



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

### Belviq

**International non-proprietary name: Lorcaserin**

**Procedure No. EMEA/H/C/002597**

### Note

List of Outstanding Issues as adopted by the CHMP with all information of a commercially confidential nature deleted.



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## 1. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Lorcaserin, as an adjunct to diet and exercise for weight control in adult obese patients (BMI  $\geq 30$  kg/m<sup>2</sup>), or adult overweight patients (BMI  $>27$  kg/m<sup>2</sup>) with associated risk factor(s), such as hypertension, dyslipidaemia, cardiovascular disease, type 2 diabetes, or sleep apnoea,

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

### Non-clinical

In rats, several tumour types were increased in males following 2 years exposure to lorcaserin, where the occurrence of schwannoma, astrocytoma, squamous cell carcinoma raise serious concern for human use as no convincing mechanistic explanations have been provided. In males, there was increased incidences of fibromas in the subcutis at all dose levels in males, thus no NOEL could be identified. The exposure margin discussions are not reassuring, given the lack of a mechanistic explanation and the fact that the functional activity at rat 5-HT<sub>2C</sub> receptors was 4-14 times lower than in humans. In both sexes, there were increased incidences of mammary gland fibroadenoma / adenocarcinoma for which the mechanistic explanation related to prolactin is not convincing to conclude on a lack of clinical relevance. These findings should also be carefully considered in the benefit/risk assessment.

The risk of carcinogenicity in man should be further considered in the light of these preclinical findings, together with a discussion on the potential impact on the risk benefit.

### Clinical/Benefit Risk Balance

-The overall risk benefit is currently considered negative; Efficacy is considered modest and does not outweigh the concerns over safety, in particular concerns over psychiatric events and valvulopathy. The applicant should further justify the overall risk/benefit and further discuss proposals for monitoring patients in relation to these events in the marketplace.

The CHMP propose to discuss the major objections in the Scientific Advisory Group (SAG) Diabetes/Endocrinology. The following list of questions is proposed to the SAG:

1. Does the SAG consider the efficacy with respect to weight loss and effect on cardiovascular risk factor established and clinically significant?
2. Is there a specific subgroup of patients in which a larger benefit could be expected, e.g. patients with very high BMI?
3. Is the SAG reassured about the overall safety profile of Lorcaserin. In particular:
  - a. Does the SAG consider the reported psychiatric events are manageable and acceptable?
  - b. The SAG is asked to comment on the risk of valvulopathy taking into account both the findings in the clinical studies as well as the potential risk based on the mechanism of action of Lorcaserin. Based on this risk assessment, could the SAG comment on the proposed monitoring for valvulopathy (i.e. auscultation) and give its view on the possible need for echocardiography or other safety measures and/or data required pre- or postmarketing.
  - c. Does the SAG consider the data on toxicology and carcinogenicity in pre-clinical studies manageable and acceptable

The CHMP will consult the Safety Working Party (SWP) on the following list of questions:

4. What is the level of certainty that the findings in non-clinical studies will not translate into a real risk of carcinogenicity in humans and what scientific evidence support that level of certainty?
5. Do the SWP consider the prolactin induction hypothesis plausible in relation to mammary tumours?
6. What is the view of the SWP on the papers by Harvey et al. on the prolactin-based mechanisms?
7. Do the SWP consider the safety margins adequate in relation to human exposure for the different tumours?

### **Proposal for Questions to be posed to additional Experts**

Please refer to the Questions to SAG and SWP above.

### **Proposal for Inspection**

NA

### **New active Substance status**

Based on the review of the data the CHMP considers that the active substance lorcaserin contained in the medicinal product Lorcaserin Arena Pharmaceuticals is to be qualified as a new active substance in itself.

## 2. EXECUTIVE SUMMARY

### 2.1. Problem statement

In the European Union, it is estimated that approximately 36% of adults are overweight (body mass index [BMI]  $\geq 25$  kg/m<sup>2</sup> and  $\leq 29.9$  kg/m<sup>2</sup>) and 17% of adults are obese (BMI  $\geq 30$  kg/m<sup>2</sup>). More males than females are considered overweight (>82 million and 61 million, respectively) while more females than males are considered obese (37 million and 31 million, respectively).

Obesity is associated with numerous co-morbidities, including dyslipidaemia, coronary artery disease, hypertension, stroke, obstructive sleep apnoea, and type 2 diabetes.

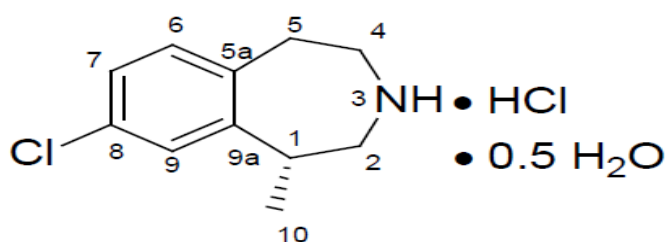
Epidemiological data indicate that obesity and being overweight are factors associated with an increased risk of death. Even a modest weight loss of 5% to 10% can result in a reduction in obesity-related metabolic and cardiovascular risk factors. Diet, exercise, and behaviour modification are standard treatments for obesity. However, many obese individuals do not achieve sustained weight reduction with this treatment option and in such situations pharmacological options may be of value as an adjunct to dietary measures and physical exercise. The only medication currently approved in the European Union for the treatment of obesity is Orlistat. In severe obesity, very low calorie diets may be applied for a limited period of time. Additionally, surgery may be an alternative as a last resort.

Although no studies have as yet confirmed an effect on mortality or morbidity, weight reduction has been associated with reduction in blood pressure in both normotensive and hypertensive individuals, improvement in lipid profiles and improved glycaemic control in both patients without diabetes and patients with type 2 diabetes. Relevant decreases in certain risk factors associated with obesity have been seen with loss of at least 5 to 10% of initial weight.

### 2.2. About the product

Lorcaserin hydrochloride ("lorcaserin") is a selective serotonin 2C (5-HT<sub>2C</sub>) receptor agonist that reduces body weight. Given that 5-HT<sub>2C</sub> receptor expression is primarily limited to a few regions of the central nervous system, lorcaserin was predicted to cause weight loss with few unintended pharmacological effects.

The structure of lorcaserin is illustrated below:



Lorcaserin was designed to activate 5-HT<sub>2C</sub> receptors without significant agonism of the 5-HT<sub>2B</sub> receptor linked to heart valve toxicity at therapeutic doses. At the same time, the agonist activity of lorcaserin at the 5-HT<sub>2A</sub> receptor, which has been linked to mood and perceptual effects, was minimized. During the clinical development of lorcaserin, preclinical data suggesting that 5-HT<sub>2C</sub> agonism may improve glycemic control independent of weight loss were published. The evaluation of glycemic control in addition to weight loss among patients with type 2 diabetes in the APD356-010 study was therefore of particular interest.

### 2.3. The development programme/Compliance with CHMP Guidance/Scientific Advice

This MAA takes into account the development criteria presented in the CHMP guidance for Clinical Evaluation of Medicinal Products Used in Weight Control (CPMP/EWP/281/96 Rev. 1)

CHMP scientific advice was received in October 2008. CHMP recommended to have trials with run-in period to assure that only patients that fail non medicated strategies will be treated with Lorcaserin, the applicant will be required to demonstrate that this was the case in the patients enrolled in the trials. CHMP also recognized that a randomized trial, controlled with placebo of one year duration will control for most of the eventual bias that could be generated by lack of the run-in period. In relation to the primary endpoints, the CHMP stressed that the hierarchical analysis must be successful in all its 3 components (1) % of patients achieving  $\geq 5\%$  weight reduction at week 52 (2) change from baseline in body weight at week 52 (3) % of patients achieving  $\geq 10\%$  weight reduction at week 52, because only the third one meets the current CHMP guidance recommendation.

#### **2.4. General comments on compliance with GMP, GLP, GCP**

No GMP issues have been identified during assessment of module 3.

A core battery of ICH safety pharmacology studies was GLP compliant. Studies designed to investigate the potential dependence and abuse liability of lorcaserin were not GLP-compliant. This is acceptable since the study results and the integrity of the data is not likely to be affected.

Toxicokinetic studies, including analytical validation, tissue distribution studies in albino and pigmented rats and excretion (mass balance) studies in rats and monkeys were GLP compliant.

The pivotal repeat-dose toxicity studies, genotoxicity testing, carcinogenicity studies, and all of the reproduction and development studies were GLP compliant.

The clinical studies were stated to have been performed in accordance with GCP.

#### **2.5. Type of application and other comments on the submitted dossier**

- *Legal basis*

The applicant submitted an application for Marketing Authorisation to the EMA for Lorcaserin Arena Pharmaceuticals through the centralised procedure under Article 3(2)a – New active Substance - of Regulation (EC) No. 726/2004. The eligibility to the centralised procedure was agreed upon by the CHMP on 30 June 2011.

The application was submitted in accordance with Article 8(3) in Directive 2001/83/EC.

- *Accelerated procedure*

NA

- *Conditional approval*

NA

- *Exceptional circumstances*

NA

- *Biosimilar application*

NA

- *1 year data exclusivity*

NA

- *Significance of paediatric studies*

No paediatric studies have been performed. This is in accordance with the waiver granted by PDCO 30<sup>th</sup> of September 2011.

## 3. SCIENTIFIC OVERVIEW AND DISCUSSION

### 3.1. Introduction

The Applicant has submitted results on a comprehensive development program for lorcaserin, a novel, first in class agent for the treatment of obesity.

### 3.2. Quality aspects

Lorcaserin hydrochloride hemihydrate is a new drug substance. It is a white solid which is very soluble in water and in aqueous solutions over the physiological pH range. It is classified as being highly soluble and highly permeable (BCS Class-1 Compound). The drug substance contains one chiral centre and is manufactured as the R-enantiomer. No polymorphism has been observed for the hemihydrate salt. The physico-chemical properties of the drug substance have been suitably characterised.

The manufacture of the drug substance is well described and controls are in place to ensure the quality of the starting material, key intermediate and final compound. The proposed drug substance specification is generally considered acceptable although there are unresolved issues regarding control of the level of the anhydrous forms in the drug substance and the assessment of and limit for sulfated ash. The enantiomeric purity is controlled during the synthesis and in the drug substance specification. Potential impurities have been discussed in relation to their origin and potential carry-over in to the final compound and are present in the drug substance at acceptably low levels.

Stability testing at long-term and accelerated conditions has shown the drug substance to be stable. The stability data indicate that no degradation occurs on storage and that drug substance manufactured is stable for at least 48 months when stored below 30°C.

### Drug Product

The drug product is presented as a film-coated tablet in a blister pack. A variety of formulation types were developed for use in the clinical studies. These formulation types have been adequately described and the relationship between the formulations used in Phase 3 clinical studies and the proposed drug product formulation discussed. Dissolution similarity has been demonstrated between the proposed drug product formulation and the formulations used in the Phase 3 clinical studies; > 85% was dissolved from each formulation within 10 minutes at pHs 1, 4.5 and 6.8. The claim for a biowaiver for the drug product based on the drug substance properties, the drug product formulation and comparative dissolution data for the drug product and the formulations used in the Phase 3 clinical studies is considered acceptable and complies with the requirements of the BCS-based biowaiver in the Guideline on the investigation of bioequivalence.

Standard excipients are used in the drug product formulation and the tablets are manufactured using a standard manufacturing process (dry granulation, compression and coating processes). The manufacturing processes have been suitably described and commercial scale validation studies have demonstrated that the drug product can be manufactured reproducibly to an acceptable standard at the proposed commercial scale.

The parameters included in the proposed drug product specification are considered appropriate. Minor amendments to the tablet diameter specification and microbiological testing frequency and the addition of identification tests for the colourants have been requested.

The drug product is stable and the proposed 24 month shelf life with no special storage conditions is supported by the submitted stability data.

## Conclusions on the chemical, pharmaceutical and biological aspects

From a quality perspective, the application may be approvable provided the outstanding quality points are suitably addressed.

### 3.3. Non clinical aspects

#### Pharmacology

Lorcaserin is a 5-HT<sub>2C</sub> receptor agonist which shows a selective profile for this subset of 5-HT receptors. Functional assays based on lorcaserin-induced IP release indicate that lorcaserin selectivity for the 5-HT<sub>2C</sub> receptor is approximately 14-fold and 61-fold relative to the 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors, respectively. However, if a different second messenger in the activation cascade is measured, this margin can be substantially reduced. Lorcaserin is only a partial 5-HT receptor agonist in 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors (~25% and ~82% 5-HT<sub>2C</sub> efficacy respectively, as compared to 100% effect of serotonin). In 5-HT<sub>2B</sub>, the results vary depending on the effect measured. Lorcaserin was 151% efficacious in 5-HT<sub>2B</sub> receptor mediated IP accumulation assays and 67% in the calcium release assay, as compared to serotonin. Given that 5-HT<sub>2C</sub> receptor expression is primarily limited to a few regions of the central nervous system (CNS), lorcaserin was predicted to cause weight loss with few unintended pharmacological effects.

The Applicant has not discussed in depth the signal transduction cascade behind the mechanism of action of lorcaserin. The complexity of the modulation *in vivo* of the signal transduction mediated by 5-HT receptors is unlikely to be fully captured in any additional preclinical test, and a further discussion is not required as some aspects could remain theoretical. Therefore no questions are raised regarding this issue. However, it is noted that the complexity of the downstream transduction cascade could have impact both on the safety and efficacy of lorcaserin. This should be taken into account in the risk-benefit of the drug, especially in non-responder patients, and borne in mind in conjunction with the assessment of the responses to the Major Objections raised from the clinical point of view.

The 5-HT<sub>2C</sub> receptor is a 7-transmembrane spanning (7-TMS) receptor family, which activates second messenger signal transduction cascades via G proteins. It has been described in published literature that the 5-HT<sub>2C</sub> receptor is subject to polymorphism, RNA- editing process, and allosteric modulation that can alter the agonist-receptor-effector coupling specificity. It has been suggested that 7-TMS receptor agonists may have the capacity to promote unique receptor conformations which can differentially activate each of multiple signalling cascades coupled to a single receptor (Clarke *et al.* 2001). This hypothesis has been termed "agonist-directed trafficking of receptor stimulus (ADTRS)". As a consequence, agonist relative efficacy differs upon depending whether phospholipase C-inositol phosphate or phospholipase A2 activity is measured and agonist efficacy order also is response-dependent (Berg *et al.* 1998). Neither the affinity for variants of the receptor nor the main signal transduction pathway activated by lorcaserin has been elucidated in order to support the selection of the most suitable potency test. Therefore, the relevance of the conditions of the *in vitro* test system and the measurement of potency based on production of IP is uncertain. Just as an example, if Ca<sup>2+</sup> release is chosen instead to measure the potency of lorcaserin, then the ratio EC<sub>50</sub> HT<sub>2A</sub>/HT<sub>2C</sub> and EC<sub>50</sub> HT<sub>2A</sub>/HT<sub>2C</sub> is 6.9 and 7.12, respectively, and not 61 and 14 to reinforce the claim of 5-HT<sub>2C</sub> receptor selectivity across Module 2.4.

Lorcaserin showed little or no appreciable interaction with other 5-HT receptors, the 5-HT transporter or a panel of 72 additional receptors and ion channels. However, potential secondary pharmacology class effects could be expected due to the 5-HT<sub>2C</sub> agonistic nature of lorcaserin, and also due to the action although to a lesser extent on other 5-HT receptors.

Lorcaserin produced a dose-dependent decrease in food intake in Sprague Dawley (SD) rats, an effect likely mediated through 5-HT<sub>2C</sub> activity, since it was attenuated by co-administration of the 5-HT<sub>2C</sub> antagonist SB242084, but was unaffected by co-administration of the 5-HT<sub>2A</sub> antagonist M100,907. Similarly, repeated dosing of lorcaserin for 28 days resulted in a dose-dependent reduction in food intake and weight gain in wild type SD rats and diet-induced obese (DIO) Levin rats. Additional characterization in selected behavioural paradigms confirmed the 5-HT<sub>2C</sub> agonist activity of lorcaserin. For example, lorcaserin dose-dependently increased periods of measured inactivity and penile grooming, both of which are characteristic effects of 5-HT<sub>2C</sub> receptor activation. Although lorcaserin



exerts its effects on food intake centrally, and both binds to and activates cells transfected with the 5-HT<sub>2A</sub> receptor *in vitro*, *in vivo* evidence of classic 5-HT<sub>2A</sub> activity in rats is limited. Lorcaserin did not release dopamine in the nucleus accumbens, and unlike DOM (2,5-dimethoxy-4-methylamphetamine) or DOI, did not consistently or dose-dependently elicit characteristic 5-HT<sub>2A</sub> behaviours: back muscle fasciculations were not increased, and wet dog shakes were modestly increased only at an intermediate lorcaserin dose. Drug discrimination testing of lorcaserin in rats demonstrated reliable discriminative control between saline and DOM, and as found with other serotonergic drugs like selective serotonin reuptake inhibitors (SSRIs) and fenfluramine, lorcaserin occasioned partial generalization to the DOM-associated cue. The subjective effects of lorcaserin were qualitatively different from DOM and support low abuse potential for lorcaserin. However, in view of the pattern of response in some rats, the potential for dependence and abuse liability cannot be excluded.

Lorcaserin produced a concentration-dependent inhibition of hERG currents with an estimated IC<sub>50</sub> of 14 µM but exerted no adverse effects (including no prolongation of the QT interval) in a monkey telemetry study at doses up to 100 mg/kg. C<sub>max</sub> calculated from the phase I clinical study is 59 ng/ml (297 nM).

There was no evidence of any adverse respiratory or central nervous system effects in rats at doses up to 50 mg/kg.

Pharmacodynamic drug interaction effects of concomitant treatments with lorcaserin have not been investigated.

## Pharmacokinetics

The pharmacokinetic characteristics of lorcaserin have been investigated in both *in vitro* and *in vivo* test systems. *In vivo* studies were conducted in CD-1 and C57BL/6 mice, Sprague Dawley (SD) and pigmented Long Evans rats, New Zealand White rabbits, beagle dogs, and cynomolgus monkeys; with the exception of pigmented rats, all species and strains used for ADME studies were the same as those used in the non-clinical pharmacology and toxicology studies. The drug substance was dosed as the hydrochloride salt in non-clinical and clinical studies.

Lorcaserin was rapidly absorbed with good oral bioavailability across species (i.e., SD rats [94%], beagle dogs [38%], and cynomolgus monkeys [49%]). Oral exposure increased dose-proportionately up to 50 mg/kg in all species. However, as dose increased, lorcaserin absorption and elimination were extended, resulting in greater than dose-proportional increases in AUC<sub>0-inf</sub> (at 75 mg/kg or more), apparent in the mouse and monkey. Saturation of absorption was evident in monkeys at doses greater than 75 mg/kg/day. Lorcaserin accumulation, in general, was two-fold or less across species, gender, and dose.

Lorcaserin was neither a substrate nor an inhibitor of P-glycoprotein.

Protein binding was moderate (60-76%) in all species examined, including humans.

Following administration of [<sup>14</sup>C]-lorcaserin, [<sup>14</sup>C]-labelled material was detected in all tissues examined with the highest levels in gastrointestinal contents, stomach, small intestine, bladder, and lungs. Lorcaserin is distributed throughout the body tissues and extensively metabolized, as parent drug accounted for only 1% to 6% of the total radioactivity in plasma.

The greatest tissue exposure in pigmented rats (Long Evans) occurred in the eyes, pigmented skin, urinary bladder, kidneys, lungs, and liver.

Target organ (CNS) exposure after oral lorcaserin administration was observed at the first time point taken, 0.25 h in mice and rats, and 1.0 h in monkeys. Under steady-state conditions at 10 mg/kg/day, the monkey brain-to-plasma ratio was more than two-fold less than the rodent brain-to-plasma ratio (26, 24, 22, and 10 brain-to-plasma ratio for mice, male rats, female rats, and monkeys, respectively). Lorcaserin accumulation after repeat dosing in plasma, brain, and cerebrospinal fluid (CSF) was less than two-fold in all species, and lorcaserin CNS accumulation at steady-state was proportional to lorcaserin plasma accumulation. M1 brain and CSF exposures after repeated lorcaserin dosing, however, were at least 80-fold less than the corresponding plasma M1 exposure. There did not appear

to be an accumulation of M1 in the CNS. These data indicate that lorcaserin accumulated in brain and CSF to the same extent as observed in plasma across species and dose.

Data on CSF levels are available in humans. Based on CSF extrapolation, a ratio for brain levels in male rat at 10 mg/kg/d and human is estimated to  $120 / 1.8 = 67$ . Based on worst case brain/plasma ratio extrapolation, a ratio for brain levels in male rat at 10 mg/kg/d and human is estimated to  $120 / 35 = 3.4$ . It is not known whether the lower degree of CSF exposure in human than in the animals will translate to also a lower degree of brain exposure in human, than in animal. Furthermore, it is not known which extrapolation is most relevant (based on CSF or brain levels), which leads to large differences in estimated levels for brain exposure in human. This should be considered when discussing the tumour findings in rat brain.

The metabolism of lorcaserin following a single oral administration was extensive and qualitatively similar in all species, including humans. Lorcaserin is metabolized by multiple human cytochrome P450 (CYP) enzymes and FMO1. M1 and M5 plasma exposure was observed in mice, rats, and monkeys after oral administration of lorcaserin. Multiple sulfotransferases and UDP-glucuronosyltransferases were responsible for the formation of M1 and M5, respectively.

It has been shown that lorcaserin induces several enzymes (e.g. CYP2B1/2, UGT1A, UGT1A6, CYP1A1, CYP3A1/2). With this induction potential, one could expect a decrease in lorcaserin exposure over time. However,, the dominating metabolite in plasma and urine in rats is a sulfamate, which does not involve any of the enzymes shown to be induced.

Lorcaserin sulfamate (M1) is the major circulating metabolite in rats, mice, monkeys, and humans. The *N*-carbamoyl glucuronide of lorcaserin (M5) is the major excreted metabolite in monkeys and humans. Minor metabolites such as glucuronide or sulfate conjugates of lorcaserin oxidative metabolites are observed in all species. All human circulating metabolites are identified in the plasma of at least one of the toxicology species, demonstrating that animals were exposed to these metabolites in repeat-dose safety studies. In general, the choice of animal species for the evaluation of lorcaserin toxicology is appropriate and relevant to human safety. In the absence of *in vivo* metabolism data in rabbits, no firm conclusions can be made concerning whether the major human metabolites were present at sufficient levels for metabolite qualification. The main metabolites in human plasma, M1 (sulfamate) and M5 (glucuronide) were not among metabolites observed *in vitro*. However, the high amount of M1 in plasma in mice, rats and monkeys would suggest this pathway to be generally important and it is agreed that rabbits are to be considered as an appropriate species for evaluation of developmental toxicity.

Lorcaserin turnover was slowest in human liver microsomes compared to other species, with a rank order of rabbit > mouse > rat > monkey > human. A clear difference in the extent of metabolism was observed between male and female liver microsomes of mice and rats. The rate of hepatic metabolism in male rats was faster than in female rats, whereas the hepatic metabolism in female mice was faster than male mice. These gender differences may be due, in part, to the gender-specific expression of drug metabolism enzymes, such as flavin-containing monooxygenase (FMO)1. In male rat liver, FMO1 expression is 2 to 3 times greater than in the female liver; whereas in mice, FMO1 expression is greater in the female liver. FMO1 is nearly undetectable in the adult human liver. The gender difference of metabolism in rodents is consistent with the differences in plasma exposures. There were no similar gender differences in rabbits, monkeys, or humans.

Lorcaserin did not show chiral conversion *in vitro* with hepatic microsomes from SD rat, cynomolgus monkey, and human liver. The (*S*)-enantiomer of lorcaserin was not detected in plasma of SD rats or cynomolgus monkeys after single or repeat oral administration of lorcaserin. Since there is no *in vivo* inter-conversion of the stereoisomers of lorcaserin, *S*-lorcaserin is considered toxicologically qualified up to the level present in the batches used for genotoxicity and long term repeat dose toxicity studies, i.e. 1%.

Mass balance of radioactive dose of lorcaserin was achieved in mice, rats, monkeys, and humans. Urinary excretion was the major elimination route of lorcaserin and its metabolites in all species, ranging from 61.9% of total administered dose in rats to 92.3% in humans. [<sup>14</sup>C] radioactivity was eliminated primarily in urine with only minor amounts excreted in faeces in all species including humans.

In rats, lorcaserin was excreted in the bile (>20%) following intravenous administration.

Lorcaserin excretion into milk was not studied. However, indirect evidence of secretion into milk could be obtained from pre- and post- natal study.

Lorcaserin was not an inhibitor of human liver microsomal CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 ( $IC_{50} > 200 \mu M$ ) enzymes. Lorcaserin was a competitive inhibitor of human microsomal CYP2D6 ( $IC_{50} = 3.99 \mu M$ ). Lorcaserin showed low potential for CYP induction in cultured human hepatocytes.

In contrast to the findings in cultured human hepatocytes, *ex vivo* induction studies in rats showed that lorcaserin was a hepatic enzyme inducer in this species: CYP2B and UGT enzymes increased in a dose-dependent manner comparable to that observed with phenobarbital, a prototype inducer. These effects provide a likely explanation for the hepatocellular and thyroid neoplasms and certain other cellular alterations in these organs observed at high doses in the 2-year rat carcinogenicity study.

## Toxicology

A complete programme of toxicity studies has been conducted. Genetic toxicology, carcinogenicity, reproduction, and development and all repeat-dose toxicology studies of 14 days duration or more were fully GLP compliant. A range of additional mechanistic studies was designed to investigate lorcaserin's proposed effect on prolactin in rats with a view to explaining tumours observed in the rat carcinogenicity test; several of which were also GLP compliant. The species selected for toxicity studies were justified based upon pharmacologic and metabolic profiles.

General toxicity studies of lorcaserin were conducted in mice, rats, and monkeys at doses that produced exposure multiples, relative to the human MRD, up to 35, 57, and 91, respectively. In repeat-dose toxicity studies, lorcaserin was generally well tolerated at doses below the MTD in all three species and there appear to be no serious adverse findings of direct relevance to humans at therapeutic doses. Main toxicity findings were as follows: changes in blood cells turn-over (e.g. low-grade anaemia, reticulocytosis, extramedullary haematopoiesis, and increased splenic pigmented macrophages); hepatocellular changes, sporadic increases in transaminases, and increase in bilirubin in rats and biliary epithelial hyperplasia in monkeys not unequivocally ascribed to treatment., all of which occurred not necessarily concomitant, with sufficient safety margin, and not observed in the clinical trials. Convulsion and emesis (the latter only in monkeys) were observed only at high doses.

In monkeys, kidney changes were observed in the 52-week study, consisted of focal tubular epithelial cell degeneration, regeneration, and cellular casts. Minimal to mild tubular epithelial degeneration was observed in 6 of 8 animals in the high dose group (125 mg/kg). Minimal to mild epithelial regeneration was observed in the renal cortex of 0/8, 1/8, 2/8, 3/8, and 6/8 animals given 0, 2, 10, 50, and 125 mg/kg lorcaserin, respectively. At the high dose, moderate epithelial regeneration was observed in 1/4 females. Cellular casts were observed in 1/4 males at 50 mg/kg and 1/4 males and 2/4 females at 125 mg/kg. The findings were not seen in any of the other species, were considered mild in monkeys and no functional consequences were observed.

An extensive body of literature strongly implicates agonism of the 5-HT<sub>2B</sub> receptor on cardiac valvular interstitial cells as the common factor in drugs that cause cardiac valvulopathy in humans, such as the non-specific serotonergic agents fenfluramine and dexfenfluramine. Lorcaserin has a selective profile for the 5-HT<sub>2C</sub> receptor over the 5-HT<sub>2B</sub> receptor. Extensive histopathologic analysis in general toxicity and carcinogenicity studies showed that lorcaserin had no effects on heart valves, other cardiac tissues, or the pulmonary vasculature in studies up to 2 years in rats and mice and up to 1 year in monkeys. In rat carcinogenicity studies there were, however, microscopic changes of the valves, endocardium, and *chordae tendineae* occurred in small numbers of rats without relationship to dose, and hence were not considered test article related. Although not standard, additional sectioning and microscopic evaluation of the heart was conducted on all animals in order to obtain a comprehensive evaluation of potential effects of lorcaserin. Although the clinical data is not considered to constitute a strong safety signal for lorcaserin there is a theoretical risk due to at least some affinity for 5-HT<sub>2B</sub> receptors.

Lorcaserin did not show genotoxic potential in a standard battery of genotoxicity studies.

Two-year carcinogenicity studies were conducted in mice and rats. In mice, due to mortality in the initial 100 mg/kg/day group, doses were reduced to 5, 25 and 50 mg/kg/day. Throughout the study, no clear reduction in body weight or effect on food intake were seen in either sex. Thus, it is questionable if a sufficiently high dose has been tested. Although no statistically significant effects were seen for neoplastic changes, there appeared to be a slightly increased number of malignant hepatocellular carcinoma in males (1, 3, 3, and 4 for controls, low dose, mid-dose and high dose, respectively). There were also in total 3 primary schwannoma in females. Both of these findings are of interest in relation to the findings in the rat study. The exposure margin was relatively limited (<4 in males, <8 in females at highest dose). No data are available for the pharmacological activity of lorcaserin at mouse 5-HT<sub>2C</sub> receptors, but there were no clear pharmacological effects in the mouse study (only small effects on body weight in males). Taken together, for pharmacologically mediated effects, it is questionable if there are any exposure margins. In conclusion, the mouse study gives no reassurance concerning potential carcinogenicity related to the pharmacological effect of lorcaserin.

In the rat carcinogenicity study, doses of 10, 30 and 100 mg/kg/day were tested. Effects on body weight were seen during the first week in both sexes, but diminished with time. Nevertheless, survival in both sexes was poor. At week 92 only one was alive, and all females were terminated week 100. Thus, this limits the value of lack of findings in the female rat. In males, the high dose group was terminated 4 weeks before the planned end of the study. A wide range of histopathological, both non-neoplastic and neoplastic, effects were observed.

Mammary gland adenocarcinoma was seen from  $\geq 30$  mg/kg/day in males and in high dose group females. Fibroadenomas were observed in all groups in both sexes, thus there is no NOAEL for this finding. The Applicant argues that these tumours were due to a prolactin enhancing effect of lorcaserin. Based on the mechanistic studies that have been provided, it seems that it has some prolactin – enhancing effect, but of considerably smaller magnitude than that induced by an active control and some data suggest that while prolactin is evidently of importance for the mammary gland hyperplasia, lorcaserin does not primarily act through prolactin release. In those cases where prolactin has been considered as a probable cause for the carcinogenesis, the increases are much more pronounced and sustained. There is no evidence that the small increase in prolactin induced by lorcaserin would result in rat mammary tumourogenesis. Based on the conclusion that the prolactin hypothesis for lorcaserin-induced mammary tumourogenesis is not verified, it is also true that the discussion whether prolactin may be associated to mammary tumours in humans is of minor importance here.

In males, there was an increased number of malignant tumours (squamous cell carcinoma) in the mid-dose group (n=4) and high dose group (n=5); with an absence in controls and the low dose group animals, and increased incidences of fibromas in the subcutis at all dose levels. In male rats, malignant schwannomas were observed in the mid-dose and high dose groups, in the subcutis (n=1 and 5, respectively) as well as single cases in other tissues (total n=2 and 9, respectively). No mechanistic explanation has been proposed by the Applicant and cannot be explained as a consequence of toxicity at the high dose.

For schwannoma and squamous cell carcinoma, the NOELs were 10 mg/kg/day. Based on systemic exposure, the safety margin to clinical exposure is less than 5-fold. When considering that lorcaserin appears to have 4-14 lower activity in functional assays for rat 5TH2C than for human receptors, and since it is not known if they are related to the primary pharmacology, it is questionable whether there are any margins of exposure for these findings and given the lack of mechanistic explanation these tumours are considered to constitute evidence of carcinogenic activity.

In males, there was an increased incidence of astrocytoma in the mid-dose and high dose group animals, thus a NOEL of 10 mg/kg/day. The Applicant argues that these tumours occurred at considerably higher brain exposures than estimated brain exposure in humans. However, these estimated exposure margins are uncertain. The Applicant assumes that the brain/CSF ratio is the same in human and in animals, while they also argue that there is a marked difference between the CSF/plasma ratio between human and rat. It is acknowledged that it is very difficult to assess levels in these tissue compartments, but these uncertainties also have to be recognised. Irrespective of whether safety margins for brain exposure are indeed valid and the rat astrocytomas are different from the human counterpart, for the overall risk assessment any rat tumour related to treatment, in absence of sufficient exposure margins and/or mechanistic understanding, are considered since they represent evidence of a carcinogenic signal.

There were also increased incidences of hepatocellular adenoma and carcinoma, and of follicular thyroid adenomas. Both of these tumour types are expected following long-term exposure to an enzyme inducing compound as lorcaserin. This mechanism is considered rodent specific and thus not a cause for concern for clinical use of lorcaserin.

To conclude: In rats, several tumour types were increased in males following 2 years exposure to lorcaserin, where the occurrence of schwannoma, astrocytoma, squamous cell carcinoma raise serious concern for human use as no convincing mechanistic explanations have been provided. In males, there was increased incidences of fibromas in the subcutis at all dose levels in males, thus no NOEL could be identified. The exposure margin discussions are not fully reassuring, given the lack of a mechanistic explanation and the fact that the functional activity at rat 5-HT<sub>2C</sub> receptors was 4-14 times lower than in humans. In both sexes, there were increased incidences of mammary gland fibroadenoma / adenocarcinoma for which the mechanistic explanation related to prolactin is not fully convincing to conclude on a lack of clinical relevance. The relevance of these tumours to humans should be re-evaluated and taken into consideration in the risk-benefit assessment of lorcaserin.

There was no apparent effect on fertility or embryo-fetal development studies in either rats or rabbits at exposures in line with the clinical exposure, except for a reduction in lactation index. Although there were changes in the prenatal and postnatal development study, most were confined to the highest dose and all appear to reflect maternal toxicity. None persisted to affect reproduction in the F<sub>1</sub> generation or the F<sub>2</sub> litters. Toxicokinetic studies suggest sufficient safety margins. Nevertheless, there was a higher number of malformations in the mid-dose and high dose groups compared with controls (n= 9, 8 and 5 malformed fetuses, respectively). Of note are 3 major heart/vascular malformations described; where the one in the mid-dose group was not fully reflected in the summaries of the study. These types of major cardiovascular malformations are however seen in control rabbits.

The toxicity to reproduction (i.e number of liveborns was reduced, the number of stillbirths increased and reduced pre-weaning F1 pup weights).

The lack of juvenile studies is acceptable since the intended patient population for lorcaserin is an adult population.

Dedicated local tolerance studies have not been conducted and none are required. There are no findings in the oral and gastrointestinal mucosa in the repeat dose studies suggesting local tolerance issues with oral lorcaserin. Emesis in monkeys could be related with secondary pharmacological effects that could not be spotted in rodents as they are no suitable models for emesis.

Preclinical phototoxicity studies are not deemed necessary despite lorcaserin binding to melanin in rats, since lorcaserin does not absorb UV/visible light and there were no related effects in clinical trials.

There is no evidence of antigenicity in the results of the animal studies that would cause a concern for humans.

No formal immunotoxicity studies are required however it is considered that the immunotoxic potential of lorcaserin has been adequately investigated. The most consistent findings in rodents were those related to increased red blood cell turnover at doses in excess of 50 mg/kg/day in mice and rats in the general toxicity studies. Acceptable safety margins were observed for increased red cell turnover in all non-clinical species.

Studies with lorcaserin designed to investigate the potential for dependence and abuse liability of lorcaserin were conducted and are reported as part of section on Safety Pharmacology. According to the results of the above mentioned studies, the potential for dependence and abuse liability cannot be excluded.

No additional studies with lorcaserin metabolites were conducted and none are required since all the human metabolites were represented in the preclinical toxicity studies.

Lorcaserin enantiomer is a low-level impurity of lorcaserin, present in most batches of drug substance tested throughout the programme. It has a pharmacological profile that is essentially the same as lorcaserin itself.

The toxicologic potential of 12 possible impurities in lorcaserin API starting materials was explored using QSAR analysis. Two compounds were positive because of the primary alkyl chloride moiety and another compound was positive because of the aziridine moiety. None of these potential impurities were detected in multiple representative intermediate and final API lots of drug product. In addition, the robustness of the manufacturing process for their removal was demonstrated by spiking experiments at intermediate stages of lorcaserin manufacture.

The toxicologic potential of a possible degradation product, *N*-formyl lorcaserin (AR308978), which corresponds to the metabolite M24, was tested using the Ames *Salmonella* MultiCASE assessment, and found to be negative for mutagenicity. AR308978 was generated from lorcaserin by Aroclor™-induced rat S9 fractions used in Ames testing. Furthermore, after oral administration of AR308978 in rats, it was converted rapidly to the parent drug lorcaserin and its major metabolite, M1. According to the Applicant, the projected tablet levels will not reach International Committee of Harmonisation (ICH) qualification threshold levels (0.5%) over a 2-year shelf-life. Since the batch data support the statement that *N*-formyl lorcaserin does not rise above ICH qualification threshold during the proposed shelf-life, further qualification studies are not deemed necessary.

## **Ecotoxicity/environmental risk assessment**

An environmental risk assessment has been conducted. The active ingredient lorcaserin hydrochloride is persistent in sediment. As a result of the inadequacy of some of the studies presented, the available data do not allow to conclude definitively on the potential risk of lorcaserin to the environment.

## **Discussion on non-clinical aspects**

Changes in modulation of the signal transduction cascade could have impact both on the safety and efficacy of lorcaserin. This should be taken into account in the risk-benefit of the drug, especially in non-responder patients. Several tumour types in rats (mammary gland fibroadenoma / adenocarcinoma, schwannoma, astrocytoma, squamous cell carcinoma) raise serious concern for human use as no convincing mechanistic explanations have been provided and sufficient safety margins in relation to human therapeutic exposure have not been established. The relevance of these tumours to humans should be re-evaluated.

Concerns have been raised that this would be the first instance of a measure against a non-genotoxic compound based on carcinogenicity findings and is proposed to be discussed at the Safety Working Party in the short-term.

## **Conclusion on non-clinical aspects**

This MAA is not approvable since there is a Major Objection regarding the carcinogenic potential.

### **3.4. Clinical aspects**

- **Tabular overview of clinical studies**

**Table1. Clinical pharmacology studies performed in healthy volunteers and patients (n= 1004)**

Study	Design	Objective	Population	Dose	
<b>PK and Initial Tolerability</b>					<b>Location 5.3.3.1</b>
<b>SINGLE DOSE</b>					
APD356-001A Phase 1	Double-blind, placebo-controlled, randomized Single dose rising study	To define the MTD	Healthy volunteers	10, 20, 40 mg	
<b>MULTIPLE DOSE</b>					
APD356-002 Phase 1	Double-blind, placebo-controlled, randomized Multi-dose rising study	To define the MTD	Healthy volunteers	3, 10, 20 mg QD for 14 days	
<b>MASS BALANCE</b>					
APD356-006 Phase 1	Open-label Single dose study	To assess mass balance To assess metabolic profile	Healthy volunteers	10 mg [ <sup>14</sup> C]-ADP356	
<b>CNS PARTITIONING</b>					
APD356-022 Phase 1	Open-label Multi dose study	To assess the PK properties of lorcaserin dosed to steady state in the cerebrospinal fluid of healthy subjects	Healthy Obese/overweight subjects	10 mg BID for 7 days	
<b>Bioequivalence</b>					<b>Location 5.3.1.2</b>
APD356-005 Phase 1	Open-label, randomized, 2-way crossover, 2-sequence Single dose bioequivalence	To assess bioequivalence	Healthy volunteers	10 mg Tablet vs. PIC	
<b>Intrinsic Factor</b>					<b>Location 5.3.3.3</b>
<b>RENAL</b>					
APD356-016 Phase 1	Multiple site, open-label, parallel-group Single dose study	To assess the effect of renal function on lorcaserin PK	Renal function: normal, mild, moderate, severe, ESRD	10 mg	
<b>HEPATIC</b>					
APD356-017 Phase 1	Multiple site, open-label, parallel-group Single dose study	To assess the effect of hepatic function on lorcaserin PK	Hepatic function: normal, mild, moderate, severe	10 mg	
<b>Study</b>	<b>Design</b>	<b>Objective</b>	<b>Population</b>	<b>Dose</b>	
<b>ELDERLY</b>					
APD356-018 Phase 1	Single site, open-label, parallel-group Single dose study	To assess the effect of age on lorcaserin PK To assess the efficacy in aged obese and overweight	Elderly > 65 Normal 18-65; Obese/overweight	10 mg	
<b>Extrinsic Factor</b>					<b>Location 5.3.3.4</b>
<b>DRUG-DRUG INTERACTION</b>					
APD356-008 Phase 1	Open-label, single- and multiple-dose, 1- sequence drug-drug interaction study Multi-dose study	To assess the effect of lorcaserin on the metabolism of dextromethorphan, a CYP2D6 substrate	Healthy volunteers	20 mg QD for 4 days	
APD356-012 Phase 1	Open-label, single- and multiple-dose, 1- sequence drug-drug interaction Multi-dose study	To assess the effect of lorcaserin on the metabolism of dextromethorphan, a CYP2D6 substrate	Healthy volunteers	10 mg BID for 4 days	
<b>FOOD EFFECT</b>					
APD356-001B Phase 1	Open-label, two-period, crossover Single dose study	To assess the effect of fed and fasted state on lorcaserin capsule formulation PK	Healthy volunteers	10 mg	
APD356-015 Phase 1	Open-label, two-period crossover Single dose study	To assess the effect of fed and fasted state on lorcaserin market image tablet PK	Obese/overweight patients	10 mg	
<b>PK and PK/PD Reports</b>					<b>Location 5.3.4.1</b>
APD356-001C Phase 1	Double-blind, placebo-controlled, randomized, 4 period, cross-over Single dose study; peak PK samples PK samples for confirmatory purposes	To assess the effect of a single dose on appetite and food intake	Healthy volunteers	0.1, 1.0, 10 mg	
<b>Patient PD and PK/PD Study Reports</b>					<b>Location 5.3.4.2</b>
APD356-014 Phase 2 Mechanism of Action	Double-blind, placebo-controlled, randomized, parallel group Multi-dose study	To evaluate the effects of lorcaserin on energy expenditure and energy intake	Obese/overweight patients	10 mg BID	
<b>Study</b>	<b>Design</b>	<b>Objective</b>	<b>Population</b>	<b>Dose</b>	
<b>Controlled Clinical Study Reports</b>					<b>Location 5.3.5.1</b>
APD356-003 Phase 2a	Double-blind, placebo-controlled, randomized, parallel group Multi-dose study; trough PK samples PK samples for confirmatory purposes	To assess the effect of lorcaserin on body weight	Obese patients	1, 5, 15 mg QD for 4 weeks	
APD356-004 Phase 2b	Double-blind, placebo-controlled, randomized, parallel group Multi-dose study; peak/trough PK samples PK samples for confirmatory purposes	To assess the effect of lorcaserin on weight loss	Obese patients	10, 15 mg QD 10 mg BID for 12 weeks	
APD356-009 Phase 3 POPPK POPPK/PD	Multi-center, randomized, double-blind, placebo-controlled, parallel-group Multi-dose study; sparse sampling	To assess the effect of lorcaserin on weight loss during 1 year of treatment To assess POPPK	Obese/overweight patients	10 mg BID for 2 years	
APD356-010 Phase 3 POPPK POPPK/PD	Multi-center, randomized, double-blind, placebo-controlled, parallel-group Multi-dose study; sparse sampling	To assess the weight loss effect of lorcaserin during 1 year of treatment To assess POPPK	Obese/overweight patients with type 2 diabetes	10 mg QD 10 mg BID for 52 weeks	
APD356-011 Phase 3 POPPK POPPK/PD	Multi-center, randomized, double-blind, placebo-controlled, parallel-group Multi-dose study; sparse sampling	To assess the weight loss effect of lorcaserin during 1 year of treatment To assess POPPK	Obese/overweight patients	10 mg QD 10 mg BID for 52 weeks	
<b>Other Study Reports</b>					<b>Location 5.3.5.4</b>
<b>THOROUGH ECG</b>					
APD356-007 Phase 1	Double-blind, placebo- and positive- controlled, randomized, parallel arm, Multi-dose study	To assess the effect on ECG parameters	Healthy volunteers	15, 40 mg QD for 7 days	
<b>ABUSE POTENTIAL</b>					
APD356-013 Phase 1	Double-blind, double-dummy, randomized placebo- and active-controlled crossover study with 7 treatment periods Single dose study; peak PK samples PK samples for confirmatory purposes	To evaluate the abuse potential of lorcaserin	Healthy recreational polydrug users	20, 40, 60 mg	

**Table 2. Phase 3 trials clinical trials**

Study ID	Number of Study Sites	Study Start/ End Date, No. of Subjects P/E/C/D <sup>a</sup>	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective	# Subjects by Arm Entered <sup>b</sup> / Completed	Duration	Sex M/F Median Age (Range) <sup>c</sup>	Diagnosis Inclusion Criteria <sup>d</sup>	Primary Endpoints
<b>LONG TERM STUDIES</b>										
APD356-009	98	11Nov2006/16Feb2009 Year 1: 3100/3182/1599/1583 Year 2: 1599/1553/1128/425	Randomized, double-blind, placebo-controlled, parallel group study	Lorcaserin: 10 mg and matching placebo, BID/104 weeks, oral	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	<b>Year 1</b> Placebo: 1587/716 Lorcaserin: 1595/883 <b>Year 2</b> Pbo/Pbo: 697/507 Lorc/Pbo: 283/195 Lorc/Lorc: 573/426	52/104 weeks	M525/F265244 (18-66)	BMI 30-45 kg/m <sup>2</sup> and BMI 27-29.9 with co-morbid condition	To assess the weight loss effect of lorcaserin after 52 weeks of treatment and to assess the ability of lorcaserin to maintain body weight at the end 104 weeks
APD356-010	64	600/604/401/203	Randomized, double-blind, placebo-controlled, parallel group study	Lorcaserin: 10 mg QD and BID and matching placebo/52 weeks, oral	Assess the weight loss effect of lorcaserin at the end of 52 weeks in overweight and obese patients with type 2 diabetes mellitus inadequately managed with oral hypoglycaemic agents	Placebo: 253 Lorcaserin 10 mg QD: 95 Lorcaserin 10 mg BID: 256	52 weeks	M276/F32753 (21-65)	BMI of 27 to 45 kg/m <sup>2</sup> with type 2 diabetes mellitus	Change from Baseline in body weight at the end of Wk 52
APD356-011	97	04Jan2008/08Jul2009 4000/4008/2155/1769	Randomized, double-blind, placebo-controlled, parallel group study	Lorcaserin: 10 mg QD and BID and matching placebo/52 weeks, oral	Assess the weight loss effect of lorcaserin at the end of 52 weeks in overweight and obese patients	Placebo: 1603/834 Lorcaserin 10 mg QD: 802/473 Lorcaserin 10 mg BID:	52 weeks	M810/F319444 (18-65)	BMI 30-45 kg/m <sup>2</sup> and BMI 27-29.9 with co-morbid condition	Change from Baseline in body weight at the end of Wk 52

## Pharmacokinetics

Twenty-one studies were conducted to characterize the safety, tolerability, efficacy and pharmacokinetics (including the influence of intrinsic and extrinsic factors) ranging in dose from 0.1 to 60 mg. Studies were conducted in male and female healthy subjects, individuals of different race (White/Caucasian, Black/African American, Hispanic/Latino, Asian, North American Indian or Alaska Native, Native Hawaiian or other Pacific Islander) and individuals in special populations (renal and hepatic insufficiency, elderly). In addition, a thorough ECG study and an abuse potential study were conducted.

The PK population consisted of 1004 patients (59 healthy volunteers and 641 obese/ overweight patients and 304 obese/overweight diabetic patients). There were 284 males and 720 females. The population age and weight ranged from 18 to 65 years (median 49 years) and 52 to 171 kg (median 94.2 kg), respectively.

Pharmacokinetic parameters were calculated with adequate statistical and analytical methods.

## Absorption

The absolute bioavailability of Lorcaserin has not been determined. However, the mass balance study (APD356-006) indicates that more than 90% of an orally administered dose was absorbed. This is corroborated by high permeability of lorcaserin across Caco-2 cell monolayers *in vitro*.

Bioequivalence was established between the capsule dosage form and the prototype tablet formulation. Based upon the API being a (BCS) Class-1 compound comparative dissolution was used to further demonstrate equivalence with the commercial tablet form.

Under fed conditions, T<sub>max</sub> was increased by approximately 1h; nevertheless the exposure was bioequivalent for lorcaserin AUC and C<sub>max</sub> between high-fat food and fasting conditions. The product information states that the product may be taken with or without food; this is agreed by the CHMP.

## Distribution

The volume of distribution after intravenous administration of Lorcaserin has not been determined. The apparent volume of distribution (V/F) was estimated to be 241 L with a body weight of 94.2 kg from population pharmacokinetic modelling. Lorcaserin has a moderate-high percentage bound to proteins, approximately 70%. The protein binding of metabolites have not been determined.

CSF concentrations were measured in a specific study where the CSF/plasma ratios were 0.017 and 0.014 for AUC and C<sub>max</sub>, respectively.



## Elimination

Approximately 94.5% of the administered radiolabel was recovered in urine and faeces with the majority of radioactivity recovered in urine (approximately 92.3%) and approximately 2.2% of the dose recovered in the faeces. Only 0.9% of the radioactive dose was excreted in urine as unchanged lorcaserin. The high percentage of urinary elimination of total radioactivity suggests that the primary excretion route for APD356 and its metabolites is renal.

Liver metabolism is the primary elimination pathway of lorcaserin followed by renal excretion. Multiple enzymes are involved in each of the major metabolic pathways; no single enzyme contributes to more than 25% of lorcaserin's total clearance. M1 was the major metabolite in plasma with 3% of dose and M5 was the major metabolite excreted in urine representing approximately 33% of total dose. The metabolites do not show relevant biological activity. Lorcaserin is a moderate inhibitor for CYP2D6 mediated metabolism. No chiral conversion is present in humans.

The dose proportionality analysis for Lorcaserin C<sub>max</sub> and AUC demonstrated that both parameters increase proportionally to Lorcaserin dose from 10 mg to 40 mg. These data support the conclusion that Lorcaserin has time-invariant PK and does not inhibit or induce its own metabolism or active transport.

No dose- or time-dependency was observed in any relevant PK parameter in the single dose study with doses from 10 mg to 40 mg or in the multiple dose study over 14 days with doses from 3 mg to 20 mg. Steady-state plasma concentrations of lorcaserin and M1 were reached by Day 3 for all dose levels.

## Variability

Between-subject variability in AUC and C<sub>max</sub> was moderate (~ 30%) across studies. Within-subject variability has not been estimated. IOV in CL/F was estimated to 25% and residual variability as well as inter-individual variability was decreased by approximately 5%

## Pharmacokinetics in target population

Phase 1 studies analyzed pk parameters in healthy volunteers whereas pk parameters in obese or overweight patients were analyzed in the phase 3 trials. The applicant has provided a Population Pharmacokinetic Analysis (ICON studies) which combines all pk parameters from healthy volunteers in phase I studies with pk parameters in obese or overweight patients from phase 3 studies. The main differences in PK parameters in the target population as compared to healthy volunteers are an increased in the apparent clearance (CL/F) resulting in lower steady-state exposure and C<sub>max</sub> in obese diabetic patients compared to obese non-diabetic and healthy volunteers. The Diabetic condition may have been the responsible of these results.

## Special populations

The applicant has investigated the exposure increase in patients with mild, moderate, severe renal impairment and end-stage renal disease (ESRD) with and without dialysis in 40 subjects. C<sub>max</sub> values were moderately lower for the mild, moderate, and severe renal impairment subjects. AUC values were higher for the mild renal impairment group, slightly higher for the moderate renal impairment group and lower for the severe renal impairment group relative to the normal renal function group when based on *ideal* body weight. The analysis on *actual* body weight showed similar trend for C<sub>max</sub> and more consistent trend for AUC that was lower with increasing renal impairment. Although lorcaserin exposure was not substantially altered by renal function, the exposure of metabolite M1, and to a lesser extent M5, was markedly increased in subjects with severe renal impairment or end stage renal impairment requiring haemodialysis. Lorcaserin and M1 were not cleared by haemodialysis; M5 was partially cleared by haemodialysis.

Based on the increased exposures of the M1 and M5 metabolites and the scarce data in severe renal impairment when calculated by actual body weight (n=1); lorcaserin should not be used in patients with severe renal impairment or end stage renal disease and should be used with caution in moderate renal impairment

PK of Lorcaserin was studied in 24 patients with mild and moderate hepatic impairment; Mean C<sub>max</sub> levels of lorcaserin for mild and moderate hepatic impairment groups were 7.82% and 11.5% lower, respectively, than for the normal hepatic function group. Relative to the normal hepatic function group, mean AUC<sub>0-inf</sub> levels were 1.27- and 1.33-fold higher (24% and 30% higher) for the mild and moderate hepatic impairment groups, respectively. Mean C<sub>max</sub>, AUC<sub>0-inf</sub> and AUC<sub>0-t</sub> levels of M1 increased 1.3- to 1.5-fold for the mild and moderate hepatic impairment groups compared to the

normal hepatic function group. These observations are consistent with the predominantly hepatic metabolism of lorcaserin; the moderate increase in exposure without imbalance in adverse events between groups support the no dose adjustments for mild and moderate hepatic impairment. Patients with severe hepatic impairment have not been investigated and the product is clearly not recommended to be used in patients with severe hepatic impairment.

In a formal population pharmacokinetic analysis gender and race did not significantly affect the apparent oral clearance or the apparent volume of distribution.

Patients with lower body weight are predicted to have slightly higher lorcaserin exposure as compared to patients with higher body weight; the difference is not clinically meaningful.

PK differences in obese elderly subjects (65-74 years) were studied as compared to obese adult subjects (18-65), 24 subjects were included in the study. AUC was shown to be equivalent between both groups whereas C<sub>max</sub> did not meet the equivalence criteria and was approximately 18% lower in the elderly group, this difference is not expected to be clinically significant and the proposed dose recommendation in section 4.2 of no dose adjustment in elderly is supported. However, Lorcaserin should be used with caution in patients over 65 years due to the lack of safety and efficacy data in this population.

No investigation of the pharmacokinetics in children has been made. This is in accordance with the waiver granted from PDCO.

### Interactions

The drug-drug interaction potential of Lorcaserin is assumed to be low since it is metabolized by multiple pathways and multiple enzymes and no single enzyme contributes to more than 25% of lorcaserin's total clearance.

#### *In vivo:*

In a dedicated interaction study, an approximately 2-fold increase in exposure was seen when lorcaserin was added to dextromethorphan (a CYP2D6-substrate according to the applicant).

#### *In vitro:*

Lorcaserin was found to inhibit CYP2D6. CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 were not inhibited by lorcaserin. M-1 did not inhibit CYP1A2, CYP2C8, CYP2C19, CYP2D6 or CYP3A4. Regarding induction, lorcaserin did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 or CYP3A4/5. M-1 did not induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4. Based on the results of the *in vitro* assays, it cannot be excluded that M-1 induces CYP2B6 and inhibits CYP2C9.

Based on caco 2 cell data, lorcaserin has no effects on P-gp-mediated efflux in the intestine or systemically.

## Pharmacodynamics

Lorcaserin is a selective agonist of the serotonin 2C (5-HT<sub>2C</sub>) receptor. Lorcaserin activates the 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors *in vitro* with potencies approximately 1/15th and 1/66th the potency at the 5-HT<sub>2C</sub> receptor.

Distribution of the 5-HT<sub>2C</sub> receptor is mainly in the CNS. The best characterized function of the 5-HT<sub>2C</sub> receptor is regulation of food intake and body weight and a possible role in glycemic control.

The 5-HT<sub>2B</sub> receptor is expressed in several tissues within the heart; activation of this receptor is thought to underlie the valvular heart disease associated with such agents as fenfluramine, ergotamine and pergolide. Activation of the 5-HT<sub>2A</sub> receptor can cause alterations in perception and mood.

Serotonin and some serotonergic agents can increase prolactin release. The effect appears to be an indirect one, and is mediated through both the hypothalamus and the pituitary. 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors have been implicated in serotonin mediated prolactin release. The possible safety issues associated with the activation of different 5-HT<sub>2</sub> receptors will be discussed in the safety part of this report.

A large number of assessments with respect to the effect of Lorcaserin on energy metabolism, appetite and satiety were performed in study 014. For the primary endpoint, 24 hour energy expenditure, there was a higher expenditure in both groups at week 56 compared to baseline with the largest change in the Lorcaserin group (p=0.05 compared to placebo). Some of the other parameters measuring energy metabolism also indicated a higher metabolism compared to placebo. There was a larger reduction in

food intake at lunch but not at dinner for Lorcaserin compared to placebo and the lorcaserin group reported a significantly larger decrease in perceived hunger compared to the placebo group after 55 days. Further, there was a statistically significant difference in weight reduction favouring Lorcaserin, even though the mean weight reduction was not impressive (3.9%).

Thus, in conclusion, even though not evident in all analyses performed, the mechanism of action of Lorcaserin (reduced appetite and increased energy expenditure) is at least to some extent supported by these results.

In the QT-study, Lorcaserin had no effect on QTcI; in both lorcaserin treatment groups (15 mg and 40mg), the upper bound confidence interval (95% one-sided) for the time-matched QTcI analysis did not exceed 10 ms. Mean change from baseline (placebo-corrected) for QTcI duration was -2 and -7 ms for the 15 mg and 40 mg lorcaserin treatments, respectively, and +6 ms for moxifloxacin. In addition, Lorcaserin group was associated with a decrease in HR of 2-3 bpm, this is in line with the results of phase 3 trials.

A study examining the abuse potential of Lorcaserin was performed in healthy male and female recreational polydrug users, single doses of lorcaserin (20/40/60 mg) were compared to placebo, zolpidem (15/30 mg) and ketamine 20 mg; the study showed that lorcaserin was disliked and does not have reinforcing effects across the range of doses tested and supratherapeutic doses were associated with negative side effects that would mitigate the risk of abuse, therefore the risk of abuse is considered low.

#### Exposure-Response

A Pharmacokinetic-Pharmacodynamic (PKPD) analysis was performed using data from 1647 obese/overweight patients randomized for PK sampling in Studies APD356-009, APD356- 010 and APD356-011. A continuous (time varying) population PKPD model was developed describing the relationship between percent weight loss from baseline and lorcaserin daily AUC (AUC<sub>ss,24hr</sub>). Logistic regression models and parameters for the relationship between Percent of Patients with FDA-defined valvulopathy (FDV) and lorcaserin AUC<sub>ss,24hr</sub> were investigated and exploratory plots of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, diastolic and systolic blood pressure, fasting insulin, C-reactive protein, HOMA-IR and hemoglobin A1c versus lorcaserin AUC<sub>ss,24hr</sub> were assessed. The final continuous PK/PD model for percent weight loss included the maximal placebo percent weight loss for non-diabetic and diabetic patients as fixed parameters, a slope parameter for the association of lorcaserin exposure to percent weight loss and an exponential time function to describe the temporal change in percent weight loss. Exploratory plots of the new occurrences of FDV versus lorcaserin AUC<sub>ss,24hr</sub> exposure at weeks 24 and 52 for the patients receiving active treatment, showed an overlap in exposure to lorcaserin between patients with and without FDV, and no relationship between lorcaserin exposure and FDV could be estimated.

## ***Discussion on clinical pharmacology***

#### Pharmacokinetics:

Lorcaserin is a new active substance, and pharmacokinetic studies should thus aim at describing the disposition of the substance, support the chosen dosage regimen and, based on the pharmacokinetic properties of the substance, identify sub-groups of patients in which exposure might be altered, and potential interactions with other medicinal products. The characterisation of Lorcaserin has been well performed and the questions raised on Day 120 have been solved.

In a dedicated renal impairment study, it was demonstrated that lorcaserin's PK parameters were unaffected across the normal, mild, moderate and severe renal impairment groups. Subjects with end stage renal disease (ESRD) had twice as high predicted steady-state exposure to lorcaserin compared to normal subjects. The results were similar irrespective if the data was analysed using actual body weight or ideal body weight. The metabolites M1 and M5 are accumulated in subjects with moderate, severe or ESRD renal status. The exposure to M1 in subjects with mild, moderate and severe renal impairment was 1.7-, 3.5- and 9-fold higher compared to subjects with normal renal function. The exposure to M5 in subjects with mild, moderate and severe renal impairment was 1.4-, 2.8- and 5.6-fold higher compared to subjects with normal renal function. The steady-state exposure to M5 in subjects with ESRD was 26-fold higher compared to subjects with normal renal function. Even though large increases are expected in M-1 and M-5 exposure in subjects close to the severe renal impairment cut off compared to a subject with normal function, the proposed SPC text is in general supported based on the available pre-clinical data showing that M-1 and M-5 could be considered

pharmacologically inactive. However, it seems adequate to state that lorcaserin should be used with caution in the moderate renal impairment group.

Hepatic impairment was studied in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function. Relative to the normal hepatic function group, mean AUC<sub>0-inf</sub> levels were 1.3-fold higher for the mild and moderate hepatic impairment groups, respectively. The same change of C<sub>max</sub> (no change) and AUC (1.3-fold increase) was seen in subjects with mild and moderate hepatic impairment (HI), in study APD356-017, even though there was a difference in CP score, the use in mild and moderate HI without any dose adjustment is supported.

#### Pharmacodynamics

The mechanism of action is considered as established. The affinity to the 5HT-2B receptor, albeit lower compared to the affinity to the 5HT-2c receptor, is worrisome considering the association to the development of valvular defects. However, the data from clinical studies is not considered to constitute a strong safety signal.

There does not seem to be any abuse potential and no effect on QT.

### **Conclusions on clinical pharmacology**

The pharmacokinetic studies performed indicate that Lorcaserin is well absorbed, fed conditions do not significantly alter the PK parameters, the apparent volume of distribution is 241 L and its binding to proteins is approximately 70%. Lorcaserin is metabolized by liver enzymes (no single enzyme contributes to more than 25% of lorcaserin total clearance, this is the reason why its interaction potential is low) and it is mainly renally excreted. Lorcaserin is a moderate inhibitor for CYP2D6 mediated metabolism. Based on the studies on special population, Lorcaserin should not be used in severe renal impairment and should be used with caution in moderate renal impairment due to the increased exposure to M1 and M5 metabolites. No dose adjustment is required for mild and moderate hepatic impairment.

The mechanism of action is considered as sufficiently documented.

### **Clinical efficacy**

#### ***Dose-response studies and main clinical studies***

##### **Introduction**

The Lorcaserin clinical development program included three pivotal Phase 3 studies (APD356-09, APD356-010 and APD356-011) that evaluated the efficacy and safety of Lorcaserin for the treatment of obesity in obese and overweight individuals with and without weight related comorbidities. In addition to the evaluation of weight loss, the program included evaluations of metabolic, cardiovascular, and glycemic endpoints. The two doses studied were 10 mg BID and 10 mg QD.

The Lorcaserin clinical development program also included two dose response studies Phase 2 studies (APD356-03, APD356-04)

##### **Dose response studies**

**APD356-003** was a 4-Week, Dose-Ranging, Double-Blind, Randomized, Placebo controlled, Parallel-Group Study to assess the effect of lorcaserin on body weight in uncomplicated obese patients. 352 uncomplicated obese male and female patients aged 19 to 65 years, with a body mass index (BMI) between 30 and 60 kg/m<sup>2</sup> (planned range 30 and 45 kg/m<sup>2</sup>), inclusive, were randomized to 1 of 4 treatment groups. Patients were equally randomized to receive lorcaserin (1 mg, 5 mg, or 15 mg) or placebo, once daily for 4 weeks

Lorcaserin at a dose of 15 mg once daily caused significant reduction in body weight after 3 weeks of treatment (-1.2 / -1.3 kg for Lorcaserin at Weeks 3/ 4 vs. -0.4 / -0.4 kg at Weeks 3/ 4, for placebo); No significant reductions in body weight for the doses of 1 mg and 5 mg. Lorcaserin at a dose of 15 mg

also significantly reduced BMI during the same time period but not significant reductions for 1 mg and 5 mg. No significant effects were seen at dose levels of 1 mg, 5mg, or 15 mg of lorcaserin on waist circumference, hip circumference, or waist: hip ratio.

**APD356-004:** A 12-Week, Dose-Ranging, Double-Blind, Randomized, Placebo controlled, Parallel-Group Study to assess the effect of lorcaserin on body weight after 12 weeks of administration to obese patients. 469 obese patients aged 25 to 65 years, with a Body Mass Index (BMI) between 30 and 45 kg/m<sup>2</sup> (inclusive) were randomized to 1 of 4 treatment groups. Patients were equally randomized to receive lorcaserin [10 mg once daily (QD), 15 mg QD, or 10 mg twice daily (BID)] or placebo for 12 weeks.

Study -004 supports further investigation of 10 mg BID in phase III. For this dose a significant reduction in body weight, BMI, waist and hip circumference was observed with good tolerance for all doses administered.

### Design of main studies

**APD356-009 (BLOOM):** A 104-Week, Double-Blind, Randomized, Placebo controlled, Parallel-Group Study to demonstrate that Lorcaserin 10 mg BID result in weight loss is greater than placebo.

The study population included adult subjects ≤65 years of age with a BMI 30 to 45 kg/m<sup>2</sup> with or without a co-morbid condition, or who were considered overweight based on a BMI of 27 to 29.9 kg/m<sup>2</sup> with at least one co-morbid condition (hypertension, dyslipidemia, CV disease, glucose intolerance, sleep apnoea). All enrolled patients were initially randomized to receive two oral doses per day of study drug for 52 weeks. After the first year of treatment, patients receiving lorcaserin were re-randomized to either remain on lorcaserin (10 mg BID) or to change to placebo for an additional 52 weeks (Year 2). Patients who received placebo during Year 1 remained on placebo for the duration of the study. Subjects with type 2 diabetes were excluded from participation.

**APD356-011 (BLOSSOM):** A 52-Week, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to evaluate the safety and efficacy of Lorcaserin 10mg BID and 10mg QD for the treatment of obesity in adult subjects ≤65 years of age with body mass index (BMI) of 30 to 45 kg/m<sup>2</sup> with or without a co-morbid condition, or BMI of 27 to 29.9 kg/m<sup>2</sup> with at least one co-morbid condition (hypertension, dyslipidemia, CV disease, glucose intolerance, sleep apnoea). Subjects with type 2 diabetes were excluded from participation.

**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 hypoglycaemic agents. The study population included adult subjects ≤65 years of age with a BMI 27 to 45 kg/m<sup>2</sup>

Inclusion criteria of Type 2 DM patients: HbA1c 7-10%; Fasting glucose at screening ≤240 mg/dL; treated with metformin, sulfonylurea (SFU), or either agent in combination with other oral medications (e.g., DPP-IV inhibitors, meglitinides, or acarbose) at a stable dose for at least 3 months prior to screening; If treated with thiazolidinediones (TZDs) in combination with SFUs or metformin, dose of TZD had been stable for at least 6 months prior to screening. Approximately 750 patients were originally planned for enrolment but due to slow enrolment; the total enrolment target was reduced by discontinuing randomization to the low dose group Lorcaserin 10mg QD.

In the pivotal studies, a rather healthy study population was aimed for with very low percentage of patients with CV disease (approx. 1%); patients with mild depression on stable therapy could also be included. Diabetic patients treated with insulin were not included in study -010. It is also noted that elderly patients > 65 years were not included in any of the phase 3 trials and that all phase 3 studies were performed exclusively in the US. It is planned that elderly patients > 65 years and true EU population will be included in the planned Post authorisation study.

The primary efficacy variables for the 3 trials were co-primary endpoints:

- Proportion (%) of patients achieving ≥ 5% weight reduction at the end of 52 weeks of treatment
- Change in body weight (kg) from Baseline to the Week 52 visit
- Proportion (%) of patients achieving ≥ 10% weight reduction at the end of 52 weeks of treatment

## Results

### *Patient Disposition*

In studies 009 and 011 (randomized set 1-year), 50.3% and 55.5% of the randomised subjects completed 1 year of treatment, respectively. The most common reasons for discontinuation from the study were patient decision (23.4% and 20.7%), lost to follow-up (13.1% and 12.8%), and adverse event (6.9% and 6%). In study -010 in type 2 DM, 66.4% of subjects completed all study visits, the most common reason for discontinuation were patient decision (14.9%), adverse event (6.5%) and lost of follow up (6.1%).

A higher percentage of subjects in the Lorcaserin 10 mg BID group than in the placebo group discontinued study drug due to an adverse event (study -009 7.1% vs 6.7%; study -011 7.2% vs 4.6% and study -010 in type 2 DM 8.6% vs 4.3%). A higher percentage of subjects in the placebo group than in the Lorcaserin BID group discontinued study drug for reasons of lost to follow-up, withdrawal of consent, and lack of efficacy.

The proportion of subjects discontinuing the studies may seem large, but this has previously been seen in other studies with weight lowering drugs. Due to the high discontinuation rate sensitivity analyses are necessary. For example, responder analyses for 5 and 10% responders should be calculated counting all withdrawals as non-responders. This will give a more accurate picture of the long-term efficacy of the product. Discontinuation due to adverse events was most common in the groups receiving Lorcaserin 10 mg BID.

### *Baseline Characteristics*

In studies -009 and -011, the majority of subjects were female (85.5% and 79.8%, respectively) and Caucasian (66.9% and 67%, respectively). The mean age of subjects was 44.1 years and 43.8 years, respectively. At baseline, mean weight was approximately 100 kg in both studies and mean BMI was 36.17 and 35.89 kg/m<sup>2</sup>, respectively. The most frequent comorbidities were hypertension (21.3% and 23.6%) and dyslipidemia (33.3% and 27.7%); other comorbidities were very scarcely represented cardiovascular disease (0.3% and 1.1%), glucose intolerance (1% and 1.5%) and sleep apnoea (4% and 4.3%). In study -010 in type 2 diabetes, the female representation was more balanced (54.25%), the majority of subjects were Caucasians (60.5%). The mean age of subjects was higher 52.7 years. At baseline, mean weight was 103.57 kg, mean BMI was 36.02kg/m<sup>2</sup> and mean HbA1C was 8.06%. As could be expected the most frequent antidiabetic medication was metformin (91.7%), sulfonylurea (50.2%) and both (42%). Lorcaserin treatment has not been assessed in diabetic patients treated with insulin.

### *Primary Efficacy outcomes*

Mean percent weight loss from baseline, as well as the proportion of patients reaching  $\geq 5\%$  weight loss and  $\geq 10\%$  weight loss, show a statistically significant effect that is consistent over the three studies, however the clinical relevance of the low weight reduction (aprox. 6% from baseline) should be discussed. In addition to further identify the population truly benefitting from treatment with Lorcaserin, it should be considered to stop treatment in patients not achieving a clinically relevant weight reduction (e.g.  $< 5\%$  weight reduction) after a specified duration of treatment. Further analysis of the predictive value of weight reduction at specific time points should be provided.

Mean percentage weight loss from baseline for non diabetic/diabetic patients was approximately 5.8/4.8% compared to 2.5/1.8% weight loss in placebo groups. Approximately 47/37.5% reached at least 5% weight loss (22.6/16.1% in the placebo groups), and 22.4/16.3% reached 10% weight loss (8.7/4.4% for placebo). The maximal weight loss seems to be gained after approx. 24-36 weeks of treatment.

**CO-PRIMARY ENDPOINT 1: PERCENT OF PATIENTS ACHIEVING  $\geq 5\%$  WEIGHT LOSS AT WEEK 52**

**Table 3. Proportion of Patients Achieving  $\geq 5\%$  Body Weight Loss after 52 Weeks of Treatment in Individual and Pooled (APD356-009 and APD356-011) Phase 3 Studies: MITT Population**

	APD356-009		APD356-011			Pooled (APD356-009 and -011)		APD356-010		
n (%) losing $\geq 5\%$ weight	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Lorcaserin 10 mg QD	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	10 mg QD
MITT										
N	1499	1538	1541	1561	771	3038	3098	248	251	94
n (%)	304 (20.3%)	731 (47.5%)	385 (25.0%)	737 (47.2%)	310 (40.2)	687 (22.61)	1460 (47.13)	40 (16.1)	94 (37.5)	42 (44.7)
Difference in Proportion (%) (95% CI) <sup>a</sup>		27.2 (24.0, 30.5)		22.23 (18.94, 25.52)	15.19 (11.11, 19.27)		24.52 (22.22, 26.82)		21.32 (13.78, 28.86)	28.55 (17.51, 39.60)
p-value <sup>a</sup>		<0.0001		<0.0001	<0.001		<0.001		<0.0001	<0.0001

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

**Table 2. Mean Weight Loss Change from Baseline at Week 52 in Individual and Pooled (APD356-009 and -011) Phase 3 Studies: MITT**

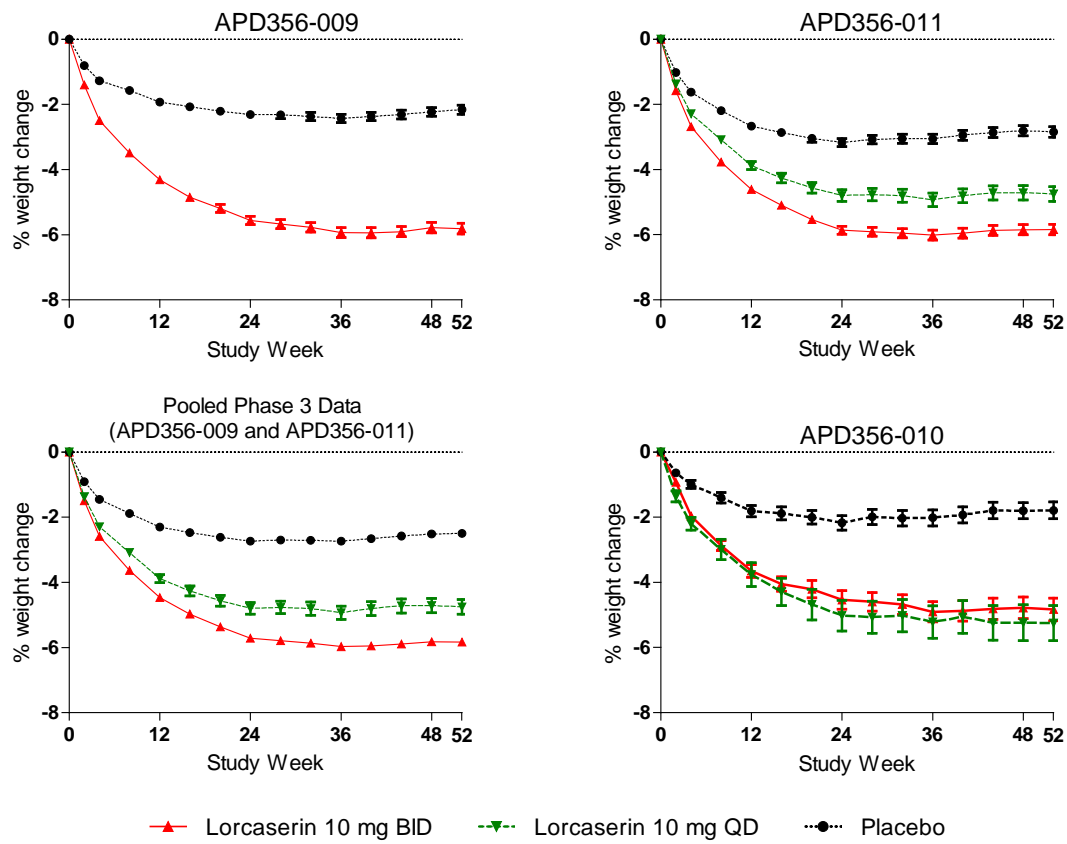
	APD356-009		APD356-011			Pooled -009 and -011		APD356-010		
	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	Placebo
MITT (Co-primary endpoint)										
N	1538	1499	771	1561	1541	3098	3038	94	251	248
Mean baseline <sup>a</sup> , kg	100.38 $\pm$ 15.69	99.66 $\pm$ 15.60	100.11 $\pm$ 16.74	100.34 $\pm$ 15.65	100.77 $\pm$ 16.22	100.36 $\pm$ 15.67	100.22 $\pm$ 15.92	106.08 $\pm$ 19.61	103.52 $\pm$ 17.18	102.27 $\pm$ 17.99
Mean ( $\pm$ SE) weight change, kg	-5.76 $\pm$ 0.16	-2.15 $\pm$ 0.14	-4.72 $\pm$ 0.24	-5.76 $\pm$ 0.17	-2.86 $\pm$ 0.15	-5.76 $\pm$ 0.12	-2.51 $\pm$ 0.10	-5.37 $\pm$ 0.57	-4.93 $\pm$ 0.37	-1.86 $\pm$ 0.27
Difference in Proportion (%) (95% CI)	nr	nr	-1.878 (-2.43, -1.33)	-2.906 (-3.35, -2.46)		3.25 (-3.56, -2.94)		-3.408 (-4.64, -2.18)	-3.053 (-3.96, -2.15)	
P-value <sup>a</sup>	<0.0001		<0.0001	<0.0001		<0.001		<0.0001	<0.0001	
Mean ( $\pm$ SE) weight change, %	-5.81 $\pm$ 0.16	-2.16 $\pm$ 0.14	-4.76 $\pm$ 0.24	-5.85 $\pm$ 0.17	-2.84 $\pm$ 0.15	-5.83 $\pm$ 0.12	-2.50 $\pm$ 0.10	-5.25 $\pm$ 0.54	-4.83 $\pm$ 0.35	-1.79 $\pm$ 0.26
P-value <sup>b</sup>	<0.0001		<0.0001	<0.0001		<0.001		<0.0001	<0.0001	
Range, kg (%)	-36.0 – 11.7 (-33.3 – 13.3)	-38.2 – 14.1 (-36.3 – 15.5)	nr	nr		-37.20-14.80 (-34.9 – 13.3)	-56.10 – 20.00 (-46.3 – 17.5)	-23.7-7.2 (-18.4-5.4)	-36.1-4.3 (-30.5-4.5)	

**CO-PRIMARY ENDPOINT 3: PERCENT OF PATIENTS ACHIEVING  $\geq 10\%$  WEIGHT LOSS AT WEEK 52**

**Table 4. Proportion of Patients Achieving  $\geq 10\%$  Body Weight Loss after 52 Weeks of Treatment in Individual and Pooled (APD356-009 and APD356-011) Phase 3 Studies: MITT Population**

	APD356-009		APD356-011			Pooled -009 and -011		APD356-010		
	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg BID	Placebo	Lorcaserin 10 mg QD	Lorcaserin 10 mg BID	Placebo
MITT										
N	1538	1499	771	1561	1541	3098	3038	94	251	248
n (%)	347 (22.6%)	115 (7.7%)	134 (17.4%)	353 (22.6%)	150 (9.7%)	695 (22.43)	264 (8.69)	17 (18.1)	41 (16.3)	11 (4.4)
Difference in Proportion (%) [95% CI]	14.9 (12.4, 17.4)		7.63 (4.58, 10.69)	12.88 (10.33, 15.43)		13.75 (11.97, 15.52)		13.65 (5.46, 21.84)	11.90 (6.66, 17.14)	
p-value <sup>a</sup>	<0.0001		<0.0001	<0.0001		<0.001		<0.0001	<0.0001	

**Figure 1** Mean Percent Weight Loss from Baseline to Week 52 in Individual and Pooled (APD356-009 and -011) Phase 3 Studies: MITT Population



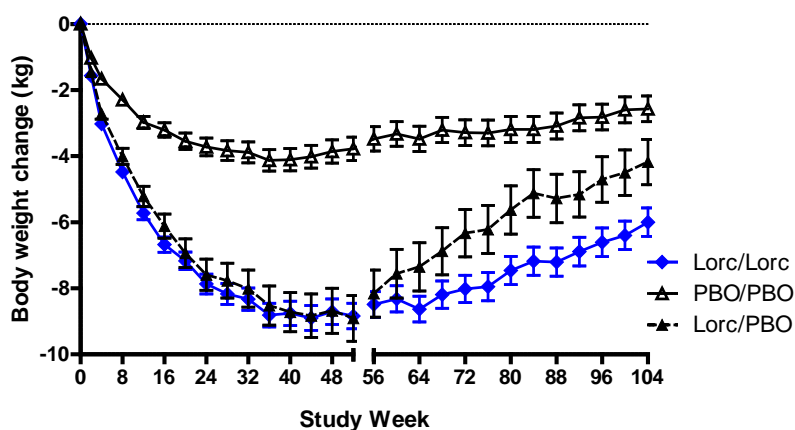


## Weight maintenance

In study APD356-009 weight maintenance was evaluated during Year 2 of the study. Patients receiving lorcaserin 10 mg BID during Year 1 were re-randomized in a 2:1 ratio either to continue receiving lorcaserin 10 mg BID or to switch to placebo, while the placebo group continued to receive placebo treatment. The re-randomization was stratified by responder status ( $\geq 5\%$  weight loss) at week 52.

Weight regain occurred in all treatment groups during Year 2.

**Figure 2. Change in Body Weight from Baseline to Week 104 in APD356-009: PP2 Population**



**Table 5. Proportion of Lorcaserin Patients Achieving  $\geq 5\%$  Reduction in Body Weight after Week 52 of Treatment (Responders) Who Maintained at Least 5% Weight Loss (based on Baseline Weight) at the End of Week 104 in APD356-009: MITT2 Population**

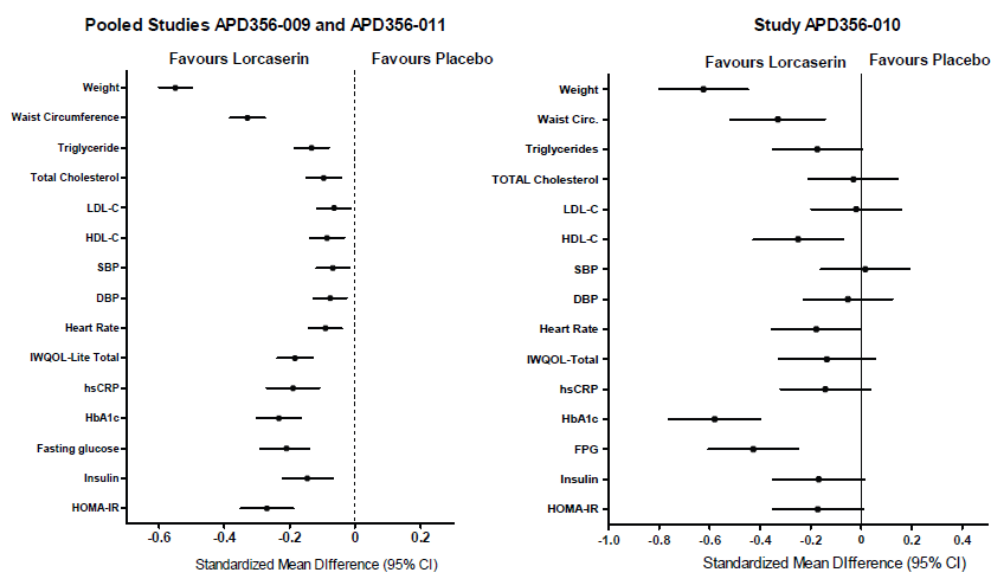
Treatment	N	n (%) Yes			
Lorc/Lorc	380	258 (67.9%)			
Lorc/Pbo	175	88 (50.3%)			
Between Comparison	Treatment	Difference in Proportion (%) (95% CI <sup>a</sup> )	p-Value <sup>a</sup>		
			Treatment	Gender	Baseline Body Weight
Lorc/Lorc vs. Lorc/Pbo		17.6 (8.8, 26.4)	< 0.0001	0.8224	0.8595

The weight regain during the second year is somewhat less pronounced for responders who continue with lorcaserin than for responders switching to placebo (68 % and 50% remained their responder status respectively).

However, there is no data presented on the second year for the non-responders at week 52. This should be provided.

## Secondary outcomes

**Figure 1. Standard Mean Differences (95% CI) for Key Study Endpoints (Lorcaserin 10 mg BID versus Placebo) in Pooled Studies APD356-009 and -011 and in Study APD356-010**



Abbreviations: FSG=fasting serum glucose; FPG=fasting plasma glucose; SBP=systolic blood pressure; DBP=diastolic blood pressure.

Lipids and body weight are percentage change from baseline.

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

## Waist Circumference

Across studies and pooled analyses, dose-related and statistically significant decreases in waist circumference were observed in the lorcaserin treatment groups as compared to placebo. In Type 2 DM patients, the effect observed in the 10 mg QD group vs placebo was of borderline significance ( $p=0.0533$ ).

## BMI

BMI also decreased significantly in all lorcaserin groups relative to placebo. The BMI decreases were dose-related in non-diabetic patients, but not in patients with type 2 diabetes, in whom the once daily dose was associated with a slightly greater mean reduction of BMI than the twice daily dose.

## Blood Pressure

Decreases in systolic and diastolic blood pressure were observed in all treatment groups in individual studies APD356-009 and APD356-011. The decreases in the lorcaserin 10 mg BID group were significantly greater than in the placebo group for both measures in APD356-009, approached significance in APD356-011, and were highly statistically significant in the pooled (APD356-009 and -011) analysis. No significant differences in systolic and diastolic blood pressure were observed between lorcaserin 10 mg QD and placebo. In study APD356-010, small decreases in systolic and diastolic blood pressure were observed in the lorcaserin 10 mg BID and placebo treatment groups, but not in the lorcaserin QD group, in which mean systolic and diastolic blood pressure increased slightly. The differences between the lorcaserin and placebo groups were not statistically significant.

## Lipid parameters

In the pooled analysis of non-diabetic patients (APD356-009 and -011), total cholesterol and triglycerides were decreased significantly more in patients treated with lorcaserin versus placebo, and HDL was increased significantly more. LDL increased in all treatment groups, but increased significantly less among patients treated with lorcaserin relative to placebo. Among the patients with type 2 diabetes (APD356-010), baseline cholesterol, LDL cholesterol and HDL cholesterol were lower than in the nondiabetic patients, possibly reflecting more aggressive treatment of dyslipidaemia among the former population; triglycerides were somewhat higher in the diabetic group. Change from baseline triglycerides did not differ significantly between the lorcaserin BID and placebo groups. While the lorcaserin-associated trends in cholesterol, HDL and LDL in APD356-010 were directionally similar to those in studies -009 and -011, formal statistical testing was not completed.

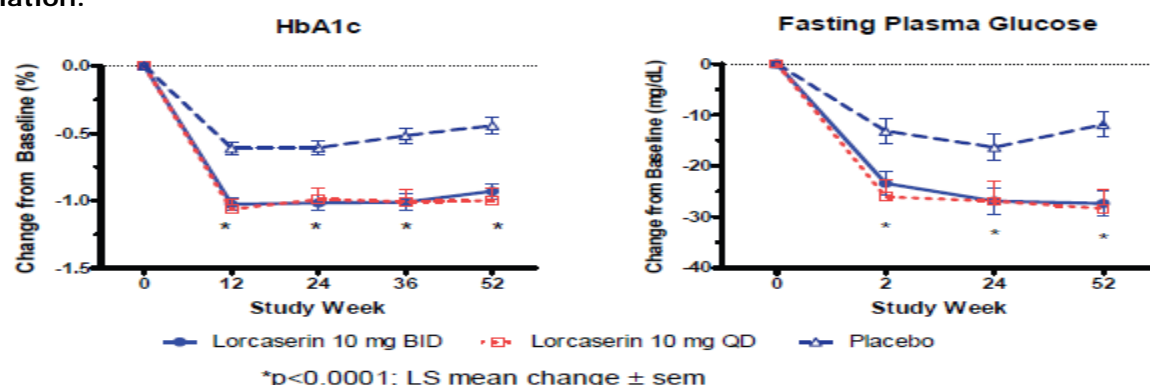
Lorcaserin effects on lipids were small but generally favourable among the non-diabetic patients. While the effects of lorcaserin were confounded by apparent aggressive concurrent treatment of dyslipidaemia in the type 2 diabetic patients, no unfavourable trends were identified.

The inconsistent total cholesterol and LDL cholesterol laboratory findings (i.e., slight increase from baseline of LDL cholesterol in study ADP356-009 in the lorcaserin arm and non-significant change of LDL cholesterol compared with placebo in study ADP356-011) may be a consequence of the heterogeneous baseline characteristics (with or without dyslipidemia and non standardized concomitant treatments).

#### Glucose related endpoints

Reductions in HbA1c and fasting plasma glucose were observed at all time points investigated in study APD356-010. The reductions were significantly greater in the lorcaserin treatment groups than in the placebo group at each time point, and were similar with once daily and twice daily lorcaserin. A decrease of approximately 1% in HbA1c occurred in the lorcaserin BID group by study Week 12, and remained through Week 52.

**Figure 2. Change in HbA1c and Fasting Glucose by Study Visit in APD356-010: MITT Population:**



#### Clinical studies/results in special populations

Results in subgroups are presented for the 1-year Phase 3 cohort that consists of all subjects who were randomised to the pivotal Phase 3 studies -009, -010 and -011.

Gender: Mean weight loss was consistently slightly greater in men than women in all treatment groups and all studies.

Age: Efficacy by age was analyzed by subgroups above and below the median age; median age was 44 years for studies APD356-009 and -11 and 54 years for study APD356-010. Across studies and treatment groups, the proportion of patients who achieved the primary endpoint was almost double in the older group. Patients >65 years were not included in the phase 3 studies; this should be reflected in the SPC.

Race: Across studies and treatment groups, weight loss in the Caucasian population was slightly higher than in African American and Hispanic populations.

BMI: In all BMI subgroups, the proportion of patients treated with lorcaserin achieving ≥5% and ≥10% reduction in body weight was greater than the proportion of patients treated with placebo. Total weight loss was also consistently higher in patients treated with lorcaserin as compared to placebo, regardless of baseline body weight and baseline BMI. Efficacy was dose responsive in non-diabetic patients but not in diabetic patients where the once daily lorcaserin dose achieved efficacy equalling or exceeding that of the twice daily dose.

DM type 2: In patients with type 2 diabetes, patients on lorcaserin QD lost slightly more weight than patients on lorcaserin BID.

#### Discussion on clinical efficacy

In the current application, the Applicant presents the results from three phase III studies (APD356 - 009, APD356 -010 and APD356-011). The 3 studies included patients 18-65 years, BMI 27-45 kg/m<sup>2</sup> and were performed in US centers exclusively. Study -009 and -011 did not include patients with type

2 diabetes mellitus, whereas study -10 was performed in type 2 diabetes patients. In study -009 and -011 ¾ of the patients were female.

The primary objective of study **APD356-009**, a 2 years study with Lorcaserin 10 mg BID, was to demonstrate that 10 mg BID of Lorcaserin result in weight loss is greater than placebo. The primary objective seemed to be confirmed in an obese patient population with weight related comorbidities as hypertension (21.3%), dyslipidemia (33.3%), sleep apnoea (4%) and in very few numbers glucose intolerance (1%) and CV disease (0.3%). Treatment with Lorcaserin 10 mg BID for 52 weeks resulted in a mean weight reduction of 5.81% vs 2.16% compared with placebo. The proportion of  $\geq 5/10\%$  responders for Lorcaserin compared to placebo were 47/22% vs 20.3/7.7%, respectively. At week 104 the proportion of responders that maintained at least 5% weight loss was 67.9% vs 50.3% respectively for Lorcaserin and placebo; this significant result supports the primary endpoints at year 1; nevertheless, it is to note that the weight maintenance in the placebo group was also high. The maximal weight loss seems to have been achieved after 36 weeks of treatment.

In study **APD356-011** of 52 weeks duration with 10mg BID and 10mg QD, the weight reducing effect of the 10 mg BID/QD dose appeared to be statistically and clinically significant with 47.2/40.2% of patients achieving at least 5 % weight loss as compared to 25% in the placebo group; patients achieving at least 10 % weight loss were 22.6/17.4% in Lorcaserin 10 mg BID/QD compared to 9.7% in the placebo group, after 52 weeks treatment. The maximal weight loss seems to be gained after approx. 24 weeks of treatment. The treatment with Lorcaserin 10 mg BID/QD resulted in a mean weight reduction of 5.85/4.76% vs 2.84% in the placebo group. The effect of the 10 mg QD dose is less pronounced than the 10 mg BID but there is still a statistically significant difference compared to placebo.

Study **APD356-010** in patients with diabetes mellitus type 2 explored the efficacy of Lorcaserin 10 mg BID and QD in 52 weeks. The weight reducing effect of the 10 mg BID/QD dose is statistically and clinically significant with 37.5/44.7% of patients achieving at least 5 % weight loss compared to 16.1% in the placebo group and 16.3/18.1% of patients on Lorcaserin BID/QD achieving at least 10 % weight loss, compared to 4.4% in the placebo group, after 52 weeks treatment. The maximal weight loss seems to be gained after approx. 24 weeks of treatment, which is consistent with the other studies. The treatment with Lorcaserin 10 mg BID/QD resulted in a mean weight reduction of 4.83/5.25% vs 1.79% in the placebo group.

There was a high percentage of patients who withdrew for "other" reasons in each of the pivotal studies. The Applicant has provided more details on the reason these patients dropped out. The retention rates were higher in the lorcaserin groups than the placebo group and the timing of discontinuation was similar in the placebo and active treatment groups even though the retention rate was higher in the active treatment groups than the placebo group

It is accepted that the discontinuation rates (approximately 40 to 50%) were very high in the 3 phase III studies similarly to other studies using weight lowering agents. Discontinuation rates due to adverse events were higher in the Lorcaserin 10 mg BID across studies, especially for diabetic patients in study -010 where the discontinuation rate was double that of placebo (8.6 vs 4.3% for Lorcaserin vs placebo). Responder analyses for 5 and 10% responders has been calculated counting all withdrawals as non-responders for all three studies.

The Applicant has provided the results of an additional analysis where patients that discontinued were considered as non-responders (in this case it was assumed their weight returned to the baseline value (BOCF). The Applicant has also provided a further sensitivity analysis where lorcaserin patients who discontinued were treated as non-responders (BOCF) and placebo patients that discontinued had their Week 52 data imputed using LOCF. In the new analyses a statistically significant effect remains but as expected the mean weight loss is lower in all treatments groups for these sensitivity analyses than the original primary analysis. (Refer to Tables 17 and 18 on the Clinical Joint Assessment Report)

According to the Guideline on clinical evaluation of medicinal products used in weight control, patients enrolled in obesity trials should be subject to an appropriate weight reducing diet run-in period for a specified minimum time, however none of the trials included a run in period. The reason for a run-in period is to see the effect a dedicated diet and exercise programme can achieve and then evaluate the effect pharmacological treatment can have on top of this programme. Patients who had lost more than 5% of body weight in the last three months were excluded from taking part in the Applicant's clinical studies. The Applicant considers these subjects to be confounders as it is claimed that subjects with

recent weight loss are in a state of negative energy balance and may have already achieved a plateau from the previous weight loss efforts. This needs further discussion. Diet and exercise should be able to reduce weight in the short-term in the majority of people. It is how pharmacological therapies can add to this weight loss that needs to be investigated. The Applicant has chosen to avoid this patient group and instead concentrates on subjects who have not lost weight recently.

During the second year in study APD356-009 weight regain occurred in all treatment groups. The weight regain during the second year is somewhat less pronounced for responders who continue with lorcaserin than for responders switching to placebo (68 % and 50% remained their responder status respectively). The Applicant has provided a good argument for restricting the use of lorcaserin to subjects who use at least 5% of weight by Week 12 of treatment. Treatment should be discontinued in patients who do not response by at least this amount by Week 12.

Concerning secondary efficacy endpoints, reductions of waist circumference, blood pressure, and lipid parameters were seen all Lorcaserin treatment groups with statistically significant results for the non-diabetic patients. There were also minor reductions in heart rate. In study -010 in diabetic patients there was a placebo-corrected reduction in HbA1c of approximately 0.5% and reduction of fasting plasma glucose approximately 10-20 mg/dl as corrected by placebo, with concurrent decreases in total daily doses of most antidiabetic medications. Thus, there are no indications that treatment with Lorcaserin would have a detrimental effect on cardiovascular risk factors. On the contrary, beneficial effects were generally recorded. However, these are likely secondary to weight loss.

The effect was affected by age, older patients analyzed by subgroups above and below the median age 44 years for studies APD356-009 and -11 and 54 years for study APD356-010, showed a markedly greater response than younger patients. It is important to note that patient's  $\geq 65$  years of age were not included in the phase 3 studies. By gender, male patients had a slightly greater response than female. By race, the response was slightly greater in Caucasians than in other races. The response was similar independent of baseline BMI, fasting plasma glucose and HbA1c.

## **Conclusions on clinical efficacy**

Treatment with Lorcaserin 10 mg BID for 52 weeks results in consistent and significant results after applying the sensitivity analysis requested. The proportion of patients achieving 10% weight loss (18 to 22% depending on analysis and population) is not impressive; however the size of the benefit improves considerably because the treatment will be restricted to patients who reach 5% weight reduction by week 12, if this criteria is not met, patients will discontinue the drug as they are unlikely to reach and sustain a clinically meaningful weight loss; with this new restriction, the size of the benefit seen on the initial analysis is improved; however it is still considered that the efficacy results are too modest to outweigh the safety concerns and the overall benefit risk balance should be further discussed. The maximum effect seems to be reached after approx. 24-36 weeks of treatment. There are no indications of a detrimental effect on cardiovascular risk factors, but rather a beneficial effect on blood pressure, glucose and lipids, most likely secondary to weight loss. The effect seems to be greater in older patients, male and Caucasians.

## **Clinical safety**

Lorcaserin is a selective serotonin 2C (5-HT<sub>2C</sub>) receptor agonist and is believed to decrease food consumption by selectively mimicking the effects of serotonin at the 5-HT<sub>2C</sub> receptor. In cell-based experiments, lorcaserin also interacts with the 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors, although with lower affinity when compared to the 5-HT<sub>2C</sub>. The 5-HT<sub>2C</sub> receptor expression is primarily limited to a few regions of the central nervous system (CNS) whereas the 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors are widely expressed in the CNS and peripherally. The 5-HT<sub>2B</sub> receptor activation is involved in heart valve disease and agonist activity of lorcaserin at the 5-HT<sub>2A</sub> receptor has been linked to mood and perceptual effects. The applicant states that given that 5-HT<sub>2C</sub> receptor expression is primarily limited to a few regions of the central nervous system (CNS), lorcaserin was predicted to cause weight loss with few unintended pharmacological effects. In addition to standard safety assessments, the safety evaluation program for lorcaserin included an evaluation of effects that could result from activation of 5-HT<sub>2A</sub> or 5-HT<sub>2B</sub> receptors. Since lorcaserin is centrally acting, the safety program included evaluations of potential behavioural, cognitive, motor, and mood effects.

## Patient exposure

At least 1 dose of lorcaserin was given to the 4347 patients included in the patients in the Phase 3 studies. A majority (79%) of the lorcaserin treated patients was exposed to a mean daily dose of  $\geq 10$  mg BID i.e. to the recommended dosage regimen of lorcaserin. Of the 4347 patients, 2034 (47%) were exposed for at least 1 year ( $\geq 365$  days), and 437 (10%) for at least 19 months ( $\geq 581$  days). A total of 1567 subjects (36%) treated with 10 mg BID was exposed for at least 1 year. It should be noted that the pooling only included Year 1 data from study APD356-009. The information that 437 subjects were exposed for 581-738 days among the patients entering the second year of the APD356-009 study has been taken from the text in the summary of clinical safety document. This information should be verified. The applicant should clarify how many of the patients in the diabetic study population were exposed to lorcaserin (total; 10 mg BID; 10 mg QD) for  $\geq 52$  weeks,  $\geq 83$  weeks and  $\geq 104$  weeks or more.

Total lorcaserin exposure for the lorcaserin 10 mg BID treated subjects in the placebo controlled phase 3 studies (based on Year 1 data only) was 3434 subject-years with a mean exposure per subject of 1.0 years.

**Table Patient exposure <sup>a</sup> (cut off date of date?) - Safety populations**

	Patients exposed to placebo or lorcaserin	Patients exposed to lorcaserin	Patients exposed to mean dose of $\geq 10$ mg BID	Patients with long term safety data $\geq 52$ weeks/ $\geq 83$ weeks/ $\geq 104$ weeks
<b>Placebo-controlled (Phase 3) <sup>b</sup></b>	<b>7784</b>	<b>4347</b>	<b>3451<sup>c</sup></b>	<b>2034/437/?</b>
Placebo controlled (Phase 2)	878	646	145	
Phase 2/3 total		4993	3596	
Clinical pharmacology (Phase 1)	520	406	245 <sup>d</sup>	
Grand total safety data base		5399	3841	

<sup>a</sup> Subjects exposed to at least 1 dose lorcaserin

<sup>b</sup> Number of subjects exposed to lorcaserin during Year 1 (data does not include Year 2 exposures in APD356-009), (Source: Summary clinical safety Table 8);

<sup>c</sup> Cumulative exposure: 3434.1 patient-years; mean exposure 263.7 (SD 133.1) days /subject;

<sup>d</sup> Patients treated with 10 mg BID, 20 mg QD, 40 mg QD, 60 mg QD (Source: Summary clinical safety Table 6);

In the Phase 3 clinical studies there are two distinct study populations, i.e. a large non-diabetic population (N=3195 patients exposed to lorcaserin 10 mg BID) and a smaller diabetic population (N=256 patients exposed to lorcaserin 10 mg BID). The non-diabetic patients included in the Phase 3 studies are rather healthy whereas the other population is a "typical" diabetes population. The two populations have different features but within each of the population the demographic and patient baseline characteristics are balanced between lorcaserin and placebo treated groups. SSRI/SNRI antidepressant medication was not allowed during the studies.

## Adverse events

The proportions of non-diabetic patients reporting events were similar among treatment groups, with 82.5% of patients exposed to any dose of lorcaserin and 75.5% of patients on placebo reporting an AE in Year 1. Slightly higher proportions of patients with type 2 diabetes reported at least 1 adverse event.

The most frequently reported SOC was Infections and Infestations, consistent with Upper Respiratory Tract Infection, Nasopharyngitis and Sinusitis appearing as 3 of the 4 most frequent PT. SOC's with a 50% or greater relative excess of events in the non-diabetic lorcaserin BID group include Nervous System (30.7% of patients versus 19.4%), General (17.2% vs. 10.7%), Eye (4.5% vs. 3.0%), Ear and Labyrinth (3.1% vs. 2.0%), and Cardiac Disorders (2.7% vs. 1.8%). Among patients with type 2 diabetes, Eye Disorders, Immune System, Ear and Labyrinth and Hepatobiliary Disorders met this criterion.

Headache was the most frequent adverse event in non-diabetic patients and among the most frequent in diabetic patients, and was over-represented in the lorcaserin groups as compared to placebo. Preferred terms that were reported by  $\geq 3$  % of patients and with a 50% or greater relative excess in

the lorcaserin arm as compared to placebo in diabetic and non-diabetic patients included fatigue, headache, vertigo, and seasonal allergy. Few adverse event terms were reported by more than 10% of patients; those that were tended to have comparable incidence among placebo and lorcaserin treated patients.

The number of adverse events was 6-9% higher in the lorcaserin treatment groups as compared to placebo for diabetes and non-diabetes patients and there was almost no difference between the two regimens of lorcaserin 10 mg QD and 10 mg BID

The difference between placebo and the Lorcaserin 10 mg BID group in adverse events considered possibly or probably related to the study drug (in the phase 3 pooled data) is more evident for nausea, fatigue, headache and dizziness for the diabetes and non-diabetes patients. The number of hypoglycaemia reported was almost double in the Lorcaserin 10 mg BID group among diabetes patients as compared to placebo (16.4% vs 13.7%), most of the hypoglycaemia events were considered mild or moderate in severity.

### ***Serious adverse events and deaths***

In the studies of non-diabetic patients, the overall frequencies of SAEs were similar in the pooled placebo (2.3% of patients) and pooled lorcaserin BID (2.7% of patients) groups; the rate in the lorcaserin QD group was slightly higher (3.4%). Among patients with type 2 diabetes in the APD356-010 study, SAE frequencies were higher in all treatment groups than in the studies on non-diabetic patients, with 6.8% of patients overall reporting a SAE in the APD356-010 study versus 2.9% in the pooled APD356-009 and APD356-011 studies. However, the rates were similar within the APD356-010 study in the placebo and lorcaserin BID groups.

The analysis of SOC and Preferred Terms reported as SAEs by more than one patient shows no clear lorcaserin-associated trends. Gallbladder related SAEs were somewhat more common overall in the lorcaserin groups relative to placebo, perhaps reflecting the greater weight loss with lorcaserin. Cancers, both individually and collectively, were reported rarely and with similar frequency amongst treatment groups. No individual PT within the psychiatric disorders SOC was reported by more than 1 patient; 1 patient on lorcaserin BID reported "conversion disorder" (verbatim term: psychogenic non-epileptic seizures), and one patient on lorcaserin QD reported an SAE of depression; no placebo patients reported an SAE in this SOC

At the SOC level, cardiac disorders and psychiatric disorders in the pooled lorcaserin groups exceeded the placebo rate by more than 0.1%. No other SOC was over-represented in the lorcaserin group by more than 0.1% of patients.

- SAEs within **cardiac disorders** SOC:

An independent Cardiovascular Clinical Events Committee reviewed all relevant SAEs from studies -009 and -011 in a blinded fashion. The result of the analysis is that the phase 3 data do not indicate that lorcaserin increases the risk of ischemic cardiovascular events. Perhaps most important observation is the lack of excess events among the high risk patients with type 2 diabetes in study APD356-010

- SAEs within **psychiatric disorders** SOC:

Within the psychiatric disorders SOC, no patients assigned to placebo experienced an SAE. However, one intentional drug overdose in the placebo group was coded to the Injury and Poisoning SOC. Seven patients assigned to lorcaserin BID experienced SAEs within the psychiatric disorders SOC. One of the events (Patient 2255-S030, Depression) did not meet the Sponsor's criteria for an SAE, but is included in the tabulation.

SAEs of cardiac and psychiatric disorders that exceeded the placebo rate by more than 0.1% in the pooled lorcaserin groups were further analyzed, the results for cardiac events indicated no clear relation between Lorcaserin and increased risk of ischemic cardiovascular events. In the analysis of psychiatric disorders, there were more cases of depression, psychosis or suicidal ideation on the Lorcaserin group than in placebo, the reported cases were low in numbers (maximum 2 per disorder); from the narratives provided of these cases, the nature of the events differs sufficiently that a common underlying mechanism seems unlikely.

### **Adverse events of Special Importance**

**Valvular Regurgitation:** Similar proportions of adverse events related to echocardiographic findings were reported between the placebo and Lorcaserin group with the exception of aortic valve incompetence that was higher in the placebo group and Pulmonary and Tricuspid valve incompetence that were higher in the Lorcaserin group. The proportion of patients with new echocardiographic FDA-

Defined Valvulopathy at Week 52 for the Lorcaserin 10 mg BID compared to placebo was similar for non-diabetic patients and among the pool of diabetic and non-diabetic, however for diabetic patients that proportion was higher for Lorcaserin BID. The RR of valvulopathy for the Lorcaserin 10 mg BID was 1.16, the applicant justifies this increased risk for the Lorcaserin group in a negative association between change in BMI and the incidence of FDA-defined valvulopathy, suggesting that weight loss per se increases the risk of echocardiographic valvulopathy. The data from clinical studies is not considered to constitute a strong safety signal.

The Applicant has verified that echocardiographic data from the studies 009, 010, and 011 were pooled in all analyses unless specifically noted. The pre-specified analyses included only data from year one. Week 104 data from the study 009 has been presented; the incidence of new valvulopathy being 2.7% (placebo/placebo), 2.6% (lorcaserin/lorcaserin), and 1.9% (lorcaserin/placebo).

**Pulmonary Artery Systolic Pressure:** Lorcaserin does not seem to be related to an increased pulmonary systolic pressure.

**Mood, Cognitive and Perceptual Effects:** Lorcaserin 10 mg BID does not seem to have effects on mood or cognitive function. In line with the non-serious adverse events, dizziness was reported as the most frequent perceptual effect. Nine (9) patients on the Lorcaserin group (BID and QD) reported euphoria that seems to be associated with the beginning of the treatment (day 1 of dosing), it is notable to consider that an euphoric effect can lead to abuse liability, however the number of cases seems low and an abuse liability study was performed to explore this possibility with reassuring results for Lorcaserin.. Cognitive impairment showed a lower rate of AEs in the second year than in year one, reaching placebo levels. For depression, the frequency of AEs did not change over time.

**Neurological adverse events:** The most common adverse events associated with lorcaserin as compared to placebo are headache (approx. 16%) and dizziness (approx. 8%) which mostly were mild to moderate in intensity. The onset of headache and dizziness was early in the studies and only few of the patients discontinued (1%).

The activation of the subtype receptor 5HT2A is associated with parkinsonism, the applicant should provide a detailed breakdown by treatment groups of parkinsonism symptoms (hypokinesia, tremor etc..) that could be related to the activation of 5HT2A.

**Psychiatric disorders:** The incidence of *Narrow Depression SMQ* terms (depression, depression mood, depressive symptom, Major depression, Decreased interest, dysthymic disorder and feeling of despair) were similar for Lorcaerin 10 mg BID and placebo in the non-diabetic and pooled group, whereas higher for the Lorcaserin 10 BID (3.5%) and Lorcaserin QD (5.3%) as compared to placebo (2.4%) for diabetic patients. The discontinuation rate due to Narrow Depression SMQ was higher in the Lorcaserin 10 mg BID for all groups. From those patients who discontinued, a higher proportion was classified as probably related to the study drug in the Lorcaserin BID group (57.1%) compared to placebo (50%), however Narrow SMQ of severe intensity were more frequent in the placebo group 11.1% vs 2.9% in the Lorcaserin BID and events of mild intensity higher in the Lorcaserin BID group as compared to placebo. The incidence of *Broad Depression SMQ* (Disturbance in attention, mood swings, initial insomnia, crying, middle insomnia, memory impairment, affect liability, apathy, etc...) was higher for Lorcaserin 10 mg BID in all the groups (diabetic, non-diabetic and pooled group). The results of the pooled analysis in diabetic and non-diabetic patients showed increase disturbance in attention, initial insomnia and memory impairment (broad SMQ) on the Lorcaserin group that were self limited and rarely led to study withdrawal. Lorcaserin 10 mg BID led more often to study discontinuation for narrow and broad depression SMQ in all groups. Depression events are of concern due to the mechanism of action of Lorcaserin, therefore it is important to look into more detail to serious and non-serious AE of depression and compare them with similar products for obesity:

	Psychiatric disorders (TEAE)	Depression (TEAE)	Major depression	Serious TEAE Depression	% of patients with depression event leading to discontinuation
Lorcaserin/Placebo	11.4%/9.5%	1.9%/1.7%	<0.1%/<0.1% 1/ 1 cases	2/0 cases	0.9%/0.5%
Rimonabant/Placebo	24.9%/13.5%	3.2%/1.6%	0.5%/0.2% 12/4 cases	6/1 cases 0.5%/0.1%	1.9%/0.8%



Depression events were not significantly higher in Lorcaserin group as compared to placebo (1.9% vs 1.7%) and clearly lower than with other similar drugs; however the risk could be underestimated in the clinical trial setting as compared to the general population. On suicidal ideation more patients randomized to Lorcaserin 10 mg BID answered positively to question 9 of suicidal ideation; however adverse events of suicidal behaviour were balanced between placebo and Lorcaserin; considering that SAE for suicidal ideation were higher for Lorcaserin (2 vs 0 cases in Lorcaserin vs placebo). In addition, the incidence of suicide/self-injury SMQ is increased more in females (0.6% vs 0.3% in placebo) than in males (0.8% vs 0.7% in placebo) when subjects are treated with lorcaserin 10 mg BID in the non-diabetic population. Similar events of anxiety were reported in both treatment groups for non-diabetic patients, whereas it was slightly higher for the lorcaserin BID group among diabetic patients. Psychosis symptoms had low incidence across the studies; when divided in Narrow SMQ and Broad SMQ; adverse events of narrow Psychosis (acute psychosis, alcoholic psychosis, hallucination, paranoia) were similar between Lorcaserin BID and placebo (2 cases vs 2 cases in a pool of the 3 studies) whereas for the Broad Psychosis SMQ (Affect liability, apathy, affective disorder, flat affect, speech disorder, etc...) the number of adverse events was higher in the Lorcaserin BID treatment (8 vs 13 cases in placebo vs Lorcaserin BID, respectively), SAE for psychosis were higher for Lorcaserin (2 vs 0 cases in Lorcaserin vs placebo).

**Gallstone disorders:** Among non-diabetic patients, 0.8% assigned to lorcaserin and 0.5% assigned to placebo reported year 1 AEs related to gallbladder; rates were comparable across studies; a possible explanation to the higher incidence in Lorcaserin BID treatment group is the more pronounced weight loss on this group.

**Neoplasms:** In an initial non-clinical study presented to FDA in 2010 there was an increased incidence of adenocarcinoma and fibroadenoma in female rats, those diagnosis have been reclassified by 5 independent pathologists and the results showed that there is no imbalance in adenocarcinoma between placebo and Lorcaserin with a safety margin of 24 times the dose administered in humans and the incidence of fibroadenoma was consistently higher for Lorcaserin across groups with no safety margin. This finding seems to be related to a prolactin hyperstimulation of the mammary gland. Prolactin was not significantly elevated in humans, whereas in rats, spikes of prolactin elevation were observed with the low/mid doses (10/30 mg) and consistently increased with high doses (100 mg) of Lorcaserin. Classified as "Breast Neoplasm SMQ" **7** cases (6 cases at year 1 and 1 case at year 2) were detected in the pooled analysis for Lorcaserin any dose (HR 1.8 (0.28, 5.09)) vs **5** cases (4 cases at year 1 and 1 case at year 2) detected in the placebo group; when classified as "breast cancer or mass" **18** cases were detected in the pooled analysis for Lorcaserin any dose (HR 0.4 (0.15, 1.36)) vs **20** cases detected in the placebo group. . The overall incidence per 100 patient years was lorcaserin vs placebo: 1.1 vs 1.4. The actual number of patients was similar. There is no apparent imbalance in the clinical studies in the incidence of breast cancer or breast masses for Lorcaserin as compared to placebo. Furthermore, unlike in rats, in humans there isn't an increase in prolactin levels, which seems to be involved in the pathology of breast tumours observed in rats. Even though data from the no clinical studies is somehow worrisome, there is no current clinical data to suggest a higher risk in humans but further reassurance is required from non-clinical data.

The Applicant has provided the number of breast cancer, but it doesn't give the exact number of fibroadenomas and adenocarcinomas, these are particularly important because are the two tumours detected in rats with higher incidence on Lorcaserin. The number of both tumours in the clinical studies should be provided and the number of fibroadenomas in the clinical studies should be included in section 4.4.

Cases of astrocytoma were higher for male rats with high doses of Lorcaserin (safety margin of 70); no cases of astrocytoma were reported in the clinical studies.

**Hypoglycaemia:** The incidence of hypoglycaemia is 13% when used as add on to metformin. However, when lorcaserin is combined with SU, with or without metformin, the incidence increases to 48% (vs 34% in placebo).

## ***Laboratory findings***

In general, no lorcaserin-related trends were observed in mean clinical chemistry laboratory values, shift analyses, or laboratory-related AEs.

No major indicators of drug induced liver disease (DILI) were observed; no excess incidence of 3-fold or greater elevations above the ULN of ALT and AST occurred in patients treated with lorcaserin as compared to placebo; no subjects experienced aminotransferase elevations 3-fold or greater above

the ULN, accompanied by total bilirubin elevations of 1.5-fold or greater. Total bilirubin elevations of 2-fold or greater above the ULN were rare, and there was no excess incidence for lorcaserin compared to placebo.

Lorcaserin did not increase the number of shifts from normal to low in creatinine clearance as compared to placebo. Because the creatinine clearance calculation using actual body weight overestimated creatinine clearance, it is also appropriate to examine shifts from high to normal or low using the actual body weight data. These shifts were slightly more frequent in the lorcaserin groups as compared to placebo, but are more likely to reflect weight loss than actual changes in glomerular filtration rate.

In study -010, the incidence of plasma glucose values <55 mg/dL was low: 1 (0.4%) patient on placebo, 1 (1.1%) on lorcaserin QD and 4 (1.7%) on lorcaserin BID. Markedly elevated fasting plasma glucose was also infrequent: 8 (3.3%) patients on placebo, 2 (2.2%) on lorcaserin QD and 7 (2.9%) on lorcaserin BID had values >250 mg/dL.

The overall rates of haematology adverse events were low in all treatment groups in phase 3 studies of non-diabetic patients, with no preferred term reported by more than 0.3% of any treatment group. "Haemoglobin decreased", "hematocrit decreased" and "white blood cell count decreased" were reported by 9, 6, and 6 patients in the lorcaserin BID group as compared to 5, 2 and 2 in the placebo group. Each term was reported by a single patient in the lorcaserin QD group, making a drug relationship less likely.

Prolactin levels had a small decrease in the placebo group from pre and post-dose and a small increase in the Lorcaserin group, but none of them were above the upper limit of normal levels.

### ***Vital signs***

In phase 3 studies mean systolic and diastolic BP decreased slightly in all treatment groups from baseline to Week 52, with a slightly greater decrease from baseline in the lorcaserin 10 mg BID group compared to lorcaserin 10 mg QD and placebo.

Heart rate decreased slightly in patients assigned to lorcaserin 10 mg BID, but not in those assigned to lorcaserin 10 mg QD, as compared to placebo in phase 3 studies APD356-009 and -011. Although the heart rate varied from week to week, the lorcaserin 10 mg BID group was consistently lower as compared to placebo. It is important to remember that the lorcaserin 10 mg QD dose was primarily studied only in study APD356-011; the -009 study did not include this dose, and only 95 patients were randomized to this dose in study APD356-010. It is for general comparison only, and is more appropriately compared to the APD356-011 placebo group rather than the pooled placebo group. In study APD356-010, heart rate decreased slightly from baseline at Week 52 in both lorcaserin groups, but not in placebo.

### ***Safety in special populations***

#### Age

The two age subgroups, > 44 years (median age) or < 44 years reported adverse events with similar frequencies. In the phase 3 studies, subjects older than 65 were not eligible to be enrolled in phase 3 studies. There is no increased frequency in the AEs in an additional analysis submitted by the Applicant for elderly patients, with the exception of dizziness. This AE shows a decisive difference in frequency for placebo groups (3.8%) in reference to treatment groups (8.5% for 10 mg BID, 6.2% for 10 mg QD, and 8.1% for all doses).

#### Gender

In women the adverse events dizziness, headache and nausea tended to occur more frequently in than in men in subjects taking lorcaserin. However, more importantly, the incidence of suicide/self-injury SMQ is increased more in females (0.6% vs 0.3% in placebo) than in males (0.8% vs 0.7% in placebo) when subjects are treated with lorcaserin 10 mg BID in the non-diabetic population. Although the incidence of suicide/self-injury SMQ are higher in females than in males in the non-diabetic population, the severity appears to be low and similar between the groups. The rate of actual suicide attempt is very low and similar between the lorcaserin and placebo groups.

#### Baseline BMI categories

The starting body weight seemed to affect lorcaserin related adverse events more than did BMI, although no large differences were noted.

#### Race

Overall no large differences were seen between Caucasian, African American or Hispanic/Latino. However, very few Asian patients were included in the studies.

#### Renal function

A limited number of patients in the phase III studies had renal impairment. While the frequency of adverse events in general increases with the level of renal impairment, this is similar between the lorcaserin BID and placebo groups and no particular adverse event appears to be associated with lorcaserin and renal impairment. However, since only a very limited number of patients had moderate renal impairment, it is difficult to draw any conclusions concerning safety in this patient group.

#### Hepatic function

A limited number of patients in the phase III studies had hepatic impairment. Separate safety data for these patients were not presented. The applicant was asked to present safety data stratified for moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively. The Applicant states that the data are lacking in order to stratify these groups (Child-Pugh class B or C hepatic impairment).

#### Pregnant women

Pregnancies reported by study subjects (30 pregnancies/lorcaserin 10 mg BID; 24 pregnancies/placebo) or by female partners (4 pregnancies/lorcaserin 10 mg BID; 1 pregnancies/placebo) of male study participants were recorded and their outcomes evaluated when possible. No trends are seen.

### ***Drug abuse***

In the human abuse potential study (APD356-013) compared to zolpidem or ketamine, lorcaserin was associated with only modest sedative and minimal perceptual effects. Based on the overall pattern of responding on the subjective measures evaluated in the human abuse potential study, lorcaserin at supratherapeutic doses is disliked and does not have reinforcing effects across the range of doses tested nor is it associated with notable perceptual or dissociative effects. However, the risk of drug abuse cannot be overseen. It is acknowledged that the higher euphoric effect for Lorcaserin in phase 3 trials at the beginning of the treatment (Day 1) was mild and low in numbers.

### ***Safety related to drug-drug interactions and other interactions***

Preclinical metabolism experiments showed lorcaserin to be a weak inhibitor of CYP2D6 *in vitro*. Lorcaserin exerted no significant effects to inhibit or induce any other CYP enzyme, and was neither a substrate nor an inhibitor of P-gp. Moreover, lorcaserin is metabolized by multiple hepatic enzymes. Based on these results, formal drug-drug interaction clinical studies were restricted to an evaluation of the effect of lorcaserin on the metabolism of the CYP2D6 substrate dextromethorphan. Lorcaserin at a dose of 10 mg BID increased dextromethorphan exposure approximately 2-fold, suggesting that it is a minimal to moderate inhibitor of CYP2D6 in man. Based on the relatively small changes in dextromethorphan exposure relative to the changes that result from genetic polymorphisms in CYP2D6, the level of CYP2D6 is not thought to represent a significant safety issue. Although use of SSRI/SNRI and other serotonergic agents was prohibited by protocol due to theoretical risk of serotonin syndrome, some patients reported use of such agents during phase 3 studies. No patient experienced serotonin syndrome.

### ***Discontinuation due to AES***

The overall rate of discontinuation in the lorcaserin group is relatively low and mostly concerned nervous system, psychiatric and gastrointestinal AEs. Given that 14-17% of the lorcaserin treated patients experiences headache only a few patients (1%) withdrew from the studies for this reason. However, only approximately 45-59% of the subjects enrolled in the Phase 3 studies completed the treatment (up to 52 weeks). The applicant has performed a thorough investigation of withdrawals for "Other" reason. Although there are some differences between studies, this investigation does not reveal any systematic differences between treatment groups within study that might have biased the results.

In pooled phase 3 studies of non-diabetic patients, 8.4% of patients assigned to lorcaserin and 6.8% of patients assigned to placebo withdrew due to an adverse event. The types of adverse events leading to

withdrawal were similar in the 2 treatment groups. Only headache caused >1% of patients in any group to discontinue; nausea or dizziness were linked to study withdrawal by 0.7% of patients in the lorcaserin BID group. Few adverse events prompted discontinuation of more than 1 patient in study APD356-010 (patients with type 2 diabetes). Withdrawals due to depression were slightly more frequent in the lorcaserin group, as compared to placebo, although this was not dose-related. The events of depression did not typically differ in incidence or severity among the treatment groups; the reason for disparate drop-out rates is not known.

Among non-diabetic patients in studies APD356-009 and -011, withdrawals due to AEs were slightly more frequent in the lorcaserin BID group (8.6% of patients) than the lorcaserin QD (7.5% of patients) and placebo groups (6.8% of patients).

Overall, discontinuation rates due to AEs were low, and differences between active and placebo groups were small but it is relevant that discontinuation rates in pooled studies -011 and -009 for depression, depressed mood or suicidal ideation were almost double in the Lorcaserin 10 mg BID as compared to placebo (0.5% vs 0.9%), (0.1% vs 0.2%) and (0.1 vs 0.2%). The reason for a higher rate of discontinuation in the lorcaserin group for depression, depressed mood or suicidal ideation doesn't seem to be apparent but neither related to severity of the events, and the overall event rates were similar for these terms.

## Discussion on clinical safety

Overall, 3451 patients have been exposed to lorcaserin 10 mg BID daily out of which 2034 have been exposed for at least 52 weeks. A total of 437 patients were exposed for at least 83 weeks.. In the phase 3 studies ¾ of the patients were female, there was no representation of patients >65 years old and the main races represented were Caucasian, Black and Hispanic.

The number of adverse events was 6-9% higher in the lorcaserin treatment groups as compared to placebo for diabetes and non-diabetes patients and there was almost no difference between the two regimens of lorcaserin 10 mg QD and 10 mg BID. The difference between placebo and the Lorcaserin 10 mg BID group in adverse events considered possibly or probably related to the study drug (in the phase 3 pooled data) is more evident for nausea, fatigue, headache and dizziness for the diabetes and non-diabetes patients. The number of hypoglycaemia reported was almost double in the Lorcaserin 10 mg BID group among diabetes patients as compared to placebo (16.4% vs 13.7%), most of the hypoglycaemia events were considered mild or moderate in severity.

The overall frequency of SAEs for non-diabetic patients (pooled group from studies -011 and -09), was similar between Lorcaserin BID and placebo (2.7% vs 2.3%), for the lorcaserin QD group the rate of SAEs was slightly higher (3.4%). Among patients with type 2 diabetes in the APD356-010 study, SAE frequencies were higher in all treatment groups than in the studies on non-diabetic patients, with 6.8% of patients overall reporting a SAE in the APD356-010 study versus 2.9% in the pooled APD356-009 and APD356-011 studies. However, the rates were similar within the APD356-010 study in the placebo and lorcaserin BID groups. SAEs of cardiac and psychiatric disorders that exceeded the placebo rate by more than 0.1% in the pooled lorcaserin groups were further analyzed, the results for cardiac events indicated no clear relation between Lorcaserin and increased risk of ischemic cardiovascular events. In the analysis of psychiatric disorders, there were more cases of depression, psychosis or suicidal ideation on the Lorcaserin group than in placebo, the reported cases were low in numbers maximum 2 per disorder; from the narratives provided of these cases, the nature of the events differs sufficiently that a common underlying mechanism seems unlikely.

Discontinuation rates due to adverse events were low in general but it is of relevance that discontinuation rates for depression, depressed mood or suicidal ideation were almost double in the Lorcaserin 10 mg BID as compared to placebo (0.9 vs 0.5%), (0.2% vs 0.1%) and (0.2 vs 0.1%), respectively; The reason for a higher rate of discontinuation in the lorcaserin group for depression, depressed mood or suicidal ideation doesn't seem to be apparent but neither related to severity of the events, and the overall event rates were similar for these terms.

Further **adverse events of special importance** were analysed. For valvular regurgitation the proportion of patients with new echocardiographic FDA-Defined valvulopathy at Week 52 for the Lorcaserin 10 mg BID compared to placebo was similar for non-diabetic patients and among the pool of diabetic and non-diabetic, however for diabetic patients that proportion was higher for Lorcaserin BID.

There was a numerical imbalance concerning incidence of valvulopathy in the phase 3 studies, albeit not statistically significant. The Applicant has investigated the overall pattern of change in valvulopathy status with time. In both placebo and Lorcaserin groups, the pattern was similar with 0.8-0.96% of patients being negative at baseline developing FDA-defined valvulopathy. Likewise, 21-29% of

patients being positive at baseline were negative at week 52. Thus, there is not much support of a serious safety signal with respect to valvulopathy in the available data. The Applicant argues that the imbalance is due to a larger weight loss in Lorcaserin groups compared to placebo. However, considering a theoretical risk due to at least some affinity for 5-HT<sub>2B</sub> receptors, further reassurance on the overall benefit risk balance is requested.

Lorcaserin does not seem to be related to an increased pulmonary systolic pressure or with significant effects in mood or cognitive function. Dizziness was reported as the most frequent perceptual effect in line with the non-serious adverse events, nine (9) patients on the Lorcaserin group (BID and QD) reported euphoria that seems to be associated with the beginning of the treatment (day 1 of dosing), it is notable to consider that an euphoric effect can lead to abuse liability, however the number of cases seems low and an abuse liability study was performed to explore this possibility with reassuring results for Lorcaserin.

Depression events were not significantly higher in Lorcaserin group as compared to placebo (1.9% vs 1.7%) and clearly lower than with other similar drugs; however the risk could be underestimated in the clinical trial setting as compared to the general population. In relation to psychosis and suicidal ideation, the risk could be also underestimated and considering that SEA of psychosis and suicidal ideation were higher for Lorcaserin (2 vs 0 cases in Lorcaserin vs placebo for both AE).

Gallstone disorders were slightly higher in the Lorcaserin treatment for diabetic and non-diabetic patients, a possible explanation is the more pronounced weight loss in Lorcaserin BID.

Prolactin levels had a small decrease in the placebo group from pre and post-dose and a small increase in the Lorcaserin group, but none of them were above the upper limit of normal levels.

In an initial non-clinical study (which was presented to FDA in 2010), there was an increased incidence of adenocarcinoma and fibroadenoma in female rats; those diagnosis have been reclassified by 5 independent pathologists and the results showed that there is no imbalance in adenocarcinoma between placebo and Lorcaserin with a safety margin of 24 times the dose administered in humans and for fibroadenoma the increase in incidence was consistently higher for Lorcaserin across groups with no safety margin. This finding seems to be related to a prolactin hyperstimulation of the mammary gland. Prolactin was not significantly elevated in humans, whereas in rats, spikes of prolactin elevation were observed with the low/mid doses (10/30 mg) and consistently increased with high doses (100 mg) of Lorcaserin. Classified as "Breast Neoplasm SMQ" **7** cases (6 cases at year 1 and 1 case at year 2) were detected in the pooled analysis for Lorcaserin any dose (HR 1.8 (0.28, 5.09)) vs **5** cases (4 cases at year 1 and 1 case at year 2) detected in the placebo group; when classified as "breast cancer or mass" **18** cases were detected in the pooled analysis for Lorcaserin any dose (HR 0.4 (0.15, 1.36)) vs **20** cases detected in the placebo group. The overall incidence per 100 patient years was lorcaserin vs placebo: 1.1 vs 1.4. The actual number of patients was similar. There is no apparent imbalance in the clinical studies in the incidence of breast cancer or breast masses for Lorcaserin as compared to placebo. Furthermore, unlike in rats, in humans there isn't an increase in prolactin levels, which seems to be involved in the pathology of breast tumours observed in rats. Even though data from the non-clinical studies is somehow worrisome, there is no current clinical data to suggest a higher risk in humans but further reassurance should be provided from non-clinical data.

The Applicant has provided the number of breast cancer, but it doesn't give the exact number of fibroadenomas and adenocarcinomas, these are particularly important because are the two tumours detected in rats with higher incidence on Lorcaserin. The number of both tumours in the clinical studies should be provided.

Cases of astrocytoma were higher for male rats with high doses of Lorcaserin (safety margin of 70); no cases of astrocytoma were reported in the clinical studies.

**Hypoglycaemia:** The incidence of hypoglycaemia is 13% when used as add on to metformin. However, when lorcaserin is combined with SU, with or without metformin, the incidence increases to 48% (vs 34% in placebo). A warning has been added in section 4.4. Patients treated with exogenous insulin are not expected to respond differently to those treated with sulphonylureas, which act releasing endogenous insulin.

From the laboratory results of phase 3 studies, liver function does not seem to be altered by Lorcaserin and there is no evidence that Lorcaserin impaired renal function. No clinically significant effects of Lorcaserin on the haematological parameters detected.

Modest blood pressure lowering effect and a small decrease in heart rate seems to be associated to Lorcaserin 10 mg BID as compared to placebo. The results of study -007 indicate that Lorcaserin has no clinically relevant influence on human cardiac repolarisation.

## Conclusions on clinical safety

The data from clinical studies is not considered to constitute a strong safety signal for the valvulopathy risk. However, considering a theoretical risk due to at least some affinity for 5-HT<sub>2B</sub> receptors, further reassurance on the overall benefit risk balance is still required. There is no apparent imbalance in the clinical studies in the incidence of breast cancer or breast masses for Lorcaserin as compared to placebo. Furthermore, unlike in rats, in humans there isn't an increase in prolactin levels, which seems to be involved in the pathology of breast tumours observed in rats. Even though data from the no clinical studies is somehow worrisome, there is no current clinical data to suggest a higher risk in humans but further reassurance should be provided from non-clinical data.

**ORPHAN MEDICINAL PRODUCTS**

N/A

## 4. BENEFIT RISK ASSESSMENT

### 4.1. Benefits

#### Beneficial effects

Non-pharmacological treatment options (nutritional education, behaviour modification and increased activity and exercise) should always be first-line therapy for subjects with overweight/obesity. However, compliance to these treatment options is sometimes disappointing, and in such situations pharmacological treatment may be of value as an adjunct to dietary measures and physical exercise.

Relevant decreases in certain risk factors associated with obesity have been seen with loss of at least 5 to 10% of initial weight, and thus these parameters are considered as relevant endpoints.

In the current application, the Applicant presents the results from three phase 3 studies and three phase 2 studies to support the efficacy associated with Lorcaserin. The duration of the studies was 104 and 52 weeks. Patients with weight-related co-morbidities were studied and one of the phase III studies was exclusively in patients with type two diabetes.

Mean percentage weight loss from baseline for non diabetic/diabetic patients was approximately 5.8/4.8% compared to 2.5/1.8% weight loss in placebo groups. Approximately 47/37.5% reached at least 5% weight loss (22.6/16.1% in the placebo groups), and 22.4/16.3% reached 10% weight loss (8.7/4.4% for placebo). Weight reduction was similar independent on BMI, fasting plasma glucose and baseline HbA1c. Weight reduction was markedly greater in older patients and slightly greater in female patients and Caucasians.

Sensitivity analysis were requested at day 120, the proportions were lower, but the difference compared to placebo was still statistically significant and more than 5% greater compared to placebo after applying the sensitivity analysis\*. The proportion of patients achieving 10% weight loss (18 to 22% depending on analysis and population) is not impressive; however the size of the benefit improves considerably if the treatment is restricted to patients who reach 5% weight reduction by week 12. If this criteria is not met, patients will discontinue the drug as they are unlikely to reach and sustain a clinically meaningful weight loss; with this new restriction, the size of the benefit seen on the initial analysis is improved; however it is still considered that the efficacy results are too modest to outweigh the safety concerns and the overall benefit risk balance should be further discussed.

The corresponding results in the main studies for rimonabant and orlistat were approx. 50 and 45% reaching 5 % weight loss respectively, while approx. 25 and 20%, respectively, reached 10% weight loss.

	Approx. proportion of subjects with 5% weight loss after 1 year treatment	Approx. proportion of subjects with 10% weight loss after 1 year treatment
Rimonabant	50 %	25 %
Orlistat	45 %	20 %
<b>Lorcaserin</b>	<b>47.1% (37.5% *)</b>	<b>22.4% (19.3% *)</b>

\*Results of the sensitivity analysis (Refer to table 17 and 18 of the Day 180 Clinical Joint AR)

There are no indications of a detrimental effect of Lorcaserin on cardiovascular risk factors, but rather a beneficial effect on blood pressure, glucose, lipids and placebo-corrected reduction in HbA1c of approximately 0.5% in diabetic patients.

#### Uncertainty in the knowledge about the beneficial effects

According to the Guideline on clinical evaluation of medicinal products used in weight control, patients enrolled in obesity trials should be subject to an appropriate weight reducing diet run-in period for a specified minimum time, however none of the trials included a run in period. The reason for a run-in period is to see the effect a dedicated diet and exercise programme can achieve and then evaluate the effect pharmacological treatment can have on top of this programme. Patients who had lost more than 5% of body weight in the last three months were excluded from taking part in the Applicant's clinical studies. The Applicant considers these subjects to be confounders as it is claimed that subjects with recent weight loss are in a state of negative energy balance and may have already achieved a plateau from the previous weight loss efforts. This needs further discussion. Diet and exercise should be able



to reduce weight in the short-term in the majority of people. It is how pharmacological therapies can add to this weight loss that needs to be investigated. The Applicant has chosen to avoid this patient group and instead concentrates on subjects who have not lost weight recently.

## 4.2. Risks

### Unfavourable effects

**Non-clinical:** Several tumour types in rats (mammary gland fibroma / carcinoma, schwannoma, astrocytoma, squamous cell carcinoma) raise serious concern for human use as no convincing mechanistic explanations or sufficient exposure margins to clinical exposure have been established.

**Clinical:** The most common short-term safety issue is headache (14-17%) in the entire study population. In the diabetic subjects the incidence of hypoglycaemia is 13% when used as add on to metformin. However, when lorcaserin is combined with SU, with or without metformin, the incidence increases to 48% (vs 34% in placebo).

With the exception of dizziness, adverse events related to perceptual and mood changes are uncommon or rare at the intended daily dose of 10 mg BID. In non-diabetic patients, disturbances in attention (0.6% vs 0.3% in placebo), memory impairment (0.7% vs 0.2% in placebo) and amnesia (0.5% vs 0.1% in placebo), "euphoric mood" (0.2% vs <0.1% in placebo), "paraesthesia" (1.2% vs 0.5% in placebo), "abnormal dreams" (0.5% vs 0.2% in placebo) and "confusional state" (0.2% vs <0.1% in placebo) are associated with lorcaserin treatment. In the much smaller diabetic patient population, "paraesthesia" (1.6% vs 0.8% in placebo) and "hypoaesthesia" (1.6% vs 0.8% in placebo) are related to lorcaserin treatment.

SAE were higher in study -10 (6.8%) as compared with the pooled on non-diabetic patients study -009 and -011 (2.9%) but similar between treatment groups for diabetic and non-diabetic patients. Classified as SAE, there were two cases of depression in lorcaserin vs none in the placebo group and there was 1 case of suicidal ideation and 1 case of suicidal attempt in Lorcaserin group vs 1 case of intentional overdose in the placebo group. The nature of the events differ sufficiently that a common underlying mechanism seems unlikely.

There was an increase of disturbance in attention, initial insomnia and memory impairment in the Lorcaserin group for pooled diabetic and non-diabetic patients that were self-limited and rarely led to study withdrawal.

### Uncertainty in the knowledge about the unfavourable effects

**Non-clinical:** Whilst functional assays based on lorcaserin-induced IP release indicate that lorcaserin selectivity for the 5-HT<sub>2C</sub> receptor is approximately 14-fold and 61-fold relative to the 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors, respectively, if a different second messenger in the activation cascade is measured, this margin can be substantially reduced. Potential secondary pharmacology class effects could be expected due to the 5-HT<sub>2C</sub> agonistic nature of lorcaserin, and also due to the action although to a lesser extent on other 5-HT receptors.

Lorcaserin interacts with the 5-HT<sub>2B</sub> receptors to some extent. The 5-HT<sub>2B</sub> receptor activation is involved in the development of **cardiac valvulopathy** which is characterized by thickening and insufficiency of the left-sided heart valves. Adverse events potentially related to 5-HT<sub>2B</sub> activation, heart valve dysfunction, were therefore extensively evaluated in the clinical program. There was no signal in the non-clinical program. In the clinical program, the RR of valvulopathy for the Lorcaserin 10 mg BID is 1.16, the applicant justifies this increased risk for the Lorcaserin group in a negative association between change in BMI and the incidence of FDA-defined valvulopathy, suggesting that weight loss per se increases the risk of echocardiographic valvulopathy. There was a numerical imbalance concerning incidence of valvulopathy in the phase 3 studies, albeit not statistically significant. The Applicant has investigated the overall pattern of change in valvulopathy status with time. In both placebo and Lorcaserin groups, the pattern was similar with 0.8-0.96 % of patients being negative at baseline developing FDA-defined valvulopathy. Likewise, 21-29 % of patients being positive at baseline were negative at week 52. Thus, there is not much support of a serious safety signal with respect to valvulopathy in the available data. The Applicant argues that the imbalance is due to a larger weight loss in Lorcaserin groups compared to placebo. The data from clinical studies is not considered to constitute a strong safety signal. However, considering a theoretical risk due to at

least some affinity for 5-HT<sub>2B</sub> receptors, further reassurance on the overall benefit risk balance is still required..

Depression events were not significantly higher in the Lorcaserin group as compared to placebo (1.9% vs 1.7%) and clearly lower than with other similar drugs; however the risk could be underestimated in the clinical trial setting as compared to the general population. Due to the lack of selectivity of Lorcaserin for 5HT receptors, the potential to cause **psychiatric disorders** is of concern and should be discussed as part of the overall benefit risk assessment.

There is a mechanistic rationale to suspect that lorcaserin would increase the risk of **serotonin syndrome/toxicity**. Serotonin syndrome is a constellation of symptoms that is thought to result from overstimulation of the 5-HT<sub>1A</sub> receptor however the 5HT<sub>2A</sub> receptor may also contribute, and is characterized by cognitive/behavioural, autonomic and neuromuscular symptoms. Within the neuroleptic malignant syndrome, narrow SMQ, a single case of "serotonin syndrome" was reported during the clinical development of lorcaserin. A higher incidence of "*serotonin syndrome related symptoms*" occurred in the lorcaserin groups when compared to placebo (1.8% vs 0.6% in placebo) in a non-diabetic population using relatively few concomitant medications. A meta-analysis of the lorcaserin phase 3 studies showed a statistically significant higher relative risk for "serotonin syndrome related symptoms" of 2.97 versus placebo (95% confidence interval 1.75-5.06; p-value <0.001). The upper confidence interval is 5.06 indicating a substantial increased risk in a patient population where medications, such as SSRIs, were excluded in the phase 3 studies.

It should be emphasised that in non-clinical **carcinogenicity** studies, lorcaserin is associated with different tumour types. Increases in the incidence of the following tumours were observed; mammary adenocarcinoma (female rats), benign mammary fibroadenoma (female rats), astrocytoma (male rats), benign fibromas of the subcutis (male rats), malignant schwannomas (male rats). The mechanisms behind these tumours have not been clarified and sufficient exposure margins to clinical exposure have not been established. A relevance to humans cannot be excluded. No imbalance in tumour events has been identified in the clinical trials although the two years duration of the longest study might not be long enough to evaluate the higher incidence of tumour events detected in rats.

## Balance

### Importance of favourable and unfavourable effects

Considering that several obese patients do not respond to life style interventions as the only treatment and that obesity is considered as a risk factor for cardiovascular disease, the results showed beneficial effects of Lorcaserin with respect to weight reduction. However, the magnitude of the weight lowering effect is modest and the duration of the effect is unknown. The treatment does not seem to be associated with a detrimental effect on other cardiovascular risk factors, but rather beneficial effects in blood pressure, heart rate, lipids and HbA1c reduction in DM patients. There are uncertainties concerning the duration of the effect. However, also short term effects (e.g. for a year) are expected to be of clinical relevance with respect to beneficial effects on orthopaedic conditions, sleep apnea etc, especially in very obese patients.

There is anticipated increased risk of **serotonin syndrome/toxicity** when taken concomitantly with SSRIs. This may be a serious concern in clinical practice considering that use of such products probably is not uncommon in the target population.

In non-clinical **carcinogenicity** studies, lorcaserin is associated with different tumour types. Increases in the incidence of the following tumours were observed; mammary adenocarcinoma (female rats), benign mammary fibroadenoma (female rats), astrocytoma (male rats), benign fibromas of the subcutis (male rats), malignant schwannomas (male rats). The mechanisms behind these tumours have not been clarified and sufficient exposure margins to clinical exposure have not been established, therefore it is difficult to assess the relevance in humans. No imbalance in tumour events has been identified in the clinical trials although the two years duration of the longest study might not be long enough to evaluate the higher incidence of tumour events detected in rats.

Lorcaserin interacts with the 5-HT<sub>2B</sub> receptors to some extent, and therefore there may be a theoretical risk of **valvulopathy**. The negative association between BMI and the incidence of valvulopathy may be a possible explanation for the unfavourable numerical imbalance for Lorcaserin in the clinical studies.

Due to the lack of selectivity of Lorcaserin for 5HT receptors, the potential to cause **psychiatric disorders** is of concern.

The efficacy results seem too modest to outweigh the current safety concerns on valvulopathy, psychiatric disorders and the clinical relevance of the non-clinical findings in carcinogenicity. The applicant should provide further discussion on the overall benefit risk assessment.

### **4.3. Benefit-risk balance**

Even though there is no current imbalance of tumours in patients treated over 2 years, the carcinogenicity results on the non-clinical studies are worrisome and the risk to translate into the clinical setting does exceed the modest efficacy results. Furthermore, it is considered that the modest efficacy results do not outweigh the concerns over safety, in particular concerns over psychiatric events and valvulopathy.

### **4.4 Conclusions**

The overall B/R of Lorcaserin is currently negative.