 μM (781 ng/mL) and 2.03 ± 0.18 μM (397 ng/mL). Lorcaserin inhibited 13.0%, 16.3%, 15%, and 4.9% of CYP1A2, CYP2C9, CYP2C19, and CYP3A4-mediated activity up to 200 μM concentration, respectively.

**CONCLUSIONS:** Lorcaserin was a competitive inhibitor of CYP2D6 mediated dextromethorphan O-demethylation. Lorcaserin did not significantly inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4-mediated metabolism up to a 200 μM concentration.

***Reviewer comment::*** *The results are acceptable. Due to the ratio of [I]/Ki is 0.14 (based on a lorcaserin mean Cmax value of 0.29 μM following 10 mg BID in humans), prediction of clinical relevance of competitive CYP inhibition is considered possible. Therefore, the sponsor conducted an in vivo drug-drug interaction study for lorcaserin and dextromethorphan.*

Inhibition Potential of Human Liver Microsomal CYP2C8 by Lorcaserin and Lorcaserin Sulfamate: Study PDR-09-117

**TITLE:** "Inhibition potential of lorcaserin and lorcaserin sulfamate on human microsomal CYP2C8 activity."

**OBJECTIVE:** To evaluate the inhibitory potential of lorcaserin and lorcaserin sulfamate on CYP2C8 mediated metabolism in human liver microsomes.

**EXPERIMENT METHODS:** Incubations were conducted in a reaction mixture with 0.25 mg/mL microsomal protein, 0 μM to 200 μM lorcaserin or lorcaserin sulfamate, and 5 μM paclitaxel. Percentage of control activity of the enzyme (remaining enzyme activity after the inhibition) for each concentration of inhibitor (lorcaserin and lorcaserin sulfamate) was calculated.

**RESULTS:** Lorcaserin and lorcaserin sulfamate inhibited 11.2% and 44.5% of CYP2C8 mediated paclitaxel 6α-hydroxylase activity by up to 200 μM concentration.

**CONCLUSIONS:** The potential of CYP2C8 mediated *in vivo* drug-drug interaction is considered to be low for lorcaserin and lorcaserin sulfamate.

***Reviewer comment:*** *The results are acceptable. Since lorcaserin and lorcaserin sulfamate did not inhibit 50% of CYP2C8 mediated paclitaxel 6α-hydroxylase activity up to 200 μM concentration, the potential of CYP2C8 mediated in vivo drug-drug interaction is considered to be low. Therefore, sponsor did not conduct an in vivo drug-drug interaction study for paclitaxel and lorcaserin or lorcaserin sulfamate. In retrospect, considering that the highest lorcaserin sulfamate concentration observed in the PK subpopulation during the phase 3 study APD356-009 was 7.33 μM, the mean observed lorcaserin sulfamate concentration was 0.812μM. A dedicated in-vivo DDI study is not required.*

Inhibition of Human Liver Microsomal CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 by Lorcaserin Sulfamate: Study PDR-08-295

**TITLE:** "Inhibition potential of lorcaserin sulfamate on human microsomal CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 acitivity."

**OBJECTIVE:** To determine the inhibitory potential of lorcaserin sulfamate on CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4-mediated metabolism in human liver microsomes.

**EXPERIMENT METHODS:** Incubations were conducted for each of the CYP enzymes (reactions): CYP1A2 (phenacetin O-deethylation), CYP2C9 (tolbutamide 4'-hydroxylation), CYP2C19 (S-mephenytoin 4'-hydroxylation), CYP2D6 (dextromethorphan O-demethylation) and CYP3A4 (1'-hydroxymidazolam). The incubation protein concentration was 1.0 mg/mL. Lorcaserin concentration was 0 μM to 200 μM. Substrate concentrations were close to Km of each CYP enzymes. For CYP2C9, incubations with human serum albumin were performed under identical conditions as above except that 10, 100 or 500 μM of human serum albumin was added to the microsomes. Percentage of control activity of the enzyme (remaining enzyme activity after the inhibition) for lorcaserin sulfamate was calculated. Kinetic parameters ($IC_{50}$ and Ki) of lorcaserin sulfamate on different enzymes mediated activity were determined.

**RESULTS:** Lorcaserin sulfamate inhibited the dextromethorphan O-demethylation and tolbutamide 4'-hydroxylation in a concentration-dependent manner with $IC_{50}$ values of 129 μM and 10.3 μM, respectively. Lorcaserin sulfamate inhibited 1.9%, 30.5%, and 35.7% of CYP1A2, CYP2C19 and CYP3A4-mediated activity up to a 200 μM concentration, respectively. With the addition of 10 μM, 100 μM, and 500 μM of human serum albumin to the microsomal incubation, $IC_{50}$ values of lorcaserin sulfamate were 14.6 μM, 85.8 μM and > 200 μM, respectively.

**CONCLUSIONS:** Lorcaserin sulfamate inhibited CYP2D6 mediated dextromethorphan O-demethylation at high concentration (> 200 μM). Lorcaserin sulfamate inhibited CYP2C9 mediated tolbutamide 4'-hydroxylation ($IC_{50}$ = 10.3 μM). Lorcaserin sulfamate did not significantly inhibit CYP1A2, CYP2C19, and CYP3A4-mediated metabolism up to a 200 μM concentration.

***Reviewer comment:****The sponsor stated that with the addition of 500 μM of human serum albumin to the microsomal incubation, which is similar to the albumin concentration in normal human plasma (600 μM), the inhibitory effect of lorcaserin sulfamate on CYP2C9 activity was decreased ($IC_{50}$ > 200*

*μM), suggesting a minimum inhibitory effect of lorcaserin sulfamate on CYP2C9. However, a paper (Carlile et al., Br J Clin Pharmacol, 1999 Jun; 47(6): 625-35) reported that an overestimation of intrinsic clearance by adding albumin into the incubation since albumin may facilitate the substrate-enzyme binding. Therefore, the $IC_{50}$ value of 10.3 μM (2840 ng/mL) obtained from the incubation without albumin should be used for prediction of clinical relevance of CYP2C9 inhibition as a conservative approach. Lorcaserin sulfamate is the major circulating metabolite in plasma, and the plasma Cmax based on the PK data collected from the Phase 3 study APD-356-009 is 147 ng/mL (0.609μM) and 196 ng/mL (0.812 μM) for the mean and median respectively. Based on the data, the calculated ratio of [I]/Ki is 0.06 – 0.0.7, and prediction of clinical relevance of CYP2C9 inhibition is considered marginally remote.*

Induction of Human Liver CYP1A2, CYP2C9, CYP2C19, CYP2B6, and CYP3A4/5 by Lorcaserin: Study XT043012

**TITLE:** "*In vitro* evaluation of lorcaserin as an inducer of cytochrome P450 expression in cultured human hepatocytes."

**OBJECTIVE:** To investigate the effect of lorcaserin on the expression of cytochrome P450 enzymes in primary cultures of human hepatocytes.

**EXPERIMENT METHODS:** Lorcaserin (0.2, 2.0, and 20 μM) and CYP inducers (omeprazole, 100 μM; Phenobarbital, 750 μM; and rifampicin, 10 μM) were incubated for 72 hours in cultured human hepatocytes obtained from three donor livers. Cells were harvested to prepare microsomes for testing the enzyme activities. Incubations were conducted for each of the CYP enzymes (reactions): CYP1A2 (7-ethoxyresorufin O-dealkylation), CYP2B6 (bupropion hydroxylation), CYP2C9 (diclofenac 4'-hydroxylation), CYP2C19 (S-mephenytoin 4'-hydroxylation), and CYP3A4/5 (testosterone 6β-hydroxylation).

**RESULTS:** Lorcaserin (0.2, 2.0 and 20 μM) showed no induction on CYP1A2. For CYP2C9, lorcaserin had no induction at 0.2 and 2.0 μM concentrations and a 1.12-fold induction at 20 μM. For CYP2B6, lorcaserin demonstrated 1.11, 1.20, and 1.85-fold induction at 0.2, 2.0 and 20 μM concentrations respectively. For CYP2C19, lorcaserin demonstrated 1.17, 1.20, and 1.34-fold induction at 0.2, 2.0 and 20 μM concentrations respectively. For CYP3A4/5, lorcaserin demonstrated 1.32, 1.35, and 1.62-fold induction at 0.2, 2.0 and 20 μM concentrations respectively. Lorcaserin demonstrated a concentration dependent induction, and the percentage of induction of positive controls (omeprazole, Phenobarbital and rifampicin) at the highest concentration (20 μM) were 20.4%, 7.84%, 6.55% and 11.3% for CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5, respectively.

**CONCLUSIONS:** Lorcaserin did not induce CYP1A2 and demonstrated a concentration dependent induction for CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5. However, the potential of induction was low compared to the positive controls, even at the highest concentrations.

***Reviewer comment:*** *The study is considered acceptable. The sponsor stated that the maximum concentration 20 μM (3900 ng/mL) of lorcaserin used in this study was 68-fold higher than the plasma Cmax value of 0.29 μM (56.8 ng/mL) of lorcaserin in humans for a 10 mg BID. Therefore, the potential of induction is considered low at the therapeutic concentrations.*

Induction of Human Liver CYP1A2, CYP2C9, CYP2C19, CYP2B6 and CYP3A4 by Lorcaserin sulfamate: Study 3210-0451-1800

**TITLE:** "*In vitro* assessment of the induction potential of lorcaserin sulfamate in primary cultures of human hepatocytes."

**OBJECTIVE:** To investigate the effect of lorcaserin sulfamate on the expression of cytochrome P450 enzymes in primary cultures of human hepatocytes.

**EXPERIMENT METHODS:** Lorcaserin sulfamate (0.2, 2.0, and 20 μM) and CYP inducers (3-methylcholanthrene, 2 μM; Phenobarbital, 1000 μM; and rifampicin, 10 μM) were incubated for three consecutive days in cultured human hepatocytes obtained from three donor livers. Cells were harvested to prepare microsomes for testing the enzyme activities. Incubations were conducted for each of the CYP enzymes (substrates): CYP1A2 (phenacetin), CYP2B6 (bupropion), CYP2C9 (diclofenac), CYP2C19 (S-mephenytoin), and CYP3A4 (testosterone).

**RESULTS:** Lorcaserin sulfamate (0.2, 2.0 and 20 μM) showed no significant increases in CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4 activities.

**CONCLUSIONS:** Lorcaserin sulfamate has low potential for drug-drug interactions due to induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4.

***Reviewer comment:*** *The study is considered acceptable.*

6. APPENDIX

*6.1 BCS Committee Meeting Minutes*

When: May 2010
Where: Ad Hoc

Meeting Participants:

| | |
|---|---|
| Mehul Mehta (Co-Chair) | Director, DCP I, OCP |
| Lawrence Yu (Co-Chair) | Director for Science, OGD |
| Dakshina Chilukuri | Reviewer, DCP III, OCP |
| Dale Conner | Director, DBE I, OGD |
| Barbara Davit | Acting Director, DBE II, OGD |
| Angelica Dorantes | Team Leader, ONDQA |
| Tapash Ghosh | Reviewer, ONDQA |
| Sam Haidar | Reviewer, OGD |
| Ramana Uppoor | Deputy Director, DCP I, OCP |
| Jayabharathi Vaidyanathan | Reviewer, DCP II, OCP |
| Donna Volpe | Researcher, LCP, OTR |
| Nam (Esther) Chun | Executive Secretary, BCS Committee, OGD |

**Agenda:**

**BCS Classification of NDA 022-529 Lorcaserin Hydrochloride Tablets**

**Background:**

The DCP requested that the BCS Committee review information submitted in NDA 022-529 in support of BCS classification for Lorcaserin Hydrochloride Tablets. Arena Pharmaceuticals, Inc. submitted a solubility study, an *in vitro* permeability study using cultured monolayers of Caco-2 cells and a human mass balance study, and a dissolution profile study to support a Biopharmaceutics Classification System (BCS) Class I waiver request. The Committee was asked to evaluate the data for a final determination regarding BCS Class 1.
***See Attachment I for additional information.***

**Conclusion:**

All committee members are in agreement that Lorcaserin Hydrochloride Tablets can be classified as a BCS Class I drug. **Please see Attachment II for additional comments.**

**Vote:**
Vote: Yes (11), No (0)

Drafted: Nam Chun 07/06/10

Comments :
D. Chilukuri : 05/24/10
D. Conner : 06/30/10
B. Davit: 07/02/10
S. Haidar: 05/16/10
M. Mehta: 05/14/10
J. Vaidyanathan: 05/18/10
D. Volpe: 05/12/10
R. Uppoor: 05/12/10
L. Yu: 05/15/10
T. Ghosh: 05/28/10
A. Dorantes: 06/23/10

V:\Division\Bio\BCS\2010 Meetings\2010-0\May-10Minutes

**ATTACHMENT I**

| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION | **OFFICE OF Clinical Pharmacology**<br>**Division of clinical Pharmacology II (HFD 870)**<br>**Review for Formal/Informal Consults** |
|---|---|

| NDA No.: 22-529 | Serial No: | SUBMISSION DATE: 12/18/2009 |
|---|---|---|
| NAME OF PRODUCT: LORQESS (lorcaserin hydrochloride) Tablets | NAME OF THE SPONSOR: Arena Pharmaceuticals Inc. | |
| OCP REVIEWER: Immo Zdrojewski | | |
| ONDQA BIOPHARMACEUTICS - Reviewer: John Duan, Ph.D. | | |

**TYPE OF SUBMISSION**

**CLINICAL PHARMACOLOGY RELATED ISSUE**

☐ PRE-IND
☐ ANIMAL to HUMAN SCALING
☐ IN-VITRO METABOLISM
☐ PHASE I PROTOCOL
☐ PHASE II PROTOCOL ()
☐ PHASE III PROTOCOL
☐ DOSING REGIMEN CONSULT
☐ PK/PD- POPPK ISSUES
☐ PHASE IV RELATED

☐ DISSOLUTION/IN-VITRO RELEASE
☐ BIOAVAILABILITY STUDIES
☐ IN-VIVO WAIVER REQUEST
☐ SUPAC RELATED
☐ CMC RELATED
☐ PROGRESS REPORT
☐ SCIENTIFIC INVESTIGATIONS
☐ MEETING PACKAGE ()

☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ ANNUAL REPORTS
☐ FAX SUBMISSION
☒ OTHER: (Biopharmaceutics Classification System Assessment for Lorcaserin HCl (drug substance) and tested-Lorcaserin HCl IR-Products

## REVIEW ACTION

☐ NAI (No action indicated)
☐ E-mail comments to:
☐ Medical ☐ Chemist ☐ Pharm-Tox
☐ Micro ☐ Pharmacometrics ☐ Others
(Check as appropriate and attach e-mail)

☐ Oral communication with
Name: [ ]
☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]

☒ Formal Review/Memo (attached)
☐ See comments below
☐ See submission cover letter
☐ OTHER *(SPECIFY BELOW)*:
[ ]

**REVIEW COMMENT(S)**

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

**Comments:**

SIGNATURE OF OCP REVIEWER: Date _____

SIGNATURE OF ONDQA-BIOPHARMACEUTICS REVIEWER: Date _____

**SIGNATURE OF OCP TEAM LEADER:** _____

**SIGNATURE OF BIOPHARMACEUTICS TEAM LEADER:** _____

**Background**

The sponsor, Arena Pharmaceuticals Inc. has submitted a 505 (b)(1) New Drug Application (NDA 22-529) seeking marketing approval for a 10 mg BID dose of Lorcaserin hydrochloride immediate release tablets. Lorcaserin, a new molecular entity, is, according to the sponsor, a selective serotonin 2C (5-HT2C) receptor agonist. The sponsor is seeking the indication for weight management, including

weight loss and maintenance of weight loss, and usage in conjunction with a reduced-calorie diet and a program of regular exercise. The intended target population is 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).

The tablet dosage form was used in two of three Phase 3 studies. Other clinical dosage forms included an oral solution, used in Phase 1, and a (b) (4) capsules, used in Phase 1, Phase 2, and the first Phase 3 clinical trial. The prototype tablet formulation was further optimized to a white-colored tablet formulation. Market-image tablet formulation has the same composition as the white tablet, except for the blue color. Furthermore, the sponsor claims BCS class I status for Lorcaserin HCl and comparative in vitro dissolution testing has been used in most cases to evaluate the effects of formulation and process changes on the product performance instead of clinical bioequivalence studies.

**Clinical Pharmacology Findings (per submitted information)**

**SOLUBILITY: Is Lorcaserin HCl a highly soluble drug substance per BCS?**

**Criteria: The highest dose strength is soluble in ≤ 250 mL of aqueous media in pH 1 – 7.5 at 37°C.**

**Figure 1.** Structure of Lorcaserin HCl

(b) (4)

The highest-dose strength of Lorcaserin HCl (10.4 mg lorcaserin HCl HH) must dissolve completely in 250 mL or less of water across the physiological pH range 1 to 7.5 at 37°C ± 1°C in order to meet the "high solubility" criterion of the BCS. This requires the solubility of Lorcaserin HCl HH to be 0.0416 mg/mL or higher under those conditions.

The sponsor determined the solubility of Lorcaserin HCl at 37°C ± 1°C hydrochlorid acid buffer, pH 1.2 and phosphate buffer, pH 7.6 in triplicate for each pH. Since Lorcaserin is a monobasic molecule with a high $pK_a$ of 9.53, the sponsor did not determine the solubility at pH = pKa, pH = pKa +1, pH = pKa-1, and at pH = 1 and 7.5 but only at pH 1 and 7.5. USP buffers were used to make pH 1.2 HCl in KCl solution and pH 7.6 phosphate buffer solution. These USP buffer solutions are described in Table 58.

**Table 58 USP Buffer Recipes**

| pH and Solution/Buffer Type | Description |
|---|---|
| Hydrochloric acid buffer, pH 1.2 | 50 mL of the potassium chloride solution and 85 mL of 0.2 M hydrochloric acid solution were added to a 200-mL volumetric flask, and diluted with water to 200 mL |
| Phosphate buffer, pH 7.6 | 50 mL of the monobasic potassium phosphate solution and 42.4 mL of 0.2 M sodium hydroxide solution were added to a 200-mL volumetric flask, then diluted with deionized water to 200 mL |

Samples were equilibrated in triplicate for each pH at 37°C ± 1°C for approximately 24 hours. A validated stability-indicating HPLC method was used to determine Lorcaserin concentration in the samples. Based on these chromatographic results, there was no degradation of Lorcaserin during equilibration. According to the sponsor, Lorcaserin HCl HH solubility is approximately 10,000 times greater than 0.0416 mg/mL, the required solubility to meet the BCS criterion for "high solubility." (Table 59) The nominal 250-mL volume used for BCS evaluation is more than 10,000 times larger than the solvent volumes capable of dissolving 10.4 mg of Lorcaserin HCl HH at gastrointestinal pH values and 37°C.

**Table 59** Solubility of Lorcaserin HCl HH in Aqueous Media at pH 1 and pH 7.5 at 37°C ± 1°C for ~24 Hours, Determined Using a Validated Stability-indicating HPLC Method

| Intended pH (Observed Range) | Average Solution Concentration ± SD (mg/mL)[a] | Solubility (mg/mL) |
|---|---|---|
| 1 (1.09 to 1.06) | 483 ± 6 | > 400 |
| 7.5 (7.49 to 7.46) | 418 ± 8 | > 400 |

[a] Determined from three injections of each sample, for nine observations per pH.

**Reviewer's Comments:**

Lorcaserin can be considered highly soluble according to BCS criteria.

**PERMEABILITY: Is Lorcaserin a highly permeable drug substance per BCS?**
**Criteria: Absolute bioavailability is ≥ 90% or ≥ 90% of the administered drug is recovered in urine. In vivo human intestinal perfusion studies, in vivo or in situ animal intestinal perfusion studies, in vitro human or animal excised intestinal tissues, or in vitro permeation study across a monolayer of cultured epithelial cells.**

To determine the permeability of Lorcaserin, the sponsor evaluated in-vitro Caco-2 permeability and conducted a human mass balance study (APD-356-006).

A total of six healthy male subjects participated in this Phase 1, open-label, single-dose, mass balance study. All subjects enrolled in the study satisfied the inclusion/exclusion criteria outlined in the protocol and all subjects completed the study. All subjects received a single 10-mg oral dose of Lorcaserin HCl containing 100 μCi $^{14}$C-Lorcaserin at hour 0 on day 1. Serial blood, urine, and feces samples were collected through 240 hours post-dose.
The mean recovery (%) during the mass balance study was approximately 94%. Urinary elimination was higher than fecal elimination, with a mean recovery of 92% (Table 60).

**Table 60** Mass Balance of Total Radioactivity Excretion Following 1 x 10 mg [14C]-lorcaserin Containing 100 μCi of Total Radioactivity

| Subject Number | Cum % dose in Urine | Cum % dose in Feces | % of Total Dose |
|---|---|---|---|
| 1 | 92.3 | 2.33 | 94.6 |
| 2 | 93.4 | 1.18 | 94.5 |
| 3 | 94.8 | 3.41 | 98.2 |
| 4 | 90.1 | 2.38 | 92.5 |
| 5 | 89.5 | 1.39 | 90.9 |
| 6 | 93.8 | 2.46 | 96.3 |
| | | | |
| N | 6 | 6 | 6 |
| Mean | 92.3 | 2.19 | 94.5 |
| SD | 2.1 | 0.81 | 2.6 |
| CV (%) | 2.3 | 36.94 | 2.8 |
| SEM | 0.9 | 0.33 | 1.1 |
| Minimum | 89.5 | 1.18 | 90.9 |
| Maximum | 94.8 | 3.41 | 98.2 |

Source Table: 14.2.18.

The stability of Lorcaserin HCl HH in the gastrointestinal tract was evaluated using simulated fluids resembling the typical gastrointestinal conditions to assess the potential for Lorcaserin degradation prior to absorption in vivo. The simulated intestinal fluid is composed of buffer salts and pancreatin to approximate the digestive function of the small intestine through both chemical and enzymatic means. The incubations were performed at 37°C and lasted 1 hour for simulated gastric fluid (SGF) and 3 hours for simulated intestinal fluid (SIF) to approximate the length of time drug would be in contact with these fluids in vivo. Lorcaserin remained unchanged during incubation in both SGF and SIF. These results indicate absorption of intact drug from the gastrointestinal tract.

Furthermore, the permeability of Lorcaserin across Caco-2 cell monolayers in the apical to basal (A-to-B) direction was determined at three different final concentrations (2 μM, 20 μM, and 200 μM) and two apical pH values (pH 6.8 and pH 7.4) along with the high permeability internal standard [redacted] (b) (4) (final concentration: 10 μM) and low permeability standard $^{3}$H-mannitol (final concentration: ~1.0 μCi/mL). Based on the sponsor's information, the permeability of Lorcaserin across Caco-2 cell monolayers was determined using a method validated with 20 drugs recommended in the FDA "biowaiver" guidance.

**Table 61** Summary of Caco-2 Cell Permeability Results for Lorcaserin, [redacted], and 3H-Mannitol

| | | $P_{app}$ (A to B) ($\times 10^{-6}$ cm/s)[a] | | |
|---|---|---|---|---|
| **Groups** | **pH (A/B)[b]** | **Lorcaserin** | **[redacted]** | **$^{3}$H-Mannitol[c]** |
| Lorcaserin (2 µM) | 6.8/7.4 | 31.9 ± 3.57 | 33.8 ± 2.20 | 0.602 ± 0.0824 |
| Lorcaserin (20 µM) | | 32.8 ± 0.145 | 31.5 ± 3.25 | 0.451 ± 0.0560 |
| Lorcaserin (200 µM) | | 37.0 ± 3.05 | 31.6 ± 1.12 | 0.491 ± 0.0723 |
| Lorcaserin (2 µM) | 7.4/7.4 | 30.4 ± 0.810 | 32.4 ± 1.71 | 0.507 ± 0.0691 |
| Lorcaserin (20 µM) | | 31.4 ± 0.834 | 32.3 ± 4.53 | 0.519 ± 0.0307 |
| Lorcaserin (200 µM) | | 35.4 ± 1.64 | 29.7 ± 1.17 | 0.562 ± 0.0598 |

a Permeability results for each condition (A-to-B direction) are presented as mean ± standard deviation of more than three Caco-2 cell monolayers.
b A: apical compartment of the Transwell unit; B: basal compartment of the Transwell unit.
c The high permeability internal standard [redacted] was included in the donor fluid along with Lorcaserin. The same monolayers used to determine the permeability of Lorcaserin and [redacted] were subsequently used

In a separate in-vitro study, the sponsor evaluated the permeability and P-glycoprotein (P-gp) interaction potential of Lorcaserin (Study PDR-08-160).

In the absence of the known P-gp inhibitor cyclosporin A, the apparent permeability coefficient ($P_{app}$) values of Lorcaserin at three different final concentrations (1, 10, and 50 µM) in the apical to basal direction (A to B) were 28.1 ± 3.69 × $10^{-6}$ cm/sec, 31.3 ± 2.74 × $10^{-6}$ cm/sec, and 34.5 ± 2.73 × $10^{-6}$ cm/sec, respectively. The efflux ratios ($P_{app\ B\ to\ A}$/ $P_{app\ A\ to\ B}$) of Lorcaserin at the three different final concentrations were 1.19, 1.19, and 1.21, respectively. In the presence of cyclosporin A (5 µM), the $P_{app}$ values of Lorcaserin at the three different final concentrations in the A to B direction were 28.9 ± 2.91× $10^{-6}$ cm/sec, 31.7 ± 1.43 × $10^{-6}$ cm/sec, and 33.9 ± 2.04 × $10^{-6}$ cm/sec, respectively. The efflux ratios of Lorcaserin at the three different final concentrations were 1.13, 1.09, and 1.05, respectively (Table 62).

**Table 62** Bidirectional Permeability of Lorcaserin across Caco-2 Cell Monolayers in the Absence and Presence of Cyclosporin A[a]

| Compounds | $P_{app(AtoB)}$ ($\times 10^{-6}$ cm/sec) | $P_{app(BtoA)}$ ($\times 10^{-6}$ cm/sec) | Efflux Ratio [b] |
|---|---|---|---|
| lorcaserin (1 µM) | 28.1 ± 3.69 | 33.3 ± 2.07 | 1.19 |
| lorcaserin (1 µM) + cyclosporin A (5 µM) | 28.9 ± 2.91 | 32.6 ± 2.75 | 1.13 |
| lorcaserin (10 µM) | 31.3 ± 2.74 | 37.3 ± 3.69 | 1.19 |
| lorcaserin (10 µM) + cyclosporin A (5 µM) | 31.7 ± 1.43 | 34.5 ± 3.36 | 1.09 |
| lorcaserin (50 µM) | 34.5 ± 2.73 | 41.9 ± 2.15 | 1.21 |
| lorcaserin (50 µM) + cyclosporin A (5 µM) | 33.9 ± 2.04 | 35.6 ± 2.88 | 1.05 |

[a] Result for each condition is presented as mean ± standard deviation of three separate experiments conducted in triplicates.

[b] Efflux ratio = $P_{app(BtoA)}/P_{app(AtoB)}$.

Based on the finding form the permeability evaluation, Lorcaserin can be classified as a highly permeable compound.

***Reviewer comment:***

- *The sponsor did not provide data for the Caco-2 cell model validation using the 20 model compounds.*
- *The sponsor did not provide the study details of the gastrointestinal stability study.*

**DISSOLUTION DATA:**

The BCS Guidance requires for a BCS-Class 1 classification, that dissolution data demonstrating that the product is rapidly dissolving be provided. The following dissolution information was provided to support the BCS-Class 1 classification for Lorcaserin HCl (drug substance) as well as for the products used in the Phase III and PK studies (food effect & special populations-elderly).

**Supportive Data**: The dissolution conditions for the tested Lorcaserin HCl-products were determined based on experimentation using various pH media, USP <711> Apparatus 1 and 2, and varied agitation speeds. Apparatus 2 (paddles) at 50 rpm was chosen since the release rate was slower compared to Apparatus 1 at 100 rpm. The 0.1 N HCl (pH = 1) was chosen as the dissolution medium because no differences in the dissolution profiles for samples measured at various pH conditions were observed for the tablet formulation and the market image tablet formulation (containing product identifiers: color and deboss code).

Dissolution testing for the clinical tablets and market image tablet were performed using Apparatus 2 at 50 rpm in a volume of 900 mL in each of the following media: (1) 0.1 N HCl, (2) a pH 4.5 buffer, and (3) a pH 6.8 buffer. The capsule and tablets used for comparison are described in Table 8. All three formulations met the definition of a rapidly dissolving dosage form with greater than (b) (4) released in 30 minutes. Furthermore, these formulations were demonstrated to be equivalent with greater than (b) (4) released in 15 minutes, and thus requiring no f2 calculation.

The following table shows Lorcaserin HCl capsule and tablets used for dissolution testing.

**Dissolution Profile of Lorcaserin HCl Market Image Tablets, Lot 0820B008, in pH = 6.8 (Phosphate)**

| | %Label Claim Released | | | | |
|---|---|---|---|---|---|
| **Unit** | **10 min** | **15 min** | **20 min** | **30 min** | **45 min** |
| 1 | (b) (4) | | | | |
| 2 | | | | | |
| 3 | | | | | |
| 4 | | | | | |
| 5 | | | | | |
| 6 | | | | | |
| 7 | | | | | |
| 8 | | | | | |
| 9 | | | | | |
| 10 | | | | | |
| 11 | | | | | |
| 12 | | | | | |
| Mean | 91 | 94 | 95 | 96 | 97 |
| %RSD | 6 | 5 | 4 | 3 | 2 |
| High | (b) (4) | | | | |
| Low | | | | | |

**RECOMMENDATION and COMMENTS:**

1. The provided solubility and permeability data support the BCS-Class 1 classification for Lorcaserin HCl (drug-substance).
2. The provided dissolution data support a BCS-Class 1 classification for the tested Lorcaserin HCl-products.
3. The reviewers from OCP and ONDQA-Biopharmaceutics recommend that Lorcaserin HCl and Lorcaserin HCl-tested products be classified as BCS- Class 1.
4. Note that the final recommendation regarding the BCS-Class 1 classification for this drug substance/drug product will be given by the FDA's BCS Committee after they evaluate the overall solubility, permeability, and dissolution data provided to support the sponsor's BCS classification request.
5. This review will be amended to include the BCS-committee's recommendation.

**ATTACHMENT II**

---

**From:** Volpe, Donna A
**Sent:** Wednesday, May 12, 2010 9:13 AM
**To:** Chun, Nam
**Cc:** Yu, Lawrence; Mehta, Mehul U
**Subject:** RE: NDA 22-529 Lorcaserin BCS Class 1 review

Good morning --

Agree with the reviewer about classification.

Would also add that results from method suitability study with the 20 model compounds should show [redacted] (b) (4) is the high permeability internal standard. Also need to show $P_{app}$ results from a model probe to show that the monolayers have efflux transporter(s).

Donna

**From:** Uppoor, Ramana S
**Sent:** Wednesday, May 12, 2010 7:19 PM
**To:** Chun, Nam
**Cc:** Yu, Lawrence; Mehta, Mehul U; Uppoor, Ramana S
**Subject:** Re: NDA 22-529 Lorcaserin BCS Class 1 review

Hi Esther,

I agree with the reviewers that Lorcaserin tablet is a BCS class 1 drug/product. I would recommend that the reviewers request the sponsor to send the method suitability for the caco-2 cell permeability method (the sponsor states that they have done this). Overall, there are 2 methods (mass balance and in vitro permeability) for assessing permeability and both point to the drug to be highly permeable. My recommendation for getting the method validation is just for completion sake.

Thanks.

Ramana Uppoor

**From:** Vaidyanathan, Jayabharathi
**Sent:** Tuesday, May 18, 2010 7:40 AM
**To:** Mehta, Mehul U; Yu, Lawrence
**Cc:** Chun, Nam
**Subject:** RE: NDA 22-529 Lorcaserin BCS Class 1 review

Solubility - Agree that it is rapidly soluble

Permeability - Based on GI stability and mass balance, lorcaserin appears to be highly permeable. Caco-2 study also supports high permeability. The review mentions that sponsor indicates that it is stable in GIT, however there is no data.

Dissolution- agree that the product is rapidly dissolving

Agree that lorcaserin can be classified as BCS class 1 pending the GI stability data and caco-2 validation.

Thanks,
Jaya

**From:** Dorantes, Angelica
**Sent:** Wednesday, June 23, 2010 10:29 PM
**To:** Chun, Nam
**Cc:** Mehta, Mehul U; Yu, Lawrence
**Subject:** RE: NDA 22-529 Lorcaserin BCS Class 1 review

Hello Esther:

My vote is YES (see attachment).

Regards,
Angelica

ADorantes BCS omments-NDA 225..

**From:** Davit, Barbara M
**Sent:** Friday, July 02, 2010 5:09 PM
**To:** Chun, Nam
**Subject:** RE: NDA 22-529 Lorcaserin BCS Class 1 review
**Importance:** High

Esther:

I vote to provisionally classify lorcaserin as BCS Class I provided that the sponsor submits the adequate missing data to support a classification of "highly permeable."

- Lorcaserin satisfies criteria to be classified as highly soluble.
- Lorcaserin can be classified as highly permeable provided that the sponsor submits the missing validation data (20 model compounds) and missing information about the GI stability study
- Lorcaserin tablets can be classified as rapidly dissolving.

Barbara

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

IMMO ZDROJEWSKI
09/30/2010

NITIN MEHROTRA
10/01/2010

CHRISTINE E GARNETT
10/01/2010

SALLY Y CHOE
10/01/2010

**ONDQA BIOPHARMACEUTICS REVIEW**

| | |
|---|---|
| **NDA#:** | **22-529** |
| **Submission Date:** | 12/22/09, 8/3/2010 |
| **Brand Name:** | LORQESS |
| **Generic Name:** | Lorcaserin HCl |
| **Formulation:** | Tablets |
| **Strength:** | 10 mg |
| **Sponsor:** | Arena Pharmaceuticals, Inc. |
| **Reviewer:** | John Duan, Ph.D. |
| **Submission Type:** | Original Application |

Lorqess is a selective serotonin 2C agonist indicated for weight management, including weight loss and maintenance of weight loss used in conjunction with a reduced-calorie diet and a program of regular exercise. The recommended dose of lorcaserin is 10 mg twice daily and the intended patient population is adults, ages 18 and older.

## COMMENTS

1. BCS Class I claim for Lorcaserin HCl Tablets is granted based on BCS committee decision (Appendix 3).

2. Although the link between the capsule and tablet formulations is not necessarily established by the BCS approach (BCS based biowaiver is only applicable for the formulations with pharmaceutical equivalence), the difference of bioavailability between tablets and capsules is not expected and the biowaiver can be granted based on the following considerations.

    a. The dissolutions between tablets and capsules in multiple media are similar.
    b. The tablet formulation has been used in two of the three Phase III clinical trials.

3. The effect of particle size on dissolution seems minimal (b) (4) in all three media (pH 1, 4.5, and 6.8) with mild agitations (apparatus I, 100 rpm and apparatus II, 50 rpm).

4. Based on available data, the following dissolution methodology and acceptance criteria are recommended.

| | |
|---|---|
| Apparatus: | USP <711> apparatus 2 (paddles) |
| Agitation speed: | 50 rpm |
| Medium: | 0.1 N HCl |
| Volume: | 900 mL |
| Temperature: | 37°C ± 0.5°C. |
| Acceptance criteria: | Q = (b) (4) at 15 min |

**RECOMMENDATION**

The claim of BCS Class I claim for Lorcaserin HCl Tablets is granted. The biowaiver requested can be granted. Please forward the comments to the review team.

The following dissolution methodology and acceptance criterion were recommended and conveyed to the sponsor. The sponsor accepted the recommendation and modified the NDA accordingly on 8/3/2010.

| | |
|---|---|
| Apparatus: | USP <711> apparatus 2 (paddles) |
| Agitation speed: | 50 rpm |
| Medium: | 0.1 N HCl |
| Volume: | 900 mL |
| Temperature: | 37°C ± 0.5°C. |
| Acceptance criteria: | Q = (b) (4) at 15 min |

_____ _____

John Duan, Ph.D. Date
**Reviewer**
**ONDQA Biopharmaceutics**

_____ _____

Patrick Marroum, Ph.D. Date
**ONDQA Biopharmaceutics**

cc: NDA 22529
Patrick Marroum, Angelica Dorantes, John Duan

**APPENDIX 1. Biopharmaceutics related issues.**

**1. Physicochemical Properties**

Physicochemical parameters that could potentially affect the performance of lorcaserin HCl 10-mg tablets have been evaluated during development. The drug substance has been shown to be highly soluble and highly permeable, meeting the criteria for Biopharmaceutics Classification System (BCS) Class-1 (the final decision was made by BCS committee). A summary of solubility, permeability and dissolution testing can be found in Appendix 2 and Appendix 3

**2. Proposed dissolution method**

The dissolution of lorcaserin HCl 10-mg tablets is rapid with (b) (4) or more of the label claim released in 30 minutes. During the development of the method, no significant difference in the dissolution profiles was observed when testing was performed across the physiological pH range using dissolution media at pH 1, 4.5, and 6.8. Method development studies also evaluated agitation speed, apparatus, and tablets produced with varying manufacturing variables; these studies are described. The following dissolution test method was selected.

| | |
|---|---|
| Apparatus: | USP <711> apparatus 2 (paddles) |
| Agitation speed: | 50 rpm |
| Medium: | 0.1 N HCl |
| Volume: | 900 mL |
| Temperature: | 37°C ± 0.5°C. |
| Acceptance criteria: | Q = (b) (4) at 30 min |

**3. The effects of particle size on dissolution**

Dissolution testing of the market-image tablets containing drug substance of varying particle size was performed in the physiological range at pH 1 (0.1 N HCl), pH 4.5 (0.02 M acetate), and pH 6.8 (0.05 M phosphate). The market-image tablets containing drug substance of varying particle size used for comparison are described in the following table.

(b) (4)

The comparisons of the dissolution profiles at pH 1, pH 4.5, and pH 6.8 for lorcaserin HCl 10-mg market-image tablets with drug substance of varying particle size are shown in the following figures. All the above tablets had similar dissolution characteristics, with an average %label claim released of = (b) (4) within 15 minutes in all three media (pH 1, pH 4.5, and pH 6.8). Therefore, the Sponsor concludes that (b) (4)

(b) (4)

**Figure 2. Comparison of Dissolution Profiles for Lorcaserin HCl 10-mg Market-image Tablets with Drug Substance of Varying Particle Size at pH = 1**

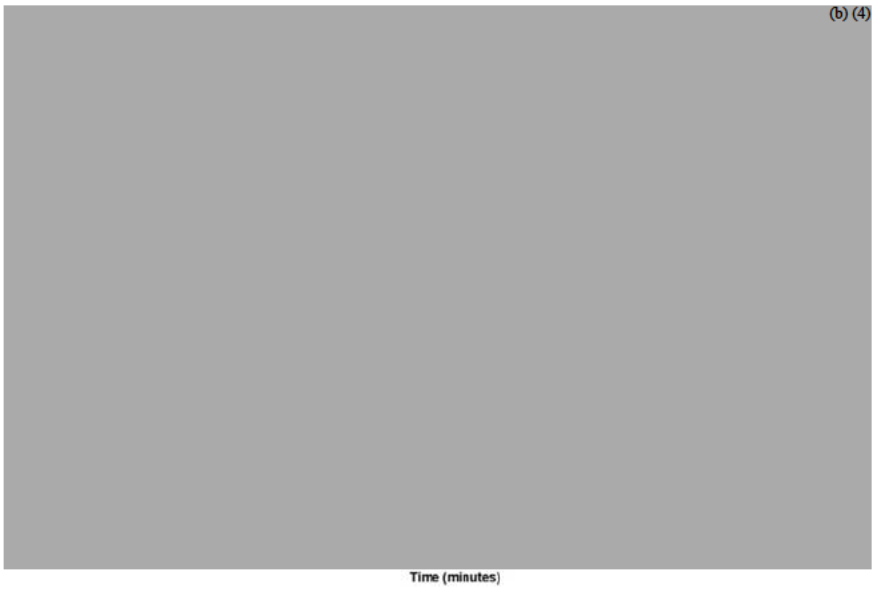



**Figure 3. Comparison of Dissolution Profiles for Lorcaserin HCl 10-mg Market-image Tablets with Drug Substance of Varying Particle Size at pH = 4.5**

Figure 4. Comparison of Dissolution Profiles for Lorcaserin HCl 10-mg Market-image Tablets with Drug Substance of Varying Particle Size a pH = 6.8


### 3. The dissolution comparisons between tablets and capsules

Lorcaserin HCl 10-mg tablets intended for commercial distribution are round, film-coated, blue-colored, immediate-release tablets. The tablet dosage form was used in two of three Phase 3 studies. Other clinical dosage forms included an oral solution, used in Phase 1, and a (b) (4) (b) (4) capsules, used in Phase 1, Phase 2, and the first Phase 3 clinical trial. Bioequivalence has been demonstrated between the capsule dosage form and a prototype tablet formulation. The prototype tablet formulation was further optimized to a white-colored tablet formulation. Market-image tablet formulation has the same composition as the white tablet, except for the blue color. The composition of Lorcaserin HCl tablets (to-be-marketed formulation) is shown in the following table.

| Component | Grade | Function | mg/tablet | %w/w |
|---|---|---|---|---|
| **Core** | | | | |
| Lorcaserin HCl Hemihydrate | Arena | Drug substance | 10.4[a] | 10.4 |
| Silicified microcrystalline cellulose[b] | (b) (4) | | | (b) (4) |
| Hydroxypropyl cellulose | NF | | | |
| Croscarmellose sodium | NF | | | |
| Magnesium stearate | NF | | | |
| | | Total | | (b) (4) |
| | | | | (b) (4) |

[a] Equivalent to 10 mg lorcaserin HCl.

[b] Detailed information and qualitative compositions can be found in 3.2.P.4, Control of Excipients [Lorcaserin HCl, Tablet, 10 mg].

[c] (b) (4)

[d]

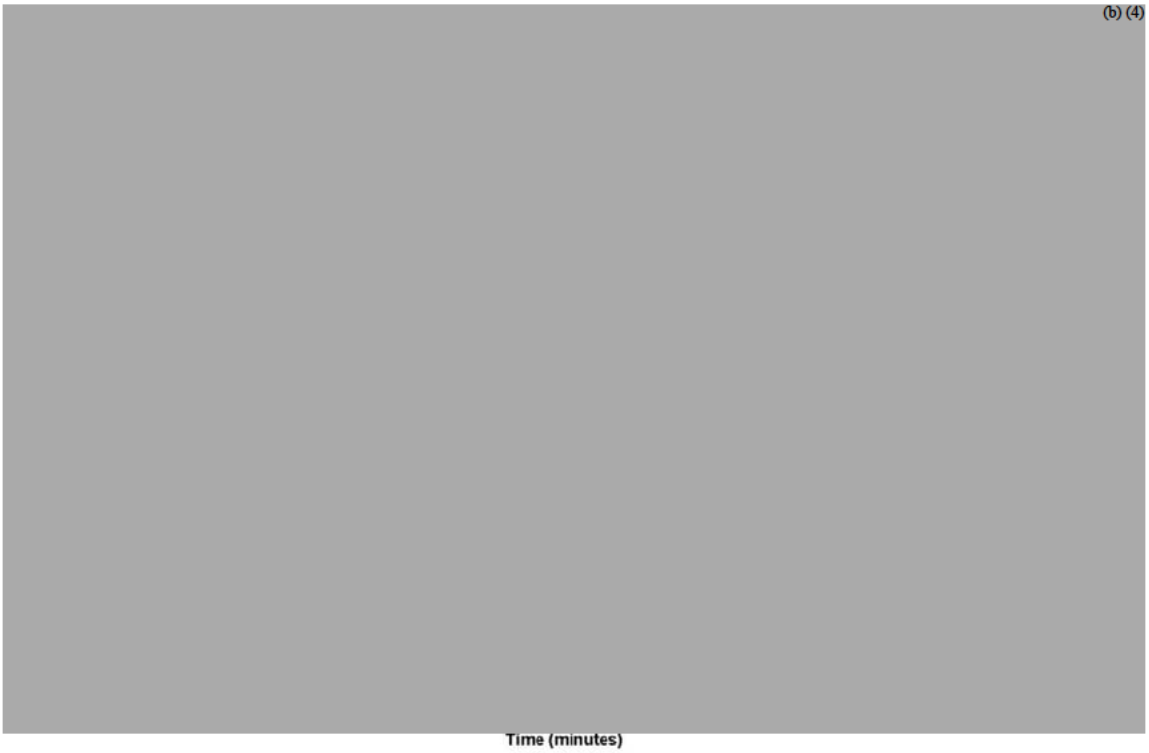
The composition of capsule formulation is shown in the following table.


Dissolution comparisons among the capsule, clinical tablet, and market image tablet were performed using Apparatus 2 at 50 rpm in a volume of 900 mL of each of the following media: (1) 0.1 N HCl, (2) a pH 4.5 buffer, and (3) a pH 6.8 buffer. The capsule and tablets used for comparison are described in the table below.


The following figure shows the comparisons of the dissolution profiles for Lorcaserine 10 mg formulations in 0.1 N HCl.


The following figure shows the comparisons of the dissolution profiles for Lorcaserine 10 mg formulations in pH 4.5 medium.


The following figure shows the comparisons of the dissolution profiles for Lorcaserine 10 mg formulations in pH 6.8 medium.




All three formulations met the definition of a rapidly dissolving dosage form with greater than (b) (4) released in 30 minutes. Furthermore, these formulations were demonstrated to be equivalent with greater than (b) (4) released in 15 minutes, and thus requiring no f2 calculation. Therefore, the dissolution between capsule and tablets can be considered similar.

## Appendix 2. Justification for a claim of BCS Class-1

### *1. Solubility*

The commercial active pharmaceutical ingredient (API), lorcaserin HCl HH (b) (4) was shown to be very soluble in water (< 1 mL water needed to dissolve 1 gram of compound). The BCS criterion for "high solubility" is based on the highest dose strength of the immediate-release product. The highest-dose strength of lorcaserin (10.4 mg lorcaserin HCl HH) must dissolve completely in 250 mL or less of water across the physiological pH range 1 to 7.5 at 37°C ± 1°C in order to meet the "high solubility" criterion of the BCS. This requires the solubility of lorcaserin HCl HH to be 0.0416 mg/mL or higher under those conditions.

The number of pH conditions for a solubility determination can be based on the ionization characteristics of the test drug substance. If the pKa falls in the range of 1 to 7.5, solubility is determined at pH = 1, pH = pKa – 1, pH = pKa, pH = pKa + 1, and pH = 7.5. Lorcaserin is a monobasic molecule with a relatively high pKa of 9.53, two units above the nominal upper limit of the gastrointestinal pH range (7.5). In addition, previous solubility work showed no pH dependence for lorcaserin HCl HH solubility throughout the gastrointestinal pH range with solubility > 400 mg/mL throughout. Therefore, only the outer limits of the physiological range were evaluated, i.e., pH = 1 and pH = 7.5.

USP buffers were used to make pH 1.2 HCl in KCl solution and pH 7.6 phosphate buffer solution. These USP buffer solutions are described in the following table.

| pH and Solution/Buffer Type | Description |
|---|---|
| Hydrochloric acid buffer, pH 1.2 | 50 mL of the potassium chloride solution and 85 mL of 0.2 M hydrochloric acid solution were added to a 200-mL volumetric flask, and diluted with water to 200 mL |
| Phosphate buffer, pH 7.6 | 50 mL of the monobasic potassium phosphate solution and 42.4 mL of 0.2 M sodium hydroxide solution were added to a 200-mL volumetric flask, then diluted with deionized water to 200 mL |

Samples were equilibrated in triplicate for each pH at 37°C ± 1°C for approximately 24 hours. A validated stability-indicating HPLC method was used for analysis. Based on these chromatographic results, there was no degradation of lorcaserin during equilibration. The following table shows the average solution concentration of the samples. Since the solutions were not saturated, solubility is conservatively stated as > 400 mg/mL for both pH conditions.

| Intended pH (Observed Range) | Average Solution Concentration ± SD (mg/mL)[a] | Solubility (mg/mL) |
|---|---|---|
| 1 (1.09 to 1.06) | 483 ± 6 | > 400 |
| 7.5 (7.49 to 7.46) | 418 ± 8 | > 400 |

[a] Determined from three injections of each sample, for nine observations per pH.

Thus, lorcaserin HCl HH solubility is approximately 10,000 times greater than 0.0416 mg/mL, the required solubility to meet the BCS criterion for "high solubility."

Lorcaserin HCl HH can be considered to have a high solubility.

***2. Permeability***

The permeability studies will be reviewed by OCP. Below is a brief summary.

A human mass balance study (APD356-006) using radiolabeled drug substance in six volunteers showed over 90% recovery in the urine. This result demonstrates that greater than 90% of the lorcaserin dose is absorbed into the blood. Drug stability in simulated gastric and intestinal fluids has been demonstrated. Additional Caco-2 permeation experiments further confirmed lorcaserin to be a high permeability compound which is not a P-glycoprotein (P-gp) substrate. Finally, dose linearity from 10-mg to 40-mg strengths has been demonstrated via a human pharmacokinetic study.

***3. Rapid and similar dissolution***

**Appendix 3. BCS Committee Memo**

BCS Committee Meeting Minutes

When: May 2010
Where: Ad Hoc

Meeting Participants:

| | |
|---|---|
| Mehul Mehta (Co-Chair) | Director, DCP I, OCP |
| Lawrence Yu (Co-Chair) | Director for Science, OGD |
| Dakshina Chilukuri | Reviewer, DCP III, OCP |
| Dale Conner | Director, DBE I, OGD |
| Barbara Davit | Acting Director, DBE II, OGD |
| Angelica Dorantes | Team Leader, ONDQA |
| Tapash Ghosh | Reviewer, ONDQA |
| Sam Haidar | Reviewer, OGD |
| Ramana Uppoor | Deputy Director, DCP I, OCP |
| Jayabharathi Vaidyanathan | Reviewer, DCP II, OCP |
| Donna Volpe | Researcher, LCP, OTR |
| Nam (Esther) Chun | Executive Secretary, BCS Committee, OGD |

**Agenda:**

**BCS Classification of NDA 022-529 Lorcaserin Hydrochloride Tablets**

**Background:**

The DCP requested that the BCS Committee review information submitted in NDA 022-529 in support of BCS classification for Lorcaserin Hydrochloride Tablets. Arena Pharmaceuticals, Inc. submitted a solubility study, an *in vitro* permeability study using cultured monolayers of Caco-2 cells and a human mass balance study, and a dissolution profile study to support a Biopharmaceutics Classification System (BCS) Class I waiver request. The Committee was asked to evaluate the data for a final determination regarding BCS Class 1.
**See Attachment I for additional information.**

**Conclusion:**

All committee members are in agreement that Lorcaserin Hydrochloride Tablets can be classified as a BCS Class I drug. **Please see Attachment II for additional comments.**

**Vote:**
Vote: Yes (11), No (0)

Drafted: Nam Chun 07/06/10

Comments :
D. Chilukuri : 05/24/10
D. Conner : 06/30/10
B. Davit: 07/02/10
S. Haidar: 05/16/10
M. Mehta: 05/14/10
J. Vaidyanathan: 05/18/10
D. Volpe: 05/12/10
R. Uppoor: 05/12/10
L. Yu: 05/15/10
T. Ghosh: 05/28/10
A. Dorantes: 06/23/10

V:\Division\Bio\BCS\2010 Meetings\2010-0\May-10Minutes

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22529 | ORIG-1 | ARENA PHARMACEUTICALS INC | LORQESS (lorcaserin hydrochloride) Tablets |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

JOHN Z DUAN
08/05/2010

PATRICK J MARROUM
08/05/2010

# *Office of Clinical Pharmacology*
# *New Drug Application Filing and Review Form*

**General Information About the Submission**

| | Information | | Information |
|---|---|---|---|
| **NDA Number** | 22-529 | **Brand Name** | *Lorqess (tbd)* |
| | | | |
| **Medical Division** | DMEP | **Drug Class** | |
| **OCP Reviewer(s)** | Immo Zdrojewski, Ph.D.<br>Weili Huang, Ph.D. (*in-vitro* studies) | **Indication(s)** | weight management, including weight loss and maintenance of weight loss |
| **OCP Team Leader** | Sally Choe, Ph.D. | **Dosage Form** | Immediate release tablet |
| | | **Proposed Dosing Regimen** | 10 mg BID without regards to meals |
| **Date of Submission** | 12/18/2009 | **Route of Administration** | Oral |
| **Estimated Due Date of OCPB Review** | | **Sponsor** | Arena Pharmaceuticals Inc. |
| **PDUFA Due Date** | 10/22/2010 | **Priority Classification** | Standard |
| **Division Due Date** | 08/27/2010 | **Submission Type** | 505 (b) (1) |

**Clin. Pharm. and Biopharm. Information**

| | **"X" if included at filing** | **Number of studies submitted** | **Number of studies reviewed** | **Critical Comments If any** |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | **X** | | | |
| **Tabular Listing of All Human Studies** | **X** | | | |
| **HPK Summary** | **X** | | | |
| **Labeling** | **X** | | | |
| **Reference Bioanalytical and Analytical Methods** | | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | **X** | **1** | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | **X** | **1** | | |
| **Plasma protein binding:** | **X** | **1** | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| ***Healthy Volunteers-*** | **X** | **2** | | |
| single dose: | | 1 | | |
| multiple dose: | | 1 | | |
| ***Patients-*** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / ~~non-fasting~~ single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | No in-vivo effect on primary drug was conducted |
| In-vivo effects of primary drug: | X | 2 | | Effect of co-administration of lorcaserin on dextromethorphan;<br>study was repeated due to the small number of completers in the first study |

| | | | | |
|---|---|---|---|---|
| In-vitro: | X | 3 | | CYP Inhibition and induction studies |
| In-vitro permeability: | X | 1 | | |
| In-vitro metabolism: | X | 8 | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | X | 1 | | Ages 18-65 and > 65 |
| renal impairment: | X | 1 | | Age range was 18-79 years |
| hepatic impairment: | X | 1 | | Age range was 18-75 years |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | X | 1 | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | X | | | Sponsor used a combination of rich and sparse data |
| Data sparse: | X | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / ~~multi dose:~~ | **X** | **1** | | **Capsule vs. tablet formulation** |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | **X** | **2** | | Capsule and tablet formulation |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | **26** | | |

| | | | | |
|---|---|---|---|---|
| **Filability and QBR comments** | | | | |
| | **"X" if yes** | **Comments** | | |
| **Application filable ?** | **X** | **Yes, it is filable.** | | |
| **Comments sent to firm ?** | | 1. Submit the bioanalytical method validation for study APD-356-001C.<br>2. Submit individual subject concentration data including their renal impairment and hepatic impairment classification information from the studies APD-356-016 and APD-356-017, respectively.<br>3. Submit the actual names of the analytes that are reported in individual subject concentration datasets for studies APD-356-012 and APD-356-002. | | |
| **QBR questions (key issues to be considered)** | • Is the dose and dosing regimen adequate?<br>• Is dose adjustment required based on covariates?<br>• What is the effect of lorcaserin on dextromethorphan?<br>• Is the capsule bioequivalent to the tablet formulation?<br>• Is lorcaserin a BCS class I compound? | | | |
| **Other comments or information not included above** | No DSI inspection is requested in this submission. | | | |
| **Primary reviewer Signature and Date** | **Immo Zdrojewski, Ph.D.** | | | |
| **Secondary reviewer Signature and Date** | **Sally Choe, Ph.D.** | | | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | ✓ | | | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | ✓ | | | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | ✓ | | | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | | ✓ | | See data request |
| 5 | Has a rationale for dose selection been submitted? | ✓ | | | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | ✓ | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | ✓ | | | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | ✓ | | | |
| **Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | **Data** | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | ✓ | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | ✓ | |
| | **Studies and Analyses** | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | ✓ | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | ✓ | | | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | ✓ | | | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | ✓ | | | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | ✓ | (b) (4) |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | ✓ | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | ✓ | | | |
| | **General** | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | ✓ | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | ✓ | | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes___**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

The purpose of this document is to identify refuse to file and special issues, describe the materials needed for review but not included in the application, and summarize the application relevant to clinical pharmacology.

## 1. Identify refuse to file issues

**Are there any refuse to file issues?**

No, the application is filable from the Clinical Pharmacology perspective.

**Does the applicant provide sufficient data to support the labeling claims?**

Yes, from a clinical pharmacology perspective, sufficient data is provided to perform appropriate evaluation of the label claims.

## 2. Identify special issues

**What are the specific issues regarding this application?**

- Is the dose and dosing regimen adequate?
- Is dose adjustment required based on covariates?
- What is the effect of lorcaserin on dextromethorphan?
- Is the capsule bioequivalent to the tablet formulation?
- Is lorcaserin a BCS class I compound?

## 3. Identify materials needed for review but not included in the application

**What are the materials needed for review but not included in the application?**

The following data need to be requested:

1. Bioanalytical method validation for study APD-356-001C
2. Individual subject concentration data including their renal impairment and hepatic impairment classification information from the studies APD-356-016 and APD-356-017, respectively
3. Actual names of the analytes that are reported in individual subject concentration datasets for studies APD-356-012 and APD-356-002

## 4. Summary of the application relevant to clinical pharmacology

The sponsor, Arena Pharmaceuticals Inc., is submitting a 505 (b)(1) new drug application (NDA 22-529) seeking marketing approval for a 10 mg BID dose of lorcaserin hydrochloride immediate release tablets. Lorcaserin, according to the sponsor, is a selective serotonin 2C (5-$HT_{2C}$) receptor agonist.

The sponsor is seeking the indication for weight management, including weight loss and maintenance of weight loss, and usage in conjunction with a reduced-calorie diet and a program of regular exercise. The intended target population is 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).

Arena Pharmaceuticals Inc. proposes a 10 mg dose given twice daily without regards to food. While there is no proposed dose adjustment in mild renal impaired patients, use with caution is recommended in moderate renal impaired patients and lorcaserin should not be used in patients with severe renal impairment and ESRD. No dose adjustment is proposed based on hepatic impairment (HI) for mild and moderate HI. Additionally, the sponsor proposes no dose adjustments based on other covariates (body weight, age, gender and race).

Lorcaserin is an inhibitor of human CYP2D6 ($IC_{50}$=3.99 μM) in liver microsomes. The following CYPs were less affected ($IC_{50}$>50 μM): CYP 1A2, 2C9, 2C19, 3A4.
In order to evaluate the drug-drug interaction potential with CYP 2D6 substrates, the sponsor conducted two DDI studies with dextromethorphan as CYP 2D6 probe. (b) (4)

Lorcaserin's site of metabolism is mainly in the liver. The main organ of excretion is the kidney. 92.3% of a radioactive dose were recovered in the urine. Metabolite 1 (M1) is formed by direct conjugation to N-sulfamate ($HSO_3$-lorcaserin). M1 is the major circulating metabolite (approx 38%), and a minor metabolite in urine (3%). The sponsor states that $HSO_3$-lorcaserin is pharmacologically inactive and the exposure in circulation is approx. 1-5 fold of that of the parent drug. The following enzymes were identified by the sponsor to be involved in the formation of $HSO_3$-lorcaserin: SULT 1A2, 1A1, 2A1, 1E1.
A second metabolite, Metabolite 2 (M2, 7-OH lorcaserin), is a minor metabolite in plasma and is proposed to be formed mainly by CYP 2D6. Five other metabolites were detected in plasma (<10% of total radioactivity each).
The N-carbomylglucuronide of lorcaserin (Metabolite 5, M5) is the major metabolite in urine (approx. 36% of total dose). The following enzymes are believed to be involved in its formation: UGT 1A9, 2B7, 2B15, 2B17.

The half life of the parent drug, lorcaserin is approx. 11 h. In contrast, the half life of the N-sulfamate is approx. 41 h. The mean accumulation of lorcaserin ranges from 1.1 to 1.4.
Lorcaserin is a chiral compound. The sponsor intends to market the (b) (4) and did not observe inter-conversion to (b) (4) in-vivo.

The tablet dosage form was used in two of three Phase 3 studies. Other clinical dosage forms included an oral solution used in Phase 1, and (b) (4) (b) (4) capsules used in Phase 1, Phase 2, and the first Phase 3 clinical trial. The prototype tablet formulation was further optimized to a white-colored tablet formulation. Market-image tablet formulation has the same composition as the white tablet, except for the blue color. Furthermore, the sponsor claims BCS class I status for lorcaserin and comparative in vitro dissolution testing has been used in most cases to evaluate the effects of formulation and process changes on product performance instead of clinical bioequivalence studies.

The clinical pharmacology program consists of the following 13 in-vivo studies:

- 3 intrinsic factor studies
  - renal impairment
  - hepatic impairment
  - obese elderly vs. obese adult pharmacokinetics
- 4 extrinsic factor studies
  - 2 fasted vs. fed pharmacokinetic studies (both tablet and capsule formulation)

    - 2 drug-drug interaction studies with CYP 2D6 probe dextromethorphan
- 4 pharmacokinetic studies
    - maximum tolerated dose (single and multiple dose)
    - mass balance study
    - relative bioavailability (capsule vs. tablet formulation)
- 1 PK/PD study
    - Effect of lorcaserin on body weight, appetite, and food intake
- 1 thorough QT study

During the clinical program the sponsor conducted two phase 2 studies, APD356-003 and APD356-004 with a total duration of 28 days and 3 month respectively. Study APD356-003 assessed doses of 1 mg, 5 mg, and 15 mg given once daily, and placebo. Study APD356-004 evaluated doses of 10 mg and 15 mg given once daily, 10 mg given twice daily, and placebo. Additionally, two phase 3 safety and efficacy studies APD356-009 and APD356-011 were conducted. An additional third phase 3 study in overweight and obese patients with type 2 diabetes mellitus is still ongoing.

Study APD356-009 evaluated doses of 10 mg BID and placebo. The total duration of the study was 104 weeks. The efficacy for weight loss and weight maintenance were evaluated. For the efficacy for weight loss, the weight loss in the 10 mg BID dosing group was compared to placebo at week 52. Efficacy for weight maintenance was assessed during the second year of the trial: at Week 52, patients assigned to lorcaserin were re-randomized 2:1 to remain on lorcaserin or to switch to placebo; all patients on placebo remained on placebo. Safety assessments included echocardiograms (for FDA-defined valvulopathy assessment) at screening, Week 24, Week 52, Week 76, and Week 104. In a subset of patients, PK samples were obtained at week 12 visit (pre-dose and 2 hours post dose).

Study APD356-011 evaluated doses of 10 mg QD and 10 mg BID compared to placebo; the total duration of the study was 52 weeks. Safety assessments included echocardiograms at baseline, Week 24 and Week 52 prolactin samples were collected at baseline and at week 4, 12, 24, and 52 (pre dose, and 2 h post dose sample). PK samples were collected in a subset of patients at weeks 12, 24 and 52 (pre-dose, 1.5 to 2.5 h, and 3.5 to 6 h post-dose)

Studies APD356-009 and APD356-011 evaluated the following co-primary endpoints:

- 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

For a detailed overview of all studies submitted during this NDA please see Attachment 1.

The sponsors reports that headache was the most commonly reported adverse event in all studies, including single dose studies of healthy subjects and phase 3 studies. In broader terms, adverse events were related to nervous system and psychiatric disorders, which may include alteration in perception and mood (thought to be mediated by 5-$HT_{2A}$). Other areas of concern include the potential increase in prolactin levels, especially in light of the pre clinical findings, and the potential of valvulopathy (thought to be mediated by 5-$HT_{2B}$), the potential of pulmonary hypertension and gallbladder related adverse events. For these areas of concerns, the exposure-response relationship for safety will be evaluated, to assess whether it supports the proposed dosing regimen.

Additionally, the sponsor included population pharmacokinetic analysis, exposure-response analysis and 14 in-vitro studies in the application. The in-vitro studies include protein binding and blood/plasma ratio, Caco-2 permeability, and metabolism studies (Attachment 2).

**Attachment 1:**



## 5.2 TABULAR LISTING OF ALL CLINICAL STUDIES

| Type of Study | Study Identifier | Location of Study Report | Primary Objective of the Study | Study Design and Type of Control | Test Product(s): Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status: Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| PK | APD356-001A | 5.3.3.1 | Define the maximum tolerated dose (MTD) of lorcaserin following a single oral dose | Double-blind, placebo-controlled, randomized, dose escalation study | Lorcaserin: 10, 20, and 40 mg; single dose, oral | 45 | Healthy Subjects | Single dose | |
| PK (Extrinsic Factor) | APD356-001B | 5.3.3.4 | Determine the PK characteristics of a single oral dose of lorcaserin in the fed versus fasted state | Open-label, 2 period crossover study | Lorcaserin: 10 mg, single dose, oral | 12 | Healthy Subjects | Single dose | |
| PD/PK | APD356-001C | 5.3.4.1 | Assess the effect of a single oral dose of lorcaserin on appetite and food intake | Double-blind, placebo-controlled, randomized, four period crossover study | Lorcaserin: 0.1, 1, and 10 mg; single dose, oral | 20 | Healthy Subjects | Single dose | |
| PK | APD356-002 | 5.3.3.1 | Define the maximum tolerated dose (MTD) of lorcaserin following multiple oral doses | Double-blind, placebo-controlled, randomized, dose-escalated study | Lorcaserin: 3, 10, and 20 mg; Placebo; QD/14 days, oral | 27 | Healthy Subjects | 14 days | |
| Safety and Efficacy | APD356-003 | 5.3.5.1 | Assess the effect of lorcaserin on body weight in uncomplicated obese patients | Double-blind, placebo-controlled, randomized, parallel group study | Lorcaserin: 1, 5, and 15 mg; Placebo; QD/28 days, oral | 352 | Obese and overweight patients | 28 days | |
| Safety and Efficacy | APD356-004 | 5.3.5.1 | Assess the effect of lorcaserin on body weight after 12 weeks of administration in obese patients | Double-blind, placebo-controlled, randomized, dose ranging, parallel group study | Lorcaserin: 10 mg QD/3 mo; 10 mg BID/3 mo; 15 mg QD/3 mo; Placebo BID/3 mo, oral | 469 | Obese and overweight patients | 3 mo | |

**Attachment 1:**



| Type of Study | Study Identifier | Location of Study Report | Primary Objective of the Study | Study Design and Type of Control | Test Product(s): Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status: Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| BA | APD356-005 | 5.3.1.2 | Assess the single-dose relative bioavailability of 10 mg lorcaserin tablets compared to 10 mg lorcaserin hard gelatin capsules, under fasting conditions | Open-label, randomized, 2-way crossover, 2-sequence, comparative bioavailability study under fasting conditions | Lorcaserin: 10 mg single dose tablet form and 10 mg single dose capsule form after 14 days, oral | 28 | Healthy Subjects | 14 days | |
| PK | APD356-006 | 5.3.3.1 | Assess the mass balance of lorcaserin following a single oral dose of $^{14}C$-labeled lorcaserin | Open-label, single-dose, mass balance study | Lorcaserin: 10 mg single dose, oral | 6 | Healthy Subjects | Single dose | |
| Thorough ECG | APD356-007 | 5.3.5.4 | Determine the effects of lorcaserin on ECG parameters | Double-blind (with exception of moxifloxacin), randomized, placebo- and positive-controlled, parallel arm, steady-state, multiple dose study | Lorcaserin: 15 mg or 40 mg or placebo, QD/7 days; and moxifloxacin: 400 mg single dose, oral | 244 | Healthy Subjects | 7 days | |
| PK (Extrinsic Factor) | APD356-008 | 5.3.3.4 | Evaluate the impact of multiple doses of lorcaserin on the plasma levels of a single dose of dextromethorphan | Open-lable, single- and multiple dose, 1-sequence, drug-drug interaction study under fasted conditions | Lorcaserin: 20 mg QD/4 days; dextromethorphan 30 mg/20 mL, 2 single doses separated by 9 days, oral | 24 | Healthy Subjects | 11 days | |

## Attachment 1:



| Type of Study | Study Identifier | Location of Study Report | Primary Objective of the Study | Study Design and Type of Control | Test Product(s): Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status: Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Safety and Efficacy | APD356-009 | 5.3.5.1 | Assess the weight loss effect of lorcaserin at the end of 52 weeks in overweight and obese patients; and the ability of lorcaserin to maintain body weight loss at the end of 104 weeks | Randomized, double-blind, placebo-controlled, parallel group study | Lorcaserin: 10 mg and matching placebo, BID/104 weeks, oral | 3182 | Obese and overweight patients | 104 weeks | |
| Safety and Efficacy | APD356-010 (ongoing) | 5.3.5.4 | Assess the weight loss effect of lorcaserin at the end of 52 weeks in overweight and obese patients with type 2 diabetes mellitus managed with oral hypoglycemic agent(s) | Randomized, double-blind, placebo-controlled, parallel group study | Lorcaserin: 10 mg and matching placebo, QD and BID/52 weeks, oral | 604 | Obese and overweight patients with Type II diabetes mellitus | 52 weeks | Ongoing |
| Safety and Efficacy | APD356-011 | 5.3.5.1 | Assess the weight loss effect of lorcaserin at the end of 52 weeks in overweight and obese patients | Randomized, double-blind, placebo-controlled, parallel group study | Lorcaserin: 10 mg QD and BID and matching placebo/52 weeks, oral | 4008 | Obese and overweight patients | 52 weeks | |

**Attachment 1:**



| Type of Study | Study Identifier | Location of Study Report | Primary Objective of the Study | Study Design and Type of Control | Test Product(s): Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status: Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| PK (Extrinsic Factor) | APD356-012 | 5.3.3.4 | Determine the impact of multiple doses of lorcaserin on the plasma levels of a single dose of dextromethorphan | Open-label, single- and multiple-dose, randomized, 1-sequence, drug-drug interaction study under fasting conditions | Lorcaserin: 10 mg, BID/4 days; dextromethorphan 60 mg/20 mL, 2 single doses separated by 9 days, oral | 24 | Healthy Subjects | 11 days | |
| Abuse Liability | APD356-013 | 5.3.5.4 | Evaluate the abuse potential of lorcaserin as measured by Drug Liking Visual Analog Scale | Randomized, double-blind, double-dummy, placebo- and active-controlled, 7-way crossover study | Zolpidem: 15 and 30 mg<br>Ketamine: 100 mg<br>Lorcaserin: 20, 40, and 60 mg, matching placebo, oral | 35 | Healthy subjects who are recreational polydrug users | 5 day 3-dose visit; followed by seven 3-day, single dose visits, each with a 7-day washout | |
| Energy Expenditure/ Metabolism | APD356-014 (ongoing) | 5.3.5.4 | To assess the effect of lorcaserin on 24h energy metabolism after 56 days of treatment | Double-blind, randomized, placebo-controlled, parallel group study | Lorcaserin 10 mg and matching placebo, BID/56 days, oral | ~56 | Overweight and obese patients | 56 days | Ongoing |
| PK (Extrinsic Factor) | APD356-015 | 5.3.3.4 | Evaluate the PK properties of lorcaserin in fed versus fasted state | Open-label, 2-period, crossover study | Lorcaserin 10 mg, single dose fed and single dose fasted separated by a 7±1 day washout period, oral | 12 | Obese and overweight patients | 11 days | |
| PK (Intrinsic Factor) | APD356-016 | 5.3.3.3 | Assess PK properties of lorcaserin in subjects with mild, moderate, or severe renal impairment as compared to subjects with normal renal function | Open-labeled, parallel group study | Group 1-4: 10 mg lorcaserin<br>Group 5: 10 mg lorcaserin Day 1 (non-dialysis) and 10 mg lorcaserin Day 8 (dialysis period), oral | 40 | 32 Renal Impaired Subjects, 8 Healthy Subjects | Groups 1-4: Single dose; Group 5: 8 days | |

## Attachment 1:



| Type of Study | Study Identifier | Location of Study Report | Primary Objective of the Study | Study Design and Type of Control | Test Product(s): Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status: Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| PK (Intrinsic Factor) | APD356-017 | 5.3.3.3 | Evaluate PK properties of lorcaserin in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function | Open-label, parallel group study | Lorcaserin: 10 mg single dose, oral | 24 | 16 Hepatically Impaired Subjects, 8 Healthy Subjects | Single dose | |
| PK (Intrinsic Factor) | APD356-018 | 5.3.3.3 | Compare the PK parameters of lorcaserin in obese or overweight elderly to those of obese or overweight adults | Open-label, parallel group study | Lorcaserin: 10 mg single dose, oral | 24 | 12 Elderly Subjects, 12 Healthy Subjects | Single dose | |

PK= pharmacokinetic; PD = pharmacodynamic; BA = bioavailability

**Attachment 2:**

| | |
|---|---|
| **Plasma Protein Binding: Human Plasma and Human Whole Blood** | |
| PDR-05-208 | *In Vitro* Determination of Plasma Protein Binding of $^{14}$C-APD356 in Human, Rat, Mouse, Monkey, Rabbit and Dog Plasma Using Equilibrium Dialysis |
| PDR-08-056 | *In Vitro* Determination of Human Whole Blood to Plasma Partition Coefficient of Lorcaserin |
| **Permeability and Transport: Caco-2 Cell Monolayers** | |
| PDR-08-160 | Permeability and P-glycoprotein (P-gp) Interaction Potential of Lorcaserin |
| **Metabolism and Enzymatic Pathways: Liver Microsomes and Recombinant Enzymes** | |
| PDR-08-281 | Identification of CYP and FMO Enzymes Responsible for Oxidative Metabolism of Lorcaserin |
| PDR-08-294 | Identification of Human UDP-glucuronosyltransferases Responsible for Lorcaserin *N*-Carbamoyl Glucuronidation |
| PDR 06-204 | Identification of Human Sulfotransferases Involved in APD356 *N*-Sulfamate Formation |
| PDR-08-206 | Species Comparison of $^{14}$C-Lorcaserin Metabolism in Human, Monkey, Rabbit, Rat and Mouse Liver Microsomes |
| PDR-09-145 | Identification of Metabolites of $^{14}$C-Lorcaserin Generated by Liver S9 Fraction from Mouse, Rat, Rabbit, Monkey, and Human |
| **Inhibition of Drug Metabolizing Enzyme: Human CYP Enzymes** | |
| PDR-07-197 | Inhibition of Human Liver Microsomal CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 by Lorcaserin |
| PDR-08-295 | Inhibition Potential of Lorcaserin Sulfamate on Human Liver Microsomal CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 |

**Attachment 2:**

| | |
|---|---|
| PDR-09-117 | Inhibition Potential of Lorcaserin and Lorcaserin Sulfamate on Human Liver Microsomal CYP2C8 Activity |
| **Induction of Drug Metabolizing Enzyme: CYP Enzymes in Cultured Human Hepatocytes** | |
| XT043012 | *In Vitro* Evaluation of APD356 and APD125 as Inducers of Other Cytochrome P450 Expression in Cultured Human Hepatocytes |
| 3210-0451-1800 | *In Vitro* Assessment of the Induction Potential of AR244208 in Primary Cultures of Human Hepatocytes |

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22529 | ORIG-1 | ARENA PHARMACEUTICALS INC | LORQESS (lorcaserin hydrochloride) Tablets |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

IMMO ZDROJEWSKI
04/05/2010

SALLY Y CHOE
04/05/2010