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RESEARCH**

APPLICATION NUMBER:

208524Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA	208524 Serials 0000, 0008, 0010
Submission Dates	September 18, 2015, March 09, 2016, and April 6, 2016
Brand Name	BELVIQ XR®
Generic Name	lorcaserin HCl
Reviewer	Renu Singh, Ph.D.
Team Leader	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Arena Pharmaceuticals Inc.
Formulation; Strength	Extended release tablets; 20 mg
Relevant IND/NDA	IND119664, NDA22529
Indication	Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of: <ul style="list-style-type: none">• 30 kg/m² or greater (obese), or• 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)

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1 Executive Summary

The applicant seeks approval of 20 mg lorcaserin extended-release (XR) once daily (q.d) tablets as an adjunct therapy to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients via the regulatory 505(b)(1) pathway. BELVIQ® (lorcaserin HCl, APD356) immediate-release (IR) tablet was approved under NDA 22529 on 27 June, 2012 at 10 mg dose twice daily (b.i.d).

1.1. Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 208524 Clinical Pharmacology data submitted on September 18, 2015, March 09, 2016, and April 6, 2016 and recommends approval. Labeling recommendations are provided on pages 19-20.

1.2. Post Marketing Requirement

None.

1.3. Summary of Important Clinical Pharmacology Findings

The applicant had submitted one pivotal bioequivalence (BE) study (APD356XR-101) and one food effect study (APD356XR-102) to bridge the approved lorcaserin HCl 10 mg IR b.i.d to 20 mg XR q.d

Pivotal BE study: APD356XR-101 was an open-label, randomized, two-way, two-sequence, crossover study to determine the pharmacokinetics (PK) and BE of single and multiple doses of lorcaserin HCl 20 mg XR q.d and 10 mg IR b.i.d tablets administered to fasted subjects. This study demonstrated that following a single dose, equivalence for only AUC-based parameters ($AUC_{0-\infty}$ and AUC_{0-t}) was achieved for the XR product as compared to the IR product (Table 1). Lorcaserin mean C_{max} following single dose of the XR product was approximately 25% lower than the corresponding value for the IR treatment; consequently, the 90% confidence interval (CI) of the geometric mean ratio (GMR) of C_{max} was outside the BE limits of 0.800-1.250 (90% CI of 0.70-0.79).

However, in a multiple dose setting the 90% CIs for the GMR for $AUC_{24,ss}$ and $C_{max,ss}$ for the lorcaserin HCl 20 mg XR tablet relative to 10 mg IR tablet were contained within the BE limits of 0.80-1.25 (Table 2). Approximately 9 hr delay in t_{max} was observed with XR formulation as compared to IR with single as well as multiple dosing. Overall, lorcaserin BE for AUC and C_{max} between the XR and IR formulations was achieved at steady state. Box plots in Figure 1 show that the distribution of $AUC_{24,ss}$ and $C_{max,ss}$ were similar for XR and IR tablets at steady state. While the sponsor did not meet BE criteria following single dose, steady state BE was considered acceptable and adequate to bridge XR and IR formulations because of the following reasons:

1. During NDA 22529, exposure-response analysis established that for IR product $AUC_{24,ss}$ was predictive of the probability of 5% and 10% weight loss achieved in patients as shown in Figure 2 (NDA 22529, Clin Pharm review dated 05/31/2012).
2. This drug is intended for chronic use and the difference in C_{max} observed with single dose is expected to have minimal impact on the long-term efficacy in patients.

Table 1. 90% CI on the GMR of lorcaserin PK parameters following a single dose oral administration of lorcaserin HCl 20 mg XR q.d. and 10 mg IR b.i.d.

Parameter	N ^a	Geometric Mean		G.M. Ratio ^d	90% CI ^e
		Test ^b	Reference ^c		
AUC _{0-∞} (hr·ng/mL)	34	1219	1235	0.987	(0.948, 1.028)
AUC _{0-t} (hr·ng/mL)	34	1169	1207	0.968	(0.931, 1.007)
C _{max} (ng/mL)	34	39.0	52.2	0.748	(0.705, 0.793)^f

^aN=34; excludes subjects #7 and #34

^bTest = 20 mg XR q.d.

^cReference = 10 mg IR b.i.d.

^dGMR = Geometric mean of the test/reference ratio

^e90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio

^fDid not meet BE.

Source: Study APD356XR-101 study report Page 55

Table 2. 90% CI on the GMR of lorcaserin PK parameters following multiple dose oral administration of lorcaserin HCl 20 mg XR q.d. and 10 mg IR b.i.d.

Parameter	N ^a	Geometric Mean		G.M. Ratio ^d	90% CI ^e
		Test ^b	Reference ^c		
AUC _{0-24,ss} (hr·ng/mL)	34	1234	1324	0.932	(0.891, 0.975)
C _{max,ss} (ng/mL)	34	73.8	79.9	0.924	(0.876, 0.975)

^aN=34; excludes subjects #7 and #34

^bTest = 20 mg XR q.d.

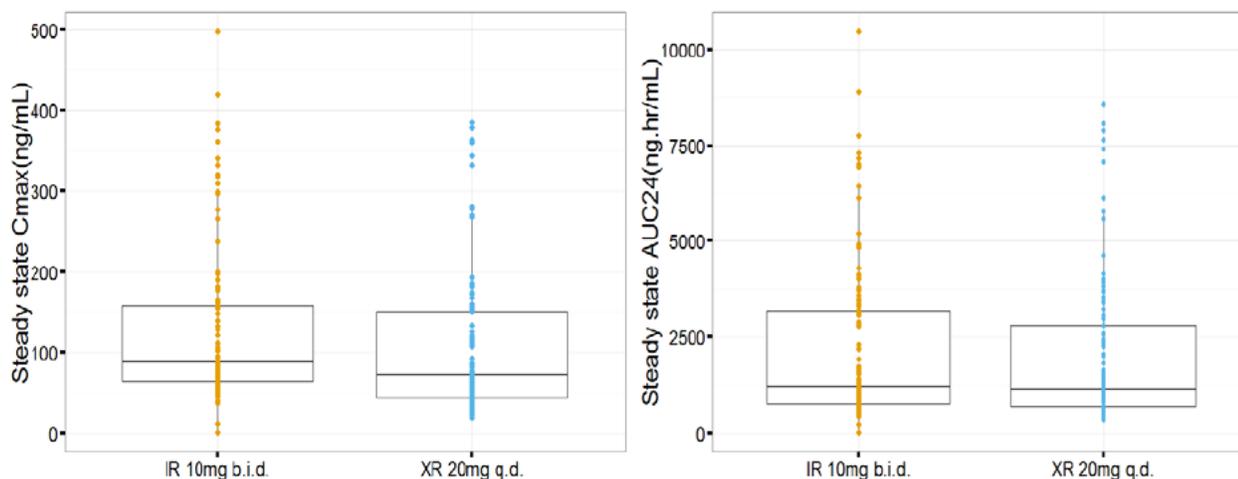
^cReference = 10 mg IR b.i.d.

^dGMR = Geometric mean of the test/reference ratio

^e90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio

Source: Study APD356XR-101 study report Page 55

Figure 1. Box plots showing steady state exposures (AUC_{24,ss} and C_{max,ss}) for IR 10 mg b.i.d and XR 20 mg q.d in APD356XR-101 study.



Source: NDA 208524 APD356XR-101 Reviewer's analysis

Food effect study: APD356XR-102 was an open-label, randomized, two-treatment, two-period, two-sequence, crossover study to assess single and multiple doses of 20 mg XR q.d lorcaserin tablets for food effect, under fasting and fed conditions. The approved IR product is recommended without regards to food. Intake of high fat, high calorie breakfast before a single 20 mg oral dose of lorcaserin XR resulted in

approximately 46% increase in C_{max} and 17% increase in $AUC_{0-\infty}$ but no change in t_{max} . Under steady state dosing conditions with lorcaserin HCl 20 mg XR, the food effect observed after single dosing was attenuated, as BE was demonstrated in both the $C_{max,ss}$ and $AUC_{24,ss}$ parameters. Higher C_{max} observed with single dose of lorcaserin 20 mg XR in the fed state were similar to that observed with the IR formulation in study APD356XR-101 in the fasted state and were not deemed to be a safety concern. Because steady state parameters are more relevant for chronic weight loss indication and no significant food effect was observed at steady state, we agree with applicant's conclusion of administering lorcaserin XR tablets without regards to food.

Overall, Clinical Pharmacology recommends the approval of NDA 208524.

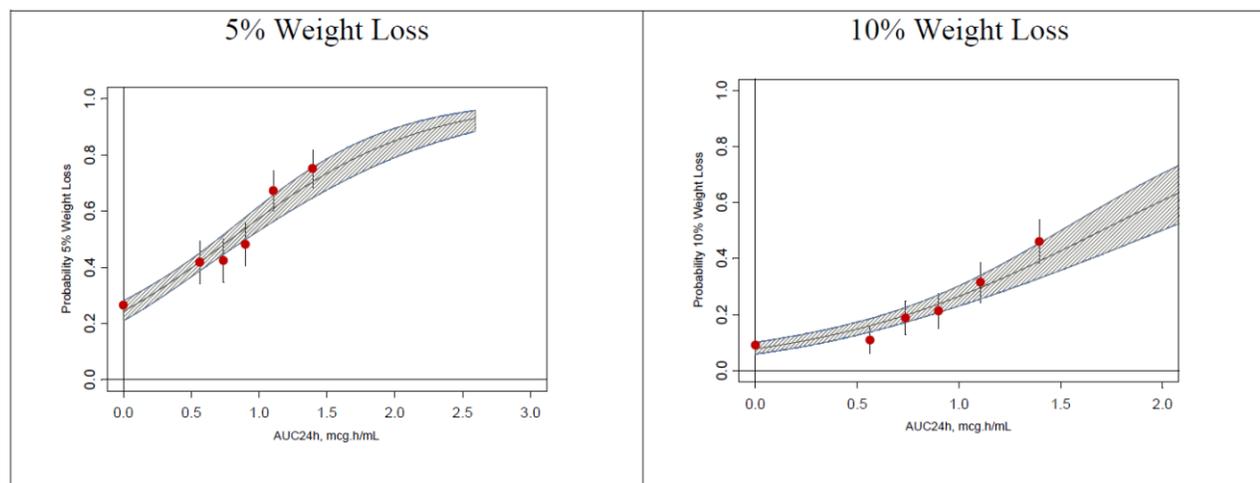
2. Question-Based Review

2.1. Background

BELVIQ® (lorcaserin HCl, APD356) is a selective serotonin 2C (5-HT_{2C}) receptor agonist that reduces body weight by selectively mimicking the effects of serotonin at the 5-HT_{2C} receptor. Serotonin is a monoamine neurotransmitter that decreases food intake through its actions in the central nervous system. Serotonin decreases food intake by increasing meal related satiety, reducing pre-meal hunger, and reducing intra-meal food intake.

The applicant's development program for the XR product is based on the exposure-response relationship as established previously in the phase 3 program for IR lorcaserin HCl (NDA 22529). Clinical pharmacology review dated 05/31/2012 for IR lorcaserin HCl (NDA 22529) included Figure 2, where a relationship of lorcaserin exposure to weight loss (response) was derived from the model-based $AUC_{24,ss}$ using pharmacokinetic/pharmacodynamics (PK/PD) modeling. The positive exposure-response analysis for probability of weight loss (Figure 2) supported the approved dose of IR 10 mg b.i.d lorcaserin. At a median $AUC_{24,ss}$ of 0.815 $\mu\text{g}\cdot\text{hr}/\text{mL}$, corresponding to the median exposure for IR 10 mg b.i.d dose, the model-predicted probability of 5% and 10% weight loss was 51% and 22%, respectively. In comparison, at a median $AUC_{24,ss}$ of 0.425 $\mu\text{g}\cdot\text{hr}/\text{mL}$, corresponding to the median exposure at the 10 mg q.d dose, the probability of 5% and 10% weight loss was 37% and 13.5%. The applicant believes that a PK/PD bridging strategy (i.e., AUC) is adequate to support approval of a once-daily, XR lorcaserin in weight management. This approach was agreed to by the Division of Metabolism and Endocrinology Products in the pre-IND meeting and noted in the agency's meeting minutes dated 18 April 2014.

Figure 2. Exposure-response analysis for 5% and 10% weight loss.



Source: NDA 22529, Clin Pharm review dated 05/31/2012

2.1.1. What are the Clinical Pharmacology and Biopharmaceutics studies submitted in the NDA? Three clinical pharmacology studies (1 pilot and 2 pivotal) were submitted by the applicant (Table 3). This review focuses on the two pivotal studies -APD356XR-101 and APD356XR-102.

Table 3. Overview of clinical studies used to characterize the biopharmaceutical properties of lorcaserin

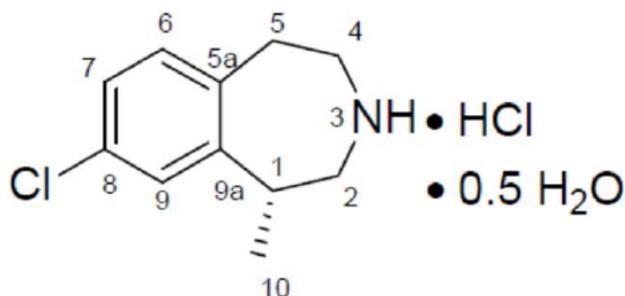
Protocol	Study Design	Objective	Lorcaserin HCl Dose
BE study			
APD356-031	Open-label, five-period, fixed-sequence, non-randomized study to evaluate the pharmacokinetics of three modified release prototype formulations of lorcaserin	To assess the relative bioavailability of single-doses of 20-mg lorcaserin modified-release prototype tablets, under fasting conditions	Single oral doses 10-mg IR tablets and 20-mg XR prototype tablets
APD356XR-101	Open-label, randomized, two-treatment, two-period, two-sequence, randomized, balanced crossover study of single and multiple doses of lorcaserin, comparative bioavailability design under fasting conditions	To assess single and multiple doses of lorcaserin for bioequivalence of 20-mg XR lorcaserin tablets and 10-mg lorcaserin IR tablets, under fasting conditions	Single and multiple oral doses 10-mg IR tablets, b.i.d, and 20-mg XR tablets, q.d
Food effect studies			
APD356XR-102	Open-label, randomized, two-treatment, two-period, two-sequence, randomized, balanced crossover study of single and multiple doses of lorcaserin	To assess single and multiple doses of lorcaserin for food effect of 20-mg XR lorcaserin tablets, under fasting and fed state conditions	Single and multiple oral doses 20-mg XR tablets, q.d

Source: NDA 208524 Module 2.7.1.

2.2. General Attributes

2.2.1. What are lorcaserin key physicochemical properties?

Figure 3. The structural formula of lorcaserin HCl.



Source: NDA 22529 Seq 0000 Module 2.2

Lorcaserin has a molecular weight of 241.16 g/mol and molecular formula of $C_{11}H_{15}ClN \cdot 0.5H_2O$.

Table 4. Physicochemical properties of lorcaserin.

Property	Lorcaserin
Appearance	White to off-white powder
pK _a	9.53
logP	2.56
Melting	On heating at 10°C/min, lorcaserin HCl hemihydrate (b) (4)
Solubility	
In water	Very soluble ^a
In Ethanol	Freely soluble ^b
In Dimethyl sulfoxide	Freely soluble ^b
In Ethyl acetate	2.4 mg/mL

^aVery soluble is < 1 g solvent needed to dissolve 1 g lorcaserin HCl hemihydrate.

^bFreely soluble is between 1 g and 10 g solvent needed to dissolve 1 g lorcaserin HCl hemihydrate.

Source: Modified from NDA 22529 Module 3.2.S.1.3.

2.2.2. What is the formulation for the to-be-marketed lorcaserin XR?

Table 5 below details the formulation of the to-be-marketed XR lorcaserin HCl tablets.

Table 5. Composition of lorcaserin HCl 20 mg XR tablets.

Component	Grade	Function	mg/tablet	%w/w
(b) (4)				
Lorcaserin HCl hemihydrate	In-house ^a	Drug substance	20.776 ^b	(b) (4)
Microcrystalline cellulose	NF, Ph. Eur.	(b) (4)	(b) (4)	(b) (4)
Mannitol	USP, Ph. Eur.			
Hypromellose	USP, Ph. Eur.			
Colloidal silicon dioxide	NF, Ph. Eur.			
Magnesium stearate	NF, Ph. Eur.			
(b) (4)				
Ethylcellulose dispersion Type B	NF			(b) (4)
(b) (4)				

^aRefer to NDA 22,529, Section 3.2.S.4.1, Specification [Lorcaserin HCl Hemihydrate, (b) (4)]

^bEquivalent to 20 mg lorcaserin HCl and (b) (4)

(b) (4) Refer to NDA 208524 Module 3.2.P.1 for composition.

Essentially removed during processing.

^cPercent of coating on (b) (4) tablet.

(b) (4) Refer to NDA 208524 Module 3.2.P.1 for composition.

Source: NDA 208524 Module 3.2.P.1

The applicant reported that batch# 14254006 manufactured at the (b) (4) tablets commercial scale was used in the APD356XR-101 and APD356XR-102 studies. The commercial tablet formulation differs from the scaled-up development/clinical formulation only with respect to the color of film coating.

2.2.3. What are the findings from OSIS inspection?

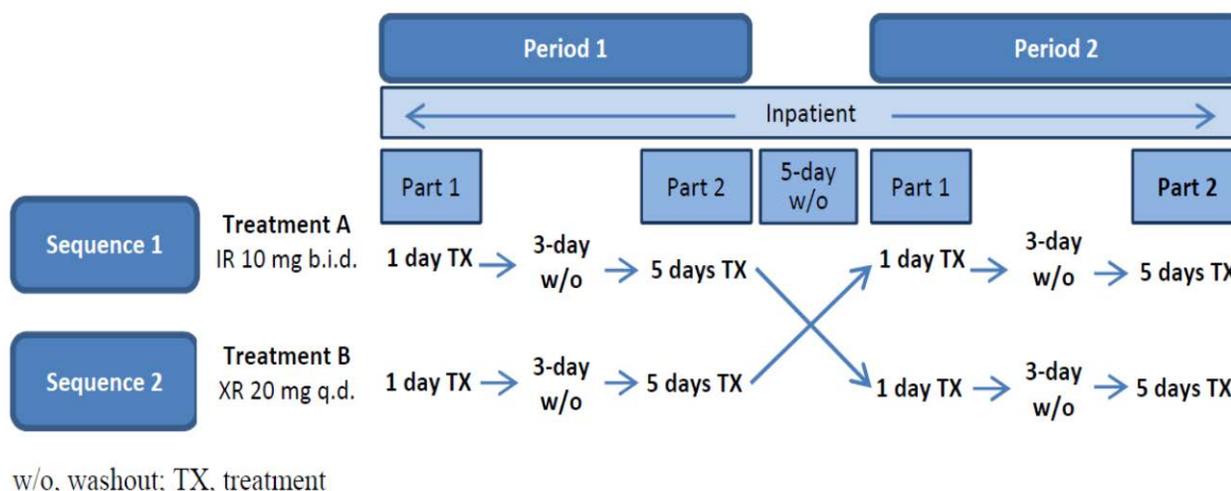
OSIS inspection was requested for the clinical and analytical sites for pivotal BE study APD356XR-101. Clinical site was not inspected based on past inspection history. However, OSIS inspection for the bioanalytical site was carried out in the week of (b) (4). No major deficiencies were observed and no Form FDA 483 was issued. Refer to audit report from OSIS for details.

2.3. General Clinical Pharmacology

2.3.1. Are the single and steady state exposures of lorcaserin HCl 20 mg XR q.d comparable to 10 mg IR b.i.d under fasting conditions?

Study APD356XR-101 was a phase 1, two-treatment, two-period, two-sequence, randomized, crossover study of single and multiple doses of lorcaserin HCl 20 mg XR q.d and 10 mg IR b.i.d administered in the fasted state to 36 healthy male and female subjects. The trial design is shown in Figure 4 below.

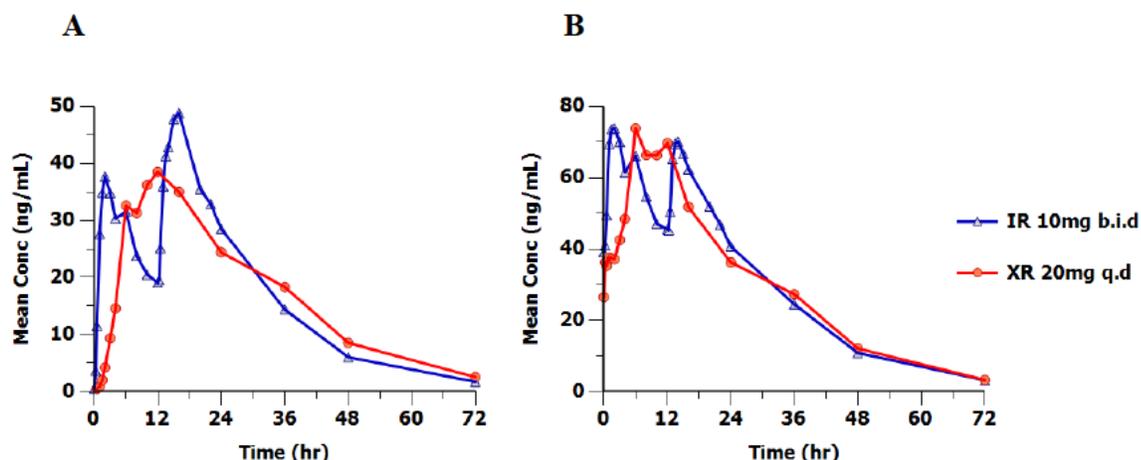
Figure 4. Schematic of APD356XR-101 study design



Source: Study APD356XR-101 study report Page 22.

The mean PK profiles of lorcaserin XR q.d vs IR b.i.d formulations after single and multiple dosing are shown in Figure 5. A single dose administration of lorcaserin XR 20 mg q.d resulted in comparable total plasma exposure ($AUC_{0-\infty}$), but approximately 25% lower C_{max} relative to IR tablets b.i.d (38.8 vs 52.3 ng/mL, respectively) (Table 6 and Figure 5). The median time to maximal lorcaserin plasma concentrations (t_{max}) were 3 and 12 hours for IR and XR formulations, respectively. In single dose BE study lorcaserin XR C_{max} is similar to first peak concentration from IR formulation. However, since the dosing frequency for IR is b.i.d and half-life is approximately 12 hr, accumulation causes second peak of IR b.i.d dosing to be higher relative to XR q.d dosing.

Figure 5. Mean plasma concentrations of lorcaserin vs. time at single dose (A) and steady state (B) following lorcaserin XR 20 mg q.d or IR 10 mg b.i.d tablets under fasted conditions (n=34)



Source: NDA 208524 APD356XR-101 Reviewer's analysis

Table 6. Geometric mean (%CV) of lorcaserin PK parameters after a single dose and under steady state conditions (n=34)

Parameter	Single Dose		Steady-State ^c	
	IR 10 mg b.i.d	XR 20 mg q.d	IR 10 mg b.i.d	XR 20 mg q.d
$t_{1/2z}$ ^a (hr)	11.8 (1.32)	13.6 (3.34)	11.9 (1.5)	11.8 (1.48)
t_{max} ^b (hr)	3 (1.5, 4)	12 (6, 16)	1.5 (1, 3)	10 (6, 12)
AUC _{0-t} (hr·ng/mL)	1212 (23.9)	1166 (27.3)	NA	NA
AUC _{0-∞} (hr·ng/mL)	1240 (24.2)	1217 (27.9)	NA	NA
AUC ₀₋₂₄ (hr·ng/mL)	754 (23.1)	633 (28.9)	1328 (26.5)	1235 (28.2)
C_{max} (ng/mL)	52.3 (24.0)	38.8 (30.8)	80.1 (25.7)	73.9 (31.1)
$C_{min,ss}$ (ng/mL)	NA	NA	35.2 (25.8)	29.9 (37.1)
C_{24} (ng/mL)	27.7 (24.2)	23.6 (27.4)	39.2 (27.8)	34.6 (32.4)
$C_{av,ss}$ (ng/mL)	NA	NA	55.3 (26.5)	51.5 (28.2)
V_z/F (L)	229 (23.1)	265 (26.7)	216 (26.0)	231 (25.8)
CL/F (L/hr)	13.5 (25.2)	13.9 (27.9)	12.7 (26.5)	13.7 (28.2)
Fluctuation ^d	NA	NA	0.800 (19.6)	0.824 (25.4)
Swing ^e	NA	NA	1.26 (26.5)	1.42 (46.4)

^aMean (sd)

^bMedian (minimum, maximum)

^cSteady-state achieved after 5 consecutive days of dosing (Figure 5)

^dFluctuation: $(C_{max,ss} - C_{min,ss}) / C_{av,ss}$

^eSwing: $(C_{max,ss} - C_{min,ss}) / C_{min,ss}$

Source: Study APD356XR-101 study report Page 56.

The pre-dose concentrations for the IR and XR formulations between the two study periods and parts were <5% of C_{max} suggesting that the washout period was adequate and pre-dose concentrations did not contribute significantly to the PK results. Under steady state conditions, the median $t_{max,ss}$ were 1.5 and 10 hours for the IR 10 mg b.i.d and XR 20 mg q.d, respectively; $C_{max,ss}$ were 80.1 (25.7%) and 73.9 (31.1%) ng/mL; and AUC_{24,ss} were 1328 (26.5%) and 1235 (28.2%) hr·ng/mL, respectively. Apparent oral clearance and apparent volume of distribution values reported in this study were similar to those reported

for IR formulation in NDA 22529 phase 3 population pharmacokinetic analysis 16.2 L/h and 241 L, CL/F and Vz/F, respectively (NDA 22529 – Module 5.3.5.3 Study Report- 0604-005). The terminal half-life ($t_{1/2z}$) was not affected by formulation type or repeat dosing. The range of half-lives (11.8 to 13.6 hr) reported in Table 6 were similar to those reported in the phase 1 studies (NDA 022529 – Module 5.3.3.1 Study Report- APD356-001A). Under steady state conditions, the average plasma concentrations (C_{av}) were similar 55.3 and 51.5 ng/mL, IR and XR, respectively.

Metabolites Pharmacokinetics

Lorcaserin metabolites are not active and were not used in assessing BE of the IR and XR formulations. The major and minor circulating metabolites of lorcaserin are designated M1 and M5; lorcaserin sulfamate and *N*-carbamoyl glucuronide of lorcaserin, respectively. Previous phase 1 trials have documented half-lives to be approximately 40 and 12 hr for M1 and M5, respectively (NDA 022529 – Module 5.3.3.1 Study Report- APD356-002). M1 and M5 levels were observed within 1 hr after administration of lorcaserin HCl IR formulation. The M1 and M5 PK parameters from XR 20 mg q.d were similar to IR at 10 mg b.i.d (Table 7 and 8) and with those reported previously after a single dose and after 14 consecutive once daily administration of lorcaserin HCl IR formulation (NDA 022529 – Module 5.3.3.3 Study Report- APD356-016). Similar to the t_{max} observations of the parent compound under steady state conditions, the t_{max} values for M1 and M5 were delayed, from 3 to 6 hr and 1 to 6 hr, respectively. Repeat dosing resulted in accumulation of M1 by 3.2 to 4.45 fold. M5 accumulation was less than 2-fold. The accumulation of M1 and M5 was consistent with half-lives of approximately 40 and 15 hr, respectively.

Note: In NDA 22529 study APD356-001A (NDA 022529 – Module 5.3.3.1 Study Report- APD356-001A) lorcaserin was not well tolerated at the 40 mg dose level particularly in one female subject where moderate and severe intensity adverse events (hallucinations, euphoric mood and tremor) were recorded. Females in general were noted to have a higher frequency of adverse events and a higher exposure of metabolite M1 (HSO3-APD356). Over a three-fold increase in M1 metabolite (HSO3-APD356) exposure, in terms of AUC, was noted as compared to the parent drug. The increased exposure of the M1 metabolite, in particular females, was hypothesized to be responsible for the increased incidence and the nature of adverse events reported following a single dose of 40 mg, however no causal relationship was established. In study APD356XR-101 M1 metabolite exposures were similar between XR and IR products as shown in Table 7.

Table 7. Geometric Means (%CV) of M1 PK parameters following oral administration of single and multiple doses of lorcaserin HCl (n=34)

Parameter	Single Dose		Multiple Dose ^c	
	IR 10 mg b.i.d	XR 20 mg q.d	IR 10 mg b.i.d	XR 20 mg q.d
Formulation	IR 10 mg b.i.d	XR 20 mg q.d	IR 10 mg b.i.d	XR 20 mg q.d
$t_{1/2}$ ^a (hr)	38.9 (16.8)	49.0 (30.2)	41.7 (10.5)	45.8 (23.1)
t_{max} ^b (hr)	4 (3, 12)	24 (0, 36)	3 (1.5, 6)	6 (3, 16)
AUC _{0-t} (hr·ng/mL)	3076 (38.1)	2591 (41.1)	NA	NA
AUC _{0-∞} (hr·ng/mL)	4449 (44)	4312 (50.4)	NA	NA
AUC ₀₋₂₄ (hr·ng/mL)	1159 (38.8)	868 (42.4)	4280 (43.8)	3866 (47.3)
C_{max} (ng/mL)	67.9 (37.1)	48.8 (42.2)	218 (45.5)	185 (48.4)

^aMean (sd)

^bMedian (minimum, maximum)

^c5 consecutive days of dosing

Source: Study APD356XR-101 study report Page 65

Table 8. Geometric means (%CV) of M5 PK parameters following oral administration of single and multiple doses of lorcaserin HCl (n=34)

Parameter	Single Dose		Multiple Dose ^c	
	IR 10 mg b.i.d	XR 20 mg q.d	IR 10 mg b.i.d	XR 20 mg q.d
Formulation	IR 10 mg b.i.d	XR 20 mg q.d	IR 10 mg b.i.d	XR 20 mg q.d
t _{1/2} ^a (hr)	10.4 (1.9)	13.6 (3.3)	12.5 (1.9)	14.2 (2.8)
t _{max} ^b (hr)	1.5 (1, 10)	8 (4, 16)	1 (1, 3)	6 (3, 12)
AUC _{0-t} (hr·ng/mL)	646 (25.3)	606 (30.9)	NA	NA
AUC _{0-∞} (hr·ng/mL)	697 (23.2)	673 (28.7)	NA	NA
AUC ₀₋₂₄ (hr·ng/mL)	505 (23.2)	405 (28.2)	678 (24.8)	590 (29.4)
C _{max} (ng/mL)	54.9 (24.1)	25.2 (28.4)	64.6 (27)	36.6 (30.2)

^aMean (sd)

^bMedian (minimum, maximum)

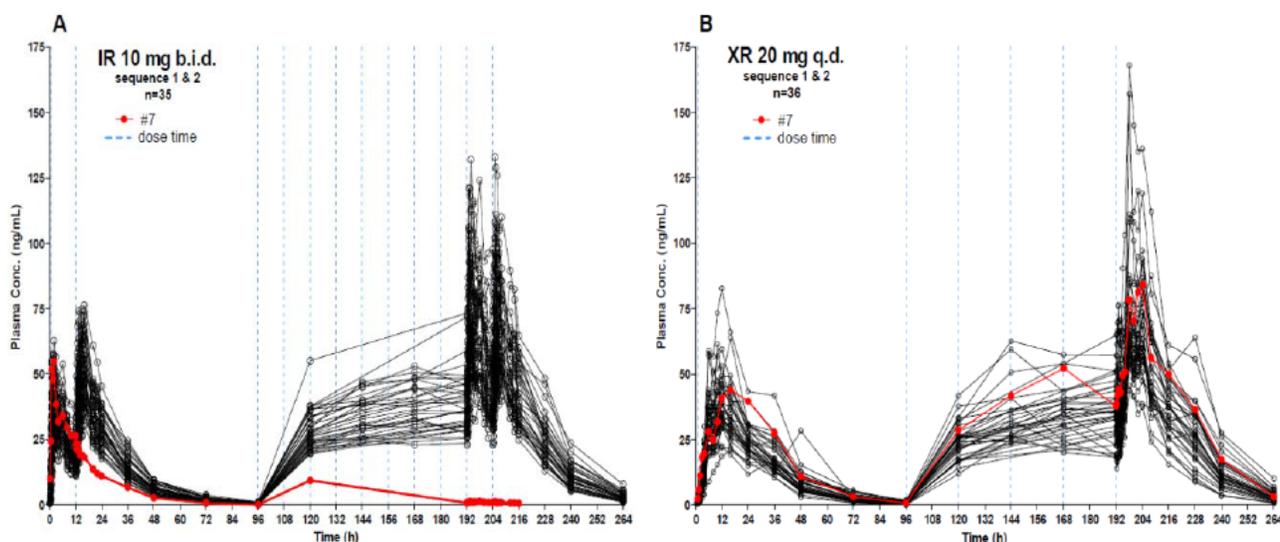
^c5 consecutive days of dosing

Source: Study APD356XR-101 study report Page 65

Outlier Subjects

Although 36 subjects were randomized and dosed in the study, BE analysis was conducted with 34 subjects. Subject #34 left the study for personal reasons after Day 9. Data from this subject were incomplete and therefore not included in the PK analysis. The applicant has qualified Subject #7 as an outlier in this study. This subject's concentration-time profiles for the IR treatment following single and multiple doses were dissimilar to the dosing population (Figure 6, panel A and B). The concentration-time profile suggests that the second, 12 hr dose and subsequent multiple doses of IR regimen was either not taken or not absorbed. The applicant reanalyzed the plasma samples of subject #7 and conducted extensive review of the clinical personnel and dosing log. However, they failed to conclusively identify a reason for this subject's highly disparate drug exposures for the IR formulation. In contrast, comparison of subject #7 plasma concentration-time profiles after single or multiple doses of the XR formulation to all individuals dosed (Figure 6, panel B) were similar to the total dosing population. This suggested that the drug absorption from the XR product was not an issue in this subject.

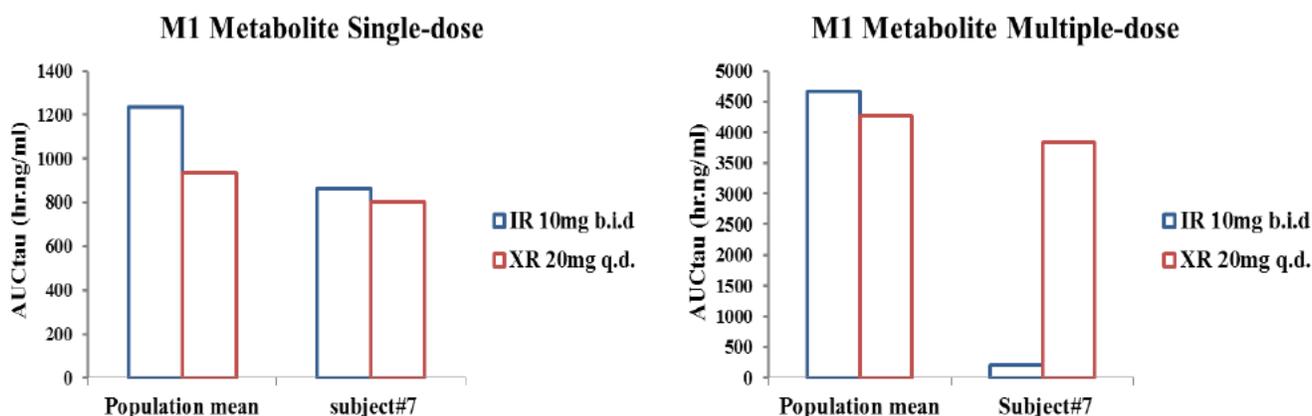
Figure 6. Mean plasma concentrations vs. time following lorcaserin HCl IR 10 mg b.i.d (panel A, left) and XR 20 mg q.d (panel B, right) under fasted conditions.



Source: Study APD356XR-101 study report Page 49.

A review of the metabolite M1 data suggested that the metabolite exposure of subject #7 tracked with the parent compound and was significantly lower than the entire population for multiple day dosing of IR formulation. (Figure 7). This suggested that the metabolite formation for subject#7 was similar to the population. Randomization sequence and safety profile for this subject were also examined. Submitted data suggests that subject#7 got IR formulation first followed by XR. This subject had mild headache and nausea with IR formulation. The nausea resolved in less than 5 hr but the headache continued for 36 hr. There were no adverse events reported with XR formulation for this subject.

Figure 7. Comparison of M1 metabolite AUC_{tau} of subject #7 versus population mean (n=34) with single and multiple dosing of XR 20 mg q.d and IR 10 mg b.i.d tablets.



Source: NDA 208524 APD356XR-101 Reviewer’s analysis

Table 9 and 10 show that when subject #7 data is included in the analysis the BE criteria is not met for both AUC and C_{max} at steady state as well as single dose C_{max}.

Table 9. 90% CI on the GMR of lorcaserin PK parameters following a single dose oral administration of lorcaserin HCl 20 mg XR q.d and 10 mg IR b.i.d (including subject #7)

Parameter	Geometric Mean			G.M. Ratio ^d	90% CI ^e
	N ^a	Test ^b	Reference ^c		
AUC _{0-∞} (hr·ng/mL)	35	1229	1222	1.005	(0.957, 1.056)
AUC _{0-t} (hr·ng/mL)	35	1178	1195	0.986	(0.939, 1.035)
C _{max} (ng/mL)	35	39.0	52.3	0.746	(0.704, 0.790)^f

^aN=34; excludes subjects #7 and #34

^bTest = 20 mg XR q.d

^cReference = 10 mg IR b.i.d

^dGMR = Geometric mean of the test/reference ratio

^e90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio

^fDid not meet BE.

Source: Study APD356XR-101 study report Page 60

Table 10. 90% CI on the GMR of lorcaserin PK parameters following multiple dose oral administration of lorcaserin HCl 20 mg XR q.d and 10 mg IR b.i.d (including subject #7)

Parameter	Geometric Mean			G.M. Ratio ^d	90% CI ^e
	N ^a	Test ^b	Reference ^c		
AUC _{0-24,ss} (hr·ng/mL)	35	1241	1174	1.057	(0.856, 1.306) ^f
C _{max,ss} (ng/mL)	35	74.2	70.8	1.047	(0.848, 1.293) ^f

^aN=34; excludes subjects #7 and #34

^bTest = 20 mg XR q.d

^cReference = 10 mg IR b.i.d

^dGMR = Geometric mean of the test/reference ratio

^e90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio

^fDid not meet BE.

Source: Study APD356XR-101 study report Page 60

Note that subject #7 is an outlier with respect to the IR (reference) product and not the XR product. We agree with applicant's assessment to consider subject#7 data as an outlier and the exclusion of subject #7 from BE analysis is acceptable.

Table 11 shows the results of the BE analysis with subject # 7 excluded. The GMR and 90% CI of the ratio with single and multiple dose treatments of lorcaserin HCl 20 mg XR q.d and 10 mg IR b.i.d, based on log-transformed parameters are represented in Table 11. The 90% CI of the GMR of steady state C_{max,ss} and AUC_{24,ss} were contained within the BE limits of 0.800-1.250 following multiple dose treatments. Lorcaserin BE between the XR and IR formulations was achieved at steady state.

Table 11. 90% CI on the GMR of lorcaserin PK parameters following a single and multiple dose oral administration of lorcaserin HCl 20 mg XR q.d and 10 mg IR b.i.d

Following Single Dose Oral Administration of Lorcaserin HCl 20 mg XR					
Parameter	Geometric Mean			G.M. Ratio ^d	90% CI ^e
	N ^a	Test ^b	Reference ^c		
AUC _{0-∞} (hr·ng/mL)	34	1219	1235	0.987	(0.948, 1.028)
AUC _{0-t} (hr·ng/mL)	34	1169	1207	0.968	(0.931, 1.007)
C _{max} (ng/mL)	34	39.0	52.2	0.748	(0.705, 0.793) ^f
Following Multiple Dose Oral Administration of Lorcaserin HCl 20 mg XR					
AUC _{0-24,ss} (hr·ng/mL)	34	1234	1324	0.932	(0.891, 0.975)
C _{max,ss} (ng/mL)	34	73.8	79.9	0.924	(0.876, 0.975)

^aN=34; excludes subjects #7 and #34

^bTest = 20 mg XR q.d

^cReference = 10 mg IR b.i.d

^dGMR = Geometric mean of the test/reference ratio

^e90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio

^fDid not meet BE.

Source: Modified from Study APD356XR101 study report Page 55

2.3.2. How does food affect the bioavailability of lorcaserin 20 mg XR q.d?

Study APD356XR-102 was a two-way, two-sequence, randomized, crossover study to determine the relative bioavailability of single and multiple doses of lorcaserin HCl XR q.d product in the fed and fasted state in 36 healthy male and female subjects. The meal selected was the standard, high-fat meal used to assess food effect as described by the FDA guidance document. Following the oral administration of a

single dose of the XR tablet, the geometric mean (GM) C_{max} values for fed and fasted were 56.1 and 38.5 ng/mL, respectively, (Table 12), a 46% increase with food. The difference in the integrated exposure (AUC_{0-t}) between fed and fasted was 18% (1294 vs. 1097 hr·ng/mL, fed vs. fasted, respectively); the GM for $AUC_{0-\infty}$ was 1.17 higher in the fed state after single dosing. BE between fed and fasted states using C_{max} and AUC_{0-t} exposure metrics was not achieved after a single dose. However, extrapolating to infinity ($AUC_{0-\infty}$) and thus capturing greater than 90% of the exposure, BE for $AUC_{0-\infty}$ was achieved between fed and fasted states with single dosing (Table 13).

Table 12. Geometric mean (%CV) for lorcaserin PK Parameters after oral administration of lorcaserin HCl XR 20 mg q.d for a single dose or under steady state conditions

Parameter ^{a, d}	Single		Steady-State	
	fasted	fed	fasted	Fed
AUC_{0-24} (hr·ng/mL)	611 (42.9)	808 (27.7)	1216 (40.4)	1318 (29.5)
$AUC_{0-\infty}$ (hr·ng/mL)	1141 (48.6)	1332 (28.6)	N	N
AUC_{0-t} (hr·ng/mL)	1097 (48.1)	1294 (28.0)	N	N
$C_{av,ss}$ (ng/mL)	N	N	50.7 (40.4)	54.9 (29.5)
C_{max} (ng/mL)	38.5 (39.4)	56.1 (31.8)	69.5 (38.4)	78.7 (30.9)
$C_{min,ss}$ (ng/mL)	N	N	28.9 (54.9)	N
$t_{1/2z}$ (hr) ^b	13.0 (2.44)	12.4 (2.35)	12.4 (1.94)	12.0 (1.68)
t_{max} (hr) ^c	12 (6, 24)	12 (8, 16)	10 (6, 12)	12 (4, 16)

NA = not applicable

^ahealthy volunteer subjects, n = 36/treatment

^bmean (SD)

^cmedian (minimum, maximum)

^dnumbers rounded to 3 significant figures

Source: Study APD356XR-102 study report Page 56.

Following a single oral dose administration of lorcaserin HCl 20 mg XR q.d, the median t_{max} was 12 hr in both the fasted and fed states. Following a multiple dose oral administration of lorcaserin HCl 20 mg XR q.d, the median t_{max} was 10 hr in the fasted state, and 12 hr in the fed state. Food did not affect the time to achieve C_{max} of lorcaserin HCl 20 mg XR (Table 12). Following maximum absorption, elimination was monoexponential. Following a single dose, the mean $t_{1/2z}$ of lorcaserin in the fasted state was 13.0 hr and 12.4 hr in the fed state. Following multiple dosing, the mean $t_{1/2z}$ of lorcaserin in the fasted state was 12.4 hr and 12.0 hr in the fed state. Elimination of lorcaserin from the systemic circulation was not affected by the presence of food.

GM $C_{max,ss}$ values at steady state for fed and fasted were 78.7 and 69.5 ng/mL, respectively, (Table 12), a 13% increase with food. The difference in the integrated exposure over a dosing interval of 24 hr ($AUC_{24,ss}$) was 8% (1318 vs. 1216 hr·ng/mL, fed vs. fasted, respectively). BE between fed and fasted states was achieved in both $C_{max,ss}$ and $AUC_{24,ss}$ parameters under steady state conditions. Table 13 presents the estimate of the PK population GMR and associated 90% CI between the fed and fasted state single and multiple dose treatments, based on log-transformed parameters.

Table 13. Bioequivalence determination between fed and fasted states based on lorcaserin AUC_{0-∞}, AUC_{0-t} and C_{max} after oral administration of lorcaserin HCl XR 20 mg q.d

Following Single Dose Oral Administration of Lorcaserin HCl 20 mg XR					
Parameter	N	Geometric Mean			
		Test ^a	Reference ^b	G.M. Ratio ^c	90% CI ^d
AUC _{0-∞} (hr·ng/mL)	36	1332	1141	1.167	(1.092, 1.247)
AUC _{0-t} (hr·ng/mL)	36	1294	1097	1.179	(1.103, 1.260) ^e
C _{max} (ng/mL)	36	56.1	38.5	1.459	(1.345, 1.581) ^e
Following Multiple Dose Oral Administration of Lorcaserin HCl 20 mg XR					
AUC _{0-24,ss} (hr·ng/mL)	36	1318	1216	1.084	(1.027, 1.145)
C _{max,ss} (ng/mL)	36	78.7	69.5	1.134	(1.071, 1.199)

^aTest = 20 mg XR q.d in the fed state (n=36)

^bReference = 20 mg XR q.d in the fasted state (n=36)

^cG.M. Ratio = Geometric mean of the test/reference ratio

^d90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio

^eBE not achieved; boundaries; BE boundaries 0.800, 1.250

Source: Study APD356XR-102 study report Page 56.

As shown in Table 12, there is a 46% and 18% increase in C_{max} and AUC_{0-t}, respectively after single dose of lorcaserin XR when given with food. This increase in exposure with food following single dose is not observed at steady-state and BE was achieved for both AUC and C_{max}. The increase in exposure on day 1 was not considered to be clinically significant based on the following reasons:

- Based on cross study comparisons, the C_{max} reported for the single dose of XR formulation in the fed state was similar to that observed with IR formulation in APD356XR-101 study in the fasted state (Table 14). The C_{max} observed in this food effect study was also consistent to that observed in the pilot study APD356-031 (Table 14).

Table 14. Comparison of C_{max} in ng/mL from single dose oral administration of lorcaserin HCl 20 mg XR q.d and 10 mg IR b.i.d across studies in NDA 208524.

Study	Formulation	Dose	Fasted	Fed
Pilot APD356-031	IR	10 mg b.i.d	35.6	
	XR	20 mg q.d	33.8	51.1
Pivotal APD356XR-101	IR	10 mg b.i.d	52.3	
	XR	20 mg q.d	38.8	
Food effect APD356XR-102	IR	10 mg b.i.d		
	XR	20 mg q.d	38.5	56.1

- A review of the treatment-emergent adverse events reported for 36 subjects showed gastrointestinal and nervous system events were 11 versus 3 and 7 versus 8 in the fasted and fed state, respectively. The majority of adverse events were mild (98.5%) or moderate (1.5%) in intensity, resolved during the course of the study, and required no concomitant medications.

Overall, similar safety profile and BE at steady state between the fed and fasted state supported the administration of lorcaserin XR 20 mg q.d without regards to food.

In studying the XR dosage form, the possibility that co-administration with food results in dose dumping was considered. If the complete dose is rapidly released from the formulation than intended there is a

potential safety risk to study subjects. *In vitro* studies suggested no alcohol dose dumping potential within the first 2 hr. Refer to CMC review for details. In this study with the XR formulation of lorcaserin, the effect of a high fat meal given prior to a single or multiple XR 20 mg q.d doses showed no evidence of dose dumping as evidenced by no change in t_{max} values (Table 12).

2.4. Bioanalytical

2.4.1. Are the bioanalytical methods properly validated to measure lorcaserin in plasma samples?

Bioanalytical method using liquid chromatography/tandem mass spectrometry (LC-MS/MS) for the quantitation of lorcaserin, and metabolites M1 (HSO3-APD356) and M5 (APD356- β -carbamoyl-glucuronide) in human plasma was validated (Table 15). Acetonitrile was added to plasma samples to precipitate proteins. After centrifugation, the supernatant was filtered through a 96-well protein precipitation plate, diluted, and injected directly onto the LC-MS/MS system for simultaneous analysis of lorcaserin, M1, and M5.

An API 5000 was operated in the selected reaction monitoring mode under optimized conditions for detection of positive ions and negative ions formed by electrospray ionization. All validations for the LC-MS/MS bioanalytical assay of lorcaserin and its metabolites appear acceptable with reasonable precision and accuracy.

Table 15. Validation summary for bioanalytical methods

Validation report	(b) (4)
Martix (anticoagulant)	Human plasma (heparin)
Sample volume	0.025 mL
Sample preparation	Protein precipitation
Sample analysis	LC-MS/MS
Linear range	0.500-200 ng/mL for lorcaserin, 0.500-200 ng/mL for M1, 2.00-800 ng/mL for M5
Regression type	Linear (1/concentration ²)
Quantitation method	Peak area ratio
Sensitivity	0.500 ng/mL (lower limit of quantitation)
Specificity/selectivity	No endogenous interference or matrix effect
Inter-assay accuracy (%Bias)	0.9% to 6.7% for lorcaserin, -4.3% to -0.7% for M1, 5.0% to 9.1% for M5
Inter-assay precision (%CV)	0.0% to 2.3% for lorcaserin, 2.3% to 8.4% for M1, 0.0% to 2.2% for M5
Freeze-thaw cycles	5 cycles
Frozen matrix stability	204 days at -70°C
Ambient matrix stability	6 hr
Studies	APD356XR-101, APD356XR-102

Source: NDA 208524 Module 2.7.1 Page 11

3. Label Recommendations

Red strikethrough text means deletion of the sponsor's proposed text. Blue underscored text means recommended addition.

12.3 Pharmacokinetics

Absorption

In an open label, randomized, crossover clinical trial (b) (4) single dose and steady state pharmacokinetics of BELVIQ XR 20 mg administered once daily were compared with lorcaserin hydrochloride immediate-release 10 mg tablet administered twice daily under fasted conditions in 34 healthy subjects. At steady state (b) (4) the time to reach peak plasma concentrations of lorcaserin (t_{max}) following BELVIQ XR 20 mg once daily was approximately (b) (4) 10 hours (b) (4) as compared to 1.5 hours with lorcaserin hydrochloride immediate release 10 mg tablet bid. A single dose administration of BELVIQ XR 20 mg resulted in comparable total plasma exposure ($AUC_{0-\infty}$), but approximately 25% lower peak exposures (C_{max}) relative to two doses of immediate-release tablets administered 12 hours apart. At steady state, however, both $C_{max,ss}$ and area under the plasma concentration versus time curve ($AUC_{0-24,ss}$) of BELVIQ XR 20 mg were bioequivalent to lorcaserin hydrochloride immediate-release 10 mg tablets bid under fasted conditions. (b) (4)

(b) (4)

Effect of Food. Intake of high fat, high calorie breakfast before a single 20 mg oral dose of BELVIQ XR resulted in approximately 46% increase in C_{max} and 17% increase in $AUC_{0-\infty}$ but no change in t_{max} . At steady state, however, there was no significant food effect on the rate or extent of absorption of BELVIQ XR. (b) (4)

4. Appendix

4.1. Analysis

Geometric mean of lorcaserin PK parameters after single and multiple dosing in study APD356XR-101 were confirmed by independent analysis and were found to be similar to that reported by the applicant.

Table 16. Geometric mean (%CV) of lorcaserin PK parameters after a single dose and under steady state conditions (n=34) (Reviewer’s analysis)

Parameter	Single Dose		Steady-State ^a	
	IR 10 mg b.i.d	XR 20 mg q.d	IR 10 mg b.i.d	XR 20 mg q.d
AUC_{0-72} (hr·ng/mL)	1212.5 (23.9)	1167.3 (27.2)	2068.5 (28.5)	1940.2 (32.5)
$AUC_{0-\infty}$ (hr·ng/mL)	1239.8 (24.3)	1217.1 (27.8)	2125.1 (29.6)	1994.6 (33.4)
AUC_{0-24} (hr·ng/mL)	754.6 (23.1)	634.6 (28.8)	1327.8 (26.5)	1228 (28.2)
C_{max} (ng/mL)	52.3 (24.0)	38.8 (30.8)	80.1 (25.7)	73.9 (31.1)
$AUC_{extrapolated}$ (%)	2.0 (42.3)	3.4 (61.9)	2.1 (61)	2.4 (54.7)

^aSteady-state achieved after 5 consecutive days of dosing

Source: Reviewer’s analysis

4.2. Individual Study Synopsis

4.2.1. APD356XR-101- BE STUDY

Study Title:

A Two-way, Two-sequence, Randomized, Crossover Study to Determine the Pharmacokinetics and Bioequivalence of Single and Multiple Doses of Lorcaserin hydrochloride Extended Release (XR) and Lorcaserin hydrochloride Immediate Release (IR) to Fasted Subjects

Primary Objectives:

- To determine the relative bioavailability of a single dose of lorcaserin HCl 20 mg XR and lorcaserin HCl 10 mg IR at the equivalent total dose (b.i.d), each administered orally under fasted conditions
- To determine the relative bioavailability of lorcaserin HCl 20 mg XR q.d and lorcaserin HCl 10 mg IR b.i.d at steady state, each administered orally under fasted conditions

Secondary Objectives:

- To evaluate the safety and tolerability of lorcaserin hydrochloride 20 mg XR q.d and 10 mg IR b.i.d in healthy subjects

- To evaluate the exposure profiles of the primary metabolites of lorcaserin, M1 and M5

Study Design:

This was a single center, 2-treatment, 2-period, 2-sequence, randomized, balanced crossover study of single and multiple doses of lorcaserin hydrochloride (HCl) extended release (XR) q.d and lorcaserin HCl immediate release (IR) b.i.d administered orally in the fasted state to 36 healthy male and female subjects. Each subject was to receive the following treatments in two treatment periods with 18 subjects per sequence.

Treatment A: consisted of a single day of treatment with lorcaserin HCl 10 mg IR b.i.d, followed by a washout period of 3 days, then followed by 5 days of treatment with lorcaserin HCl 10 mg IR b.i.d (approximately 12 hours apart), all under fasted conditions.

Treatment B: consisted of a single day of treatment with lorcaserin HCl 20 mg XR q.d, followed by a washout period of 3 days, then followed by 5 days of treatment with lorcaserin HCl 20 mg XR q.d, all under fasted conditions.

There was an inpatient washout period of 5 days between treatments.

Treatments A and B were administered in one of 2 sequences of 18 subjects each.

Sequence 1: Treatment A (IR) → Treatment B (XR)

Sequence 2: Treatment B (XR) → Treatment A (IR)

Thirty-six (36) subjects were enrolled. Each subject went through a screening period of up to 21 days. Thirty-six subjects, 18 subjects per sequence, were admitted to the clinical unit in the evening prior to product administration (Day -1) and remained on site through the entire sequence (both treatment periods and the washout interval between periods).

Number of Subjects (Planned and Analyzed):

Thirty-six (36) subjects were planned and enrolled; 36 subjects were analyzed for safety; 34 subjects were included in the analyses of pharmacokinetic variables.

Diagnosis and Main Criteria for Inclusion:

The target study population consisted of 36 healthy male and female subjects (a minimum of 10 per sex) ages 18–45 with a BMI of 18–45 kg/m².

Duration of Treatment: ~7 weeks total: up to 21 days of screening followed by a 27-day inpatient period: check-in on Day -1, Treatment A (IR) or B (XR) (Days 1–9), 5-day washout (Days 10–14), Treatment A (IR) or B (XR) (Days 15–23), additional procedures on Days 24 and 25, exit procedures on Day 26.

Test Product, Dose and Mode of Administration, Lot Number:

Lorcaserin HCl 10 mg IR single dose oral tablets, Lot No. 13057008. Lorcaserin HCl 20 mg XR single dose oral tablets, Lot No. 14254006.

Criteria for Evaluation:

Pharmacokinetic Assessments:

Blood samples were collected for determination of plasma concentrations of lorcaserin and metabolites M1 and M5.

Part 1

In Part 1 IR b.i.d dosing, PK samples were taken on Day 1 and Day 15 pre-morning dose, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 (pre-evening dose), 12.25, 12.5, 13, 13.5, 14, 15, 16, 20, 22, 24, 36, 48 and 72 hours post-dose.

In Part 1 XR q.d dosing, PK samples were taken on Day 1 and Day 15 pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours post-dose.

Part 2

In Part 2 IR b.i.d dosing, PK samples were taken pre-morning dose on Day 5 and Day 19, and Day 6 and Day 20. On Day 9 and Day 23, blood samples were taken pre-morning dose, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 (pre-evening dose), 12.25, 12.5, 13, 13.5, 14, 15, 16, 20, 22, 24, 36, 48, and 72 hours post-dose.

In Part 2 XR q.d dosing, PK samples were taken pre-dose on Day 5 and Day 19, and Day 6 and Day 20. On Day 9 and Day 23, blood samples were taken pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours post-dose.

Pharmacokinetic Methods:

The lorcaserin plasma concentration-time profiles were analyzed using industry standard software (WinNonlin, Phoenix, Version 6.4, Pharsight Corporation, Mountain View, CA) using appropriate non-compartmental techniques to obtain estimates of the pharmacokinetic parameters.

Safety Assessments:

Safety was evaluated by analyzing physical examination findings, clinical laboratory tests (coagulation, serum chemistry, hematology, and urinalysis), vital signs, 12-lead ECGs, and AE reporting.

Statistical Methods:

In agreement with the Food and Drug Administration (FDA) (PreIND 119664 meeting minutes [WRO] dated Feb. 18, 2014) determination of bioequivalence (BE) was based on the steady state AUC values of lorcaserin; XR C_{max} values were assessed to demonstrate either similarity to or lower than the IR C_{max} values. In addition, exposure parameters after single dose administration of lorcaserin were also examined.

ANOVA was performed on log-transformed lorcaserin PK parameters for a single dose (AUC_{0-t} , $AUC_{0-\infty}$, and C_{max}) and multiple dosing (AUC_{0-24} and C_{max}) including terms for treatment, period, sequence, and subject within sequence. Following back-transformation, the ratios of geometric means (i.e. XR product/IR product) and 90% confidence intervals were determined.

Safety: Continuous variables were summarized by treatment group using descriptive statistics, and discrete safety endpoints were summarized by treatment group using frequency and percentages.

CONCLUSIONS

Pharmacokinetic Conclusions:

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

- The lorcaserin HCl 20 mg extended release (XR) formulation is bioequivalent to the immediate release commercially available tablet formulation based on AUC comparisons under single and steady state conditions in fasted volunteers.
- The geometric mean maximum plasma lorcaserin concentration (C_{max}) was lower for the XR formulation under single dose conditions in the fasted state and did not achieve BE; however, BE was met for C_{max} under steady state conditions.
- After administration of the IR formulation, M1 (lorcaserin sulfamate) and M5 (N-carbamoyl glucuronide of lorcaserin) pharmacokinetic profiles were similar to those previously reported. The XR formulation delayed absorption of lorcaserin and, as expected, in turn delayed the formation of M1 and M5. C_{max} values for M1 and M5 each occurred later following XR administration compared to IR administration, and were lower following XR compared to IR administration. After multiple dosing, the resultant XR M1 and M5 ($AUC_{0-24,ss}$) were similar to those observed at the equivalent IR dose.

Safety Conclusions:

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

- Lorcaserin HCl IR 10 mg b.i.d and lorcaserin HCl XR 20 mg q.d were generally well tolerated by healthy male and female subjects in the fasted state.
- A total of 84 treatment-emergent AEs (TEAEs) (multiple occurrences by the same subject in the same treatment period were counted once) were reported by 28 (77.8%) subjects following administration of lorcaserin HCl. Of these, 33 were reported by 18 (50%) subjects during Treatment A (IR 10 mg b.i.d), 32 were reported by 17 (48.6%) subjects during Treatment B (XR 20 mg q.d), and 19 were reported by 10 (27.8%) subjects during the 5-day washout period.
- All TEAEs were mild (95.2%) or moderate (4.8%) in intensity and resolved without concomitant medications.
- The most common TEAEs by subject were headache (19 [52.8%]), dizziness (6 [16.7%]), and nausea (6 [16.7%]). All were considered by the investigator to be related to study drug, were mild in intensity, and resolved without concomitant medication.
- Treatment-related TEAEs were less frequent during treatment with XR 20 mg q.d than with IR 10 mg b.i.d
- More than twice as many AEs of headache were reported during treatment with IR 10 mg b.i.d than with XR 20 mg q.d
- There were no AEs or clinically significant findings reported in clinical laboratory evaluations, vital sign assessments, ECG recordings, or physical examination findings.
- There were no SAEs or deaths reported during the study.

4.2.2. APD356XR-102 – FOOD EFFECT STUDY

Study Title:

A Two-way, Two-sequence, Randomized, Balanced, Crossover Study to Determine the Relative Bioavailability of Single and Multiple Doses of Lorcaserin hydrochloride Extended Release (XR) QD Product in the Fed and Fasted State

Primary Objective:

To determine the relative bioavailability of lorcaserin after administration of 20 mg lorcaserin HCl extended release (XR) q.d product in single and multiple doses in the fed and fasted state.

Secondary Objectives:

To provide information on the safety and tolerability of lorcaserin HCl in healthy subjects.

Study Design:

This was a single center, 2-sequence, randomized, balanced, single and multiple dose, 2-way crossover study in 36 healthy male and female subjects. Each subject received the following two treatments in two treatment periods with 18 subjects per sequence.

Treatment A (fasted state) consisted of a single day of treatment with lorcaserin HCl 20 mg XR q.d in the *fasted* state, followed by a washout period of 3 days, then followed by 5 days of treatment with lorcaserin HCl 20 mg XR q.d in the *fasted* state.

Treatment B (fed state) consisted of a single day of treatment with lorcaserin HCl 20 mg XR q.d in the *fed* state, followed by a washout period of 3 days, then followed by 5 days of treatment with lorcaserin HCl 20 mg XR q.d in the *fed* state.

There was an inpatient washout period of 5 days between treatments.

Treatments A and B were administered in one of two sequences of 18 subjects each.

Sequence 1: Treatment A (fasted) → Treatment B (fed)

Sequence 2: Treatment B (fed) → Treatment A (fasted)

Thirty-six (36) subjects were enrolled. The study included a 21-day screening period. Thirty-six subjects, 18 subjects per sequence, were admitted to the clinical unit in the evening prior to product administration (Day -1) and remained on site through the entire treatment sequence.

Dosing:

Study drug administration was performed on Day 1 or Day 15 (i.e., Day 1/15) and Days 5 through 9 or Days 19 through 23 (i.e., Days 5-9/19-23) with an appropriate interval between subjects based on logistical requirements (e.g. ~5 min).

Subjects in Treatment A (fasted state) received study drug in the morning following an overnight fast (at least 10 hours) on treatment days (Day 1/15 and Days 5-9/19-23). Subjects were maintained in the fasted state for 4 hours following dosing on treatment days.

Subjects in Treatment B (fed state) received study drug in the morning following an overnight fast (at least 10 hours) and 30 minutes after the start of a standardized high-fat meal on treatment days (Day 1/15 and Days 5-9/19-23). Study subjects should have eaten this meal in 30 minutes or less; however, the study drug was administered 30 minutes after start of the meal irrespective of whether the meal had been completed.

Number of Subjects (Planned and Analyzed):

Thirty-six (36) subjects were planned and enrolled; all 36 subjects were analyzed for safety and included in the analyses of pharmacokinetic variables.

Diagnosis and Main Criteria for Inclusion:

The target study population consisted of 36 healthy male and female subjects (a minimum of 10 per sex) ages 18–45 with a BMI of 18–45 kg/m².

Duration per Subject:

~7 weeks total: ~21 days for screening followed by an inpatient period of 27 days: Period 1 (10 days [check-in on Day -1, single dose on Day 1, and a 3-day washout followed by 5 days q.d dosing to steady state]), a 5-day washout, and Period 2 (10 days [single dose on Day 1, 3-day washout followed by 5 days q.d dosing to steady state, 2 days of PK sampling and 1 day follow-up/exit]).

Test Product, Dose and Mode of Administration, Lot Number:

Lorcaserin HCl 20 mg XR single dose oral tablets, Lot No. 14254006.

Subject Assignment:

Subjects were randomly assigned to one of two treatment sequences, Sequence 1 or Sequence 2. Subjects assigned to Sequence 1 received Treatment A, followed by a washout of 5 days, and then Treatment B. Subjects assigned to Sequence 2 received Treatment B, followed by a washout of 5 days, and then Treatment A.

Sample Size:

Thirty-six (36) healthy subjects were dosed to ensure data in 31 evaluable subjects for the primary objective.

Subjects withdrawn due to a drug related adverse event were not to be replaced.

Subjects who were withdrawn for non-drug related adverse events could have been replaced as required to ensure 31 evaluable subjects at the end of the clinical study.

Estimates of the intra-subject coefficient of variation (CV%) were obtained from the single dose study APD356-031 (QBR115165): C_{max} ~22.5% and AUC_{0-t} ~12.5%. Assuming a Fed/Fasted ratio of 1.05 and the aforementioned estimates of CV%, a study with 31 and 12 subjects (minimum) for C_{max} and AUC_{0-t} , respectively, has 90% power to conclude comparative bioavailability, i.e. 90% CI of the geometric mean ratios to be within an acceptance interval of 0.8 to 1.25. As a result, 31 evaluable subjects were required.

CRITERIA FOR EVALUATION**Pharmacokinetic Assessments:**

From an individual subject, ~60 venous blood samples were withdrawn via an indwelling cannula or by venipuncture at regular time intervals. PK samples were collected in both treatment periods.

PK samples were taken on Day 1 (or Day 15) pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours post-dose; pre-dose on Day 5 (or Day 19), Day 6 (or Day 20), Day 7 (or Day 21), Day 8 (or Day 22); and on Day 9 (or Day 23) pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours post-dose.

The plasma concentration data for lorcaserin were analyzed using industry standard software (WinNonlin, Phoenix, version 6.4, Pharsight Corporation, Mountain View, CA) using appropriate non-compartmental techniques to obtain estimates of PK parameters.

Safety Assessments:

Safety was evaluated by analyzing physical examination findings, clinical laboratory tests (coagulation, serum chemistry, hematology, and urinalysis), vital signs, 12-lead ECGs, and AE reporting.

STATISTICAL METHODS

Pharmacokinetics:

Per agreement with the FDA determination of bioequivalence (BE) was based on the steady-state C_{max} and AUC values (PreIND 119664 meeting minutes (WRO) dated Feb. 18, 2014). In addition, exposure parameters after single dose administration were also examined.

ANOVA was performed on log-transformed lorcaserin PK parameters for a single dose (AUC_{0-t} , $AUC_{0-\infty}$, and C_{max}) and multiple dosing (AUC_{0-24} and C_{max}) including terms for treatment, period, sequence, and subject within sequence. Following back-transformation, the ratios of geometric means (i.e. XR product/IR product) and 90% confidence intervals were determined.

The effect of food on the lorcaserin exposure after administration of a single-dose (AUC_{0-t} , $AUC_{0-\infty}$ and C_{max}) or under steady state conditions (AUC_{0-24} and C_{max}) of lorcaserin HCl XR, 20 mg, q.d was analyzed using an analysis of variance (ANOVA) model appropriate for a 2- period, crossover design. The ANOVA model contained factors for sequence, subject within sequence, period, and treatment.

The influence of food on lorcaserin exposure was tested by constructing the 90% CI for the C_{max} and AUC GMR (fed/fasted) from the ANOVA model and comparing it against the Food and Drug Administration (FDA) recommended bounds of 0.800, 1.250. T_{max} in fed and fasted states were analyzed using Wilcoxon Signed rank test for paired samples at a 0.05 level of significance.

Safety:

Safety information after administration of single and multiple doses of 20 mg lorcaserin HCl XR with and without food in healthy subjects was evaluated by tabulating adverse experiences and by clinical assessment of laboratory data. Continuous variables were summarized by treatment group using descriptive statistics, and discrete safety endpoints were summarized by treatment group using frequency and percentages.

Statistical Results:

CONCLUSIONS

Pharmacokinetic Conclusions:

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

- After a single oral dose of lorcaserin HCl XR, the rate of absorption after a standard high fat high caloric meal was higher relative to the fasted state; mean C_{max} increased approximately 46%, while bioequivalence was observed with respect to $AUC_{0-\infty}$.
- Under steady state dosing conditions with lorcaserin HCl XR, bioequivalence was achieved for both the C_{max} and AUC_{0-24} exposure parameters, and similarity in t_{max} values was confirmed between fed and fasted conditions.
- Although there was a small effect of a high fat high caloric meal on lorcaserin C_{max} but not AUC after a single dose, demonstration of BE for both C_{max} and AUC values at steady state indicate that the difference is not clinically meaningful. Therefore, lorcaserin HCl 20 mg XR formulation can be administered without regard to food.

Safety Conclusions:

- Administration of lorcaserin HCl XR as a single or multiple doses of 20 mg in the fed and fasted state was generally well-tolerated by the healthy male and female subjects.
- The majority of subjects (61.1%) reported at least one AE. The majority of AEs (98.5%) were mild in intensity and resolved without treatment.
- Adverse events were similar to those most frequently associated with lorcaserin in phase 3 trials. Headache (12 AEs) and nausea (5 AEs) were the most commonly reported AEs; all were considered by the Investigator to be treatment-related.
- The number of subjects reporting AEs in Treatment A (fasted state) was slightly higher than those reported in the Treatment B (fed), with the difference primarily comprised of GI events.
- There were no AEs or clinically significant findings reported in clinical laboratory evaluations, vital sign assessments, ECG recordings, or physical examination findings.
- There were no SAEs reported during the study and no AEs leading to study discontinuation.

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/s/

RENU SINGH
06/01/2016

JAYABHARATHI VAIDYANATHAN
06/01/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208524	SDN	0000
Applicant	Arena Pharmaceuticals, Inc.	Submission Date	18 th September 2015
Generic Name	Lorcaserin hydrochloride	Brand Name	BELVIQ XR®
Drug Class	Selective serotonin 2C (5-HT _{2C}) receptor agonist		
Indication	Weight Management		
Dosage Regimen	20 mg Once daily		
Dosage Form	Tablet	Route of Administration	Oral
OCP Division	DCP 2	OND Division	DMEP
OCP Review Team Division	Primary Reviewer(s) Renu Singh, PhD	Secondary Reviewer/ Team Leader Jayabharathi Vaidyanathan, PhD	
Pharmacometrics			
Genomics			
Review Classification	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	11/17/2015	74-Day Letter Date	12/1/2015
Review Due Date	6/1/2016	PDUFA Goal Date	7/18/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

Yes

No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

Yes

No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

Yes

No

If yes explain: OSIS consult request sent for Pivotal BE study APD356XR-101

Clinical Pharmacology Package

Tabular Listing of All Human Studies	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Clinical Pharmacology Summary	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Bioanalytical and Analytical Methods	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Labeling	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
<input type="checkbox"/> Metabolism Characterization		
<input type="checkbox"/> Transporter Characterization		
<input type="checkbox"/> Distribution		
<input type="checkbox"/> Drug-Drug Interaction		

In Vivo Studies				
Biopharmaceutics				
<input type="checkbox"/> Absolute Bioavailability				
<input type="checkbox"/> Relative Bioavailability				
<input checked="" type="checkbox"/> Bioequivalence	2	APD356XR-101 (Module 5.3.1.2) (pivotal BE effect study) APD356-031 (Module 5.3.1.2)		
<input checked="" type="checkbox"/> Food Effect	2	APD356XR-102 (Module 5.3.1.1) (pivotal food effect study) APD356-031 (Module 5.3.1.2)		
<input type="checkbox"/> Other				
Human Pharmacokinetics				
Healthy Subjects	<input checked="" type="checkbox"/> Single Dose	3	APD356-031 (Module 5.3.1.2)	
	<input checked="" type="checkbox"/> Multiple Dose	3	APD356XR-101 (Module 5.3.1.2) (pivotal BE effect study) [single dose as well as multiple dose PK] APD356XR-102 (Module 5.3.1.1) (pivotal food effect study) [single dose as well as multiple dose PK]	
Patients	<input type="checkbox"/> Single Dose			
	<input type="checkbox"/> Multiple Dose			
<input type="checkbox"/> Mass Balance Study				
<input type="checkbox"/> Other (e.g. dose proportionality)				
Intrinsic Factors				
<input type="checkbox"/> Race				
<input type="checkbox"/> Sex				
<input type="checkbox"/> Geriatrics				
<input type="checkbox"/> Pediatrics				
<input type="checkbox"/> Hepatic Impairment				
<input type="checkbox"/> Renal Impairment				
<input type="checkbox"/> Genetics				
Extrinsic Factors				
<input type="checkbox"/> Effects on Primary Drug				
<input type="checkbox"/> Effects of Primary Drug				
Pharmacodynamics				
<input type="checkbox"/> Healthy Subjects				
<input type="checkbox"/> Patients				
Pharmacokinetics/Pharmacodynamics				
<input type="checkbox"/> Healthy Subjects				
<input type="checkbox"/> Patients				
<input type="checkbox"/> QT				
Pharmacometrics				
<input type="checkbox"/> Population Pharmacokinetics				
<input type="checkbox"/> Exposure-Efficacy				
<input type="checkbox"/> Exposure-Safety				
Total Number of Studies	3			
Total Number of Studies to be Reviewed	2	In Vitro		In Vivo
				3

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Batch 14254006 manufactured at the 1.1 million tablets commercial scale was used in the APD356XR-101 and APD356XR-102. The commercial tablet formulation differs from the scaled-up development/clinical formulation only with respect to the color of film coating.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Cross- reference to NDA 022529
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Comparative study information provided for XR and IR forms in the 505(b)(1) application.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	No PD data provided. For PD data Cross-reference to NDA 022529.
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
Complete Application 10. Did the applicant submit studies including	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	PDR-15-035 (Module 5.3.1.3) – Alcohol-induced dose-dumping study.

study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		QBR115165 (Module 5.3.1.3) - In Vitro In/Vivo Correlation (IVIVC) Analysis for Lorcaserin HCl Modified Release Tablets.
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. 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)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Cross- reference to NDA 022529
6. 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?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Cross- reference to NDA 022529
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Request for a waiver of studies in children ages 0 – 6 years, and a deferral request for ages 7 – 11 years and 12 – 17 years of age was granted by FDA on Sep 17, 2015. Sponsor proposes to cross reference the studies being conducted for BELVIQ under NDA 022529 in support of BELVIQ XR.
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	



NDA 208524 Filing Meeting

BELVIQ XR (lorcaserin hydrochloride)

Sponsor: Arena Pharmaceuticals Inc.

Submitted: 18th Sep 2015

OCP Review Team:

Clin Pharm Reviewer: Renu Singh, PhD

Clin Pharm Team Leader: Jayabharathi Vaidyanathan, PhD



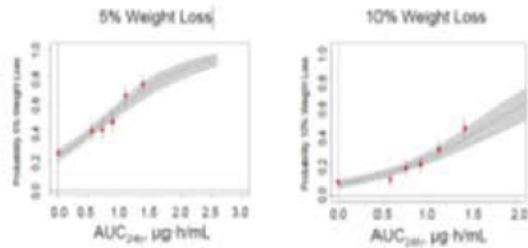
Overview

- **Type of Submission:** 505(b)(1) [21 USC 355]
 - IR application submitted under NDA 022529 and approved in 2012.
 - IR dose approved was 10 mg b.i.d.
- **Proposed Indications:**
 - BELVIQ XR indication identical to approved IR formulation
 - Indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index of: 30 kg/m² or greater (obese), or 27 kg/m² or greater (overweight) in the presence of at least one weight-related and comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)
- **Formulation:**
 - 20 mg film-coated tablet
- **Administration:**
 - Oral
- **Proposed dose:**
 - 20 mg orally once daily.
 - Administered as a single dose without regards to food (same as IR)

Background

- BELVIQ® (lorcaserin HCl, APD356) is a selective 5-HT_{2C} receptor agonist.
- PK/PD modeling supports the relationship of lorcaserin exposure (AUC₀₋₂₄) to weight loss with IR formulation (Figure 1).
- Doses evaluated for lorcaserin IR tablet in the clinical studies:
 - Phase 1: 0.1 mg to 40 mg q.d. and 10 mg b.i.d.
 - Phase 2: 1 to 15 mg q.d. and 10 mg b.i.d.
 - Phase 3: 10 mg q.d. and 10 mg b.i.d.
- A BA/BE development plan was agreed upon in the PreIND meeting briefing document.

Figure 1. Exposure Response Analysis for 5% and 10% Weight Loss



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Overview

- Clinical Pharmacology/Biopharmaceutics Studies:

Table 1. Overview of Clinical Studies Used to Characterize the Biopharmaceutical Properties of Lorcaserin.

Protocol	Study Design	Objective	Lorcaserin HCl Dose
BE study			
APD356-031 (Pilot)	Open-label, five-period, fixed sequence, non-randomized study to evaluate the PK of three modified release prototype formulations of lorcaserin	To assess the relative bioavailability of single-doses of 20-mg lorcaserin modified-release prototype tablets, under fasting conditions	Single oral doses 10-mg IR tablets and 20-mg XR prototype tablets
APD356XR-101 (Pivotal)	Open-label, randomized, two-treatment, two-period, two sequence, randomized, balanced crossover study of single and multiple doses of lorcaserin, comparative bioavailability design under fasting conditions	To assess single and multiple doses of lorcaserin for bioequivalence of 20-mg XR lorcaserin tablets and 10-mg lorcaserin IR tablets, under fasting conditions	Single and multiple oral doses 10-mg IR tablets, b.i.d., and 20-mg XR tablets, q.d.
Food effect studies			
APD356XR-102 (Pivotal)	Open-label, randomized, two-treatment, two-period, two sequence, randomized, balanced crossover study of single and multiple doses of lorcaserin	To assess single and multiple doses of lorcaserin for food effect of 20-mg XR lorcaserin tablets, under fasting and fed state conditions	Single and multiple oral doses 20-mg XR tablets, q.d.

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Study-APD356-031 (Pilot BE)

- (b) (4) release prototype appeared to have the optimal characteristics (lowest C_{max} , highest C_{min} , preservation of AUC) and was selected for further clinical testing.

Table 2: APD356-031- Key Pharmacokinetic Parameters

Group	A (10 mg) IR	B (20 mg) MR	C (20 mg) MR	D (20 mg) MR	E (20 mg) MR
Formulation	NA	(b) (4) Release	(b) (4) Release	(b) (4) Release	(b) (4) Release
Fasted/Fed	Fasted	Fasted	Fasted	Fasted	High Fat Breakfast
Population	PK Analysis Dataset 1 (n = 10)				
T_{lag} (h)	0.00 (0.00-0.00)	0.50 (0.00-0.50)	1.00 (0.50-1.50)	0.00 (0.00-0.50)	1.50 (1.00-2.00)
T_{max} (h)	1.50 (1.00-6.00)	7.00 (6.00-12.00)	12.00 (9.00-23.53)	6.00 (6.00-6.00)	12.00 (6.00-20.00)
C_{max} (ng/mL)	35.6 (31.9)	38.2 (29.2)	33.8 (29.0)	44.8 (28.0)	51.1 (22.6)
C_{12} (ng/mL)	16.4 (32.0)	34.0 (30.9)	31.4 (26.5)	32.5 (24.1)	46.7 (23.3)
C_{24} (ng/mL)	5.86 (43.6)	18.7 (32.1)	23.6 (26.6)	16.6 (32.6)	20.8 (39.9)
AUC ₀₋₂₄ (ng·h/mL)	479 (30.7)	907 (27.1)	927 (24.7)	886 (23.0)	1020 (23.6)
AUC ₀₋₄₈ (ng·h/mL)	568 (20.1)	909 (24.4)	978 (33.5)	887 (31.5)	1060 (25.3)
$t_{1/2}$ (h)	11.45 (19.6)	12.90 (23.1)	12.21 (14.4)	11.37 (17.3)	10.52 (15.3)
Frel (%)	NA	99.4 (5.5) (n = 7)	104.3 (7.3) (n = 5)	94.5 (10.0) (n = 5)	103.8 (14.9) (n = 8)

C_{max} increases 51% with high fat diet

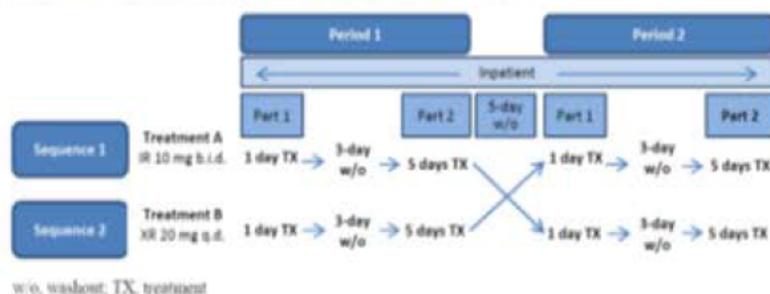
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APD356XR-101 (Pivotal BE)

Phase 1 Single Dose and Steady State Bioequivalence between Immediate Release and XR Formulation

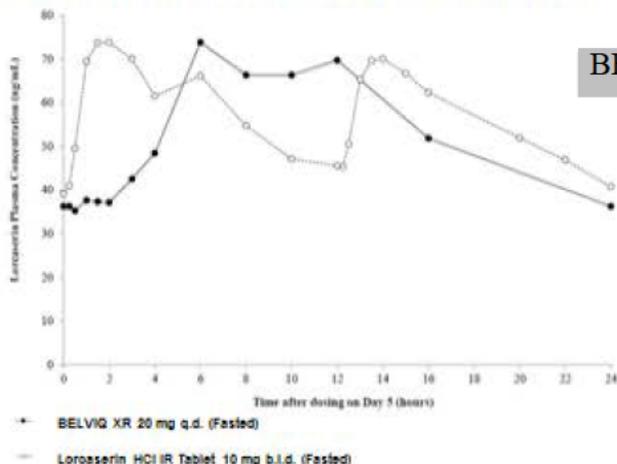
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Figure 2. Schematic of APD356XR-101 Study Design



APD356XR-101 (Pivotal BE)

Figure 3. Mean Plasma Concentrations of Lorcaserin vs. Time at Steady State following BELVIQ XR 20 mg q.d. or IR Tablets 10 mg b.i.d. under Fasted Conditions



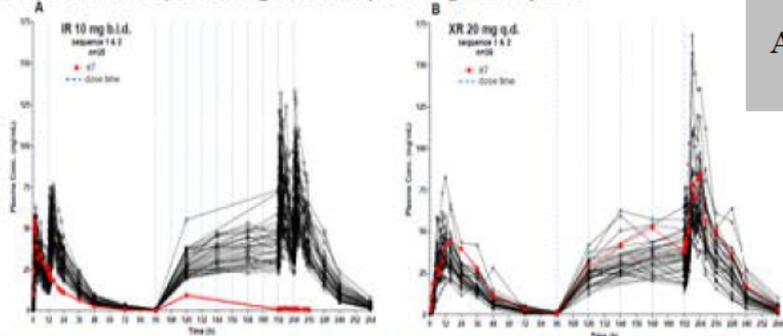
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APD356XR-101 (Pivotal BE)

Subject #7

- Subject #7 lorcaserin concentration-time profiles for the IR treatment but not the XR treatment following single and multiple doses were dissimilar to the dosing population. Sponsor has no firm reasoning for the deviance and speculates that subject didn't take doses after the first dose of IR treatment.

Figure 4. Individual Lorcaserin Plasma Concentration-Time Profiles Following Oral Administration. Sequential single and multiple dosing to steady-state



Panel A: IR 10 mg b.i.d.; Panel B: XR 20 mg q.d.; blue dashed lines represent dosing times; Subject #7 red symbols and lines

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APD356XR-101 (Pivotal BE)

Single dose BE analysis with and without subject #7

Table 3. 90% CI on the G.M. Ratios of Lorcaserin PK Parameters following a Single Dose Oral Administration of Lorcaserin HCl 20 mg XR q.d. and 10 mg IR b.i.d.

Excludes Subject #7 IR and XR Data

Parameter	N*	Geometric Mean		G.M. Ratio ^d	90% CI ^e
		Test ^b	Reference ^c		
AUC _{0-∞} (hr·ng/mL)	34	1219	1235	0.987	(0.948, 1.028)
AUC _{0-t} (hr·ng/mL)	34	1169	1207	0.968	(0.931, 1.007)
C _{max} (ng/mL)	34	39.0	52.2	0.748	(0.705, 0.793) ^f

Includes Subject #7 IR and XR Data

Parameter	N*	Geometric Mean		G.M. Ratio ^d	90% CI ^e
		Test ^b	Reference ^c		
AUC _{0-∞} (hr·ng/mL)	35	1229	1222	1.005	(0.957, 1.056)
AUC _{0-t} (hr·ng/mL)	35	1178	1195	0.988	(0.939, 1.035)
C _{max} (ng/mL)	35	39.0	52.3	0.746	(0.704, 0.790) ^f

* excludes subject #34; ^b Test = 20 mg XR q.d.; ^c Reference = 10 mg IR b.i.d.; ^d G.M. Ratio = Geometric mean of the test/reference ratio; ^e 90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio; ^f Did not meet BE

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APD356XR-101 (Pivotal BE)

Multiple dose BE analysis with and without subject #7

Table 4. 90% CI on the G.M. Ratios of Lorcaserin PK Parameters following Multiple Dose Oral Administration of Lorcaserin HCl 20 mg XR q.d. and 10 mg IR b.i.d.

Excludes Subject #7 IR and XR Data

Parameter	N*	Geometric Mean		G.M. Ratio ^d	90% CI ^e
		Test ^b	Reference ^c		
AUC _{0-24,IR} (hr·ng/mL)	34	1234	1324	0.932	(0.891, 0.975)
C _{max,IR} (ng/mL)	34	73.8	79.9	0.924	(0.876, 0.975)

Includes Subject #7 IR and XR Data

Parameter	N*	Geometric Mean		G.M. Ratio ^d	90% CI ^e
		Test ^b	Reference ^c		
AUC _{0-24,IR} (hr·ng/mL)	35	1241	1174	1.057	(0.856, 1.306) ^f
C _{max,IR} (ng/mL)	35	74.2	70.8	1.047	(0.848, 1.293) ^f

* excludes subject #34; ^b Test = 20 mg XR q.d.; ^c Reference = 10 mg IR b.i.d.; ^d G.M. Ratio = Geometric mean of the test/reference ratio; ^e 90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio; ^f Did not meet BE

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APD356XR-101 (Pivotal BE)

Multiple dose BE analysis with and without subject #7

Table 5. 90% CI on the G.M. Ratios of Lorcaserin PK Parameters following Multiple Dose Oral Administration of Lorcaserin HCl 20 mg XR q.d. and 10 mg IR b.i.d.

Excludes Subject #7 IR and XR Data

Parameter	N ^a	Geometric Mean		G.M. Ratio ^d	90% CI ^e
		Test ^b	Reference ^c		
AUC _{0-24,ss} (hr·ng/mL)	34	1234	1324	0.932	(0.891, 0.975)
C _{max,ss} (ng/mL)	34	73.8	79.9	0.924	(0.876, 0.975)

Includes Subject #7 XR Data only

Parameter	N ^a	Geometric Mean		G.M. Ratio ^d	90% CI ^e
		Test ^b	Reference ^c		
AUC _{0-24,ss} (hr·ng/mL)	35	1241	1330	0.933	(0.892, 0.976)
C _{max,ss} (ng/mL)	35	74.2	80.1	0.925	(0.877, 0.976)

^a excludes subject #34; ^b Test = 20 mg XR q.d.; ^c Reference = 10 mg IR b.i.d.; ^d G.M. Ratio = Geometric mean of the test/reference ratio; ^e 90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio

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APD356XR-102 (Fed/Fasted study)

- After a single oral dose of lorcaserin HCl XR, the mean C_{max} increased approximately 46% after a standard high fat meal.
- Bioequivalence achieved at steady state with multiple day dosing.
- Sponsor recommends lorcaserin HCl 20 mg XR formulation to be administered without regard to food.

Table 6. Bioequivalence Determination Between Fed and Fasted States Based on Lorcaserin AUC_{0-∞}, AUC₀₋₄ and C_{max} After Oral Administration of Lorcaserin Hydrochloride XR, 20 mg, q.d.

Following Single Dose Oral Administration of Lorcaserin HCl 20 mg XR

Parameter	N	Geometric Mean		G.M. Ratio	90% CI
		Test ^a	Reference ^b		
AUC _{0-∞} (hr·ng/mL)	36	1332	1141	1.167	(1.092, 1.247)
AUC ₀₋₄ (hr·ng/mL)	36	1294	1097	1.179	(1.103, 1.260)
C _{max} (ng/mL)	36	56.1	38.5	1.459	(1.345, 1.581)

Following Multiple Dose Oral Administration of Lorcaserin HCl 20 mg XR

AUC _{0-24,ss} (hr·ng/mL)	36	1318	1216	1.084	(1.027, 1.145)
C _{max,ss} (ng/mL)	36	78.7	69.5	1.134	(1.071, 1.199)

^aTest = 20 mg XR q.d. in the fed state (n=36); ^bReference = 20 mg XR q.d. in the fasted state (n=36)

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Review Focus

- Is the steady state exposure of lorcaserin 20 mg XR q.d. comparable to 10 mg IR b.i.d under fasting conditions?
 - Explanation for the anomalous data for subject #7
 - Data and analysis methods for the pivotal fasting BE study APD356XR-101 with emphasis on inclusion/exclusion of subject #7
- Is there a food effect for lorcaserin 20 mg XR q.d.?
 - Data and analysis methods of fed/fasted relative bioavailability study APD356XR-102
 - Impact and implications (if any) of higher C_{max} with food on lorcaserin XR single dose in study APD356XR-102 under fed conditions

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Filing Status and Consults

- Clin Pharm recommends NDA 208524 to be **fileable** because:
 - Clinically-tested formulation in the BE pivotal studies is the same as the to-be-marketed formulation except for the color of the tablet
 - PK data for the test formulation and RLD for the pivotal BE studies provided
 - Bioanalytical and method validation reports for the pivotal BE studies provided
 - Proposed product labeling provided
- OSIS consult:
 - Yes, for the clinical and analytical sites for pivotal BE study APD356XR-101
- Request for Sponsor:
 - None

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Filing Memo

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes No

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comments to Sponsor: None

Renu Singh 5 Nov, 2015

Reviewing Clinical Pharmacologist Date

Jayabharathi Vaidyanathan 5 Nov, 2015

Acting Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENU SINGH
11/06/2015

JAYABHARATHI VAIDYANATHAN
11/06/2015