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LORCASERIN FOR THE TREATMENT OF OBESITY

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SUMMARY

Obesity is a worldwide epidemic and there is an urgent need for the development of effective pharmacological therapies that target the metabolic and behavioral factors of body weight regulation. Serotonin (5-HT) has been implicated as a critical factor in the short-term (meal-by-meal) regulation of food intake and pharmaceutical companies have invested millions of dollars to discover and develop drug targets for the serotonergic pathway. Lorcaserin is a novel selective agonist of the 5-HT_{2C} receptor for weight loss therapy. Preclinical and clinical studies indicate lorcaserin is well tolerated and not associated with cardiac valvulopathy or pulmonary hypertension, suggesting that lorcaserin is a selective 5-HT_{2C} receptor agonist and has little or no activation of the 5-HT_{2B} and 5-HT_{2A} receptors, respectively. Lorcaserin acts to alter energy balance through a reduction in energy intake and without an increase in energy expenditure and achieved the U.S. Food and Drug Administration guidelines for weight loss efficacy. It remains to be determined whether or not lorcaserin will be approved for the long-term management of obesity.

INTRODUCTION

Obesity is a worldwide epidemic. Body weight in the U.S. has increased dramatically since 1980. In epidemiological studies the body mass index (BMI) calculated as weight in kilograms divided by height in meters squared is used to classify body weight. Body weight is considered to be healthy when the BMI is 18.5–24.9 kg/m². An individual is classified overweight with a BMI of 25–29.9 kg/m² and obese with a BMI > 30 kg/m². The National Health and Nutrition Examination Survey (NHANES) has been collating data for BMI in the U.S. since 1960. The first report (NHANES I) found that 44.9% of adults aged 20–74 years were overweight or obese (1). Data from the last available report (NHANES 2007–2008) indicate a dramatic increase in the prevalence rates of overweight and obesity in adults. Now a staggering 68% of adults aged 20–74 years were overweight or obese (2). The prevalence of obesity appears to be continually rising in men while the prevalence rates for women may have leveled off (2). Nevertheless, the prevalence of obesity exceeds 30% in most age groups for men and women (2).

The secular rise in overweight and obesity can be explained mostly by changes in social and environmental cues (the drivers) and modulated by physiological and behavioral factors (the modulators). However, ultimately the balance between energy intake (calories consumed)

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DISCLOSURES

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and energy expenditure (calories burned) determines body energy stores. The obvious culprit for the increase in body fat is excess food intake relative to decreased energy expenditure, which can be attributed to an abundance of calorically dense food in a sedentary environment (3). For many years scientists and clinicians have tested many different diets and physical activity regimens aimed to reduce body weight in the hope of reversing the obesity trend; however, success with these methods does not appear to be on the horizon and obesity-related health costs are dramatically increasing and estimated to have reached USD 147 million, 10% of all medical-related spending (4). There is, therefore, an urgent need for the development of effective pharmacological therapies that target the metabolic and behavioral factors of body weight regulation. In absence of a reversal of our obesogenic environment, it is foreseeable that to reverse the obesity epidemic, a multifaceted approach needs to be adopted where pharmacotherapy targets for modifying both food intake and energy metabolism are combined with traditional weight management programs.

SEROTONIN AND 5-HT RECEPTORS

Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter that exerts its physiological effects through at least 14 subtypes of the serotonin receptor family. Serotonin has been implicated as a critical factor in the short-term (meal-by-meal) regulation of food intake through its effects on satiety (5). Therefore, millions of dollars have been invested to discover and develop drug targets for the serotonergic pathway. The development of the 5-HT_{2C} receptor knockout mouse in the mid-1990s was a hallmark achievement in the identification and development of serotonergic drugs for weight loss (6). Tecott and colleagues observed that mice lacking 5-HT_{2C} receptors developed late-onset obesity coupled with other comorbidities when fed a high-fat diet (6). The fact that the 5-HT_{2C} knockout mice failed to fully respond to the anorectic actions (decreased food intake and weight loss) of 5-HT_{2C} agonists provided a strong validation of the 5-HT_{2C} receptor as a target for the regulation of food intake and body weight.

The 5-HT_{2C} receptor belongs to the 5-HT₂ receptor subfamily which also includes the receptors 5-HT_{2A} and 5-HT_{2B}. These three receptors share more than 80% sequence homology within the transmembrane domains (7), therefore providing a major challenge for the development of 5-HT_{2C} agonists with high selectivity over 5-HT_{2A} and 5-HT_{2B} receptor subtypes.

Human 5-HT_{2C} receptors are primarily located in the CNS with significant expression in the choroid plexus, prefrontal cortex, hippocampus and basal ganglia (7). The 5-HT_{2A} receptors are also located in the CNS, mainly in the cortex and hypothalamus and are targets for several psychiatric agents. Activation of 5-HT_{2A} receptors leads to CNS-related side effects such as changes in perception and hallucinations. 5-HT_{2B} receptors are located on cardiac vessels and cardiac valves (8, 9) and activation of these receptors is believed to result in heart valvulopathy and pulmonary hypertension (10).

Activation of 5-HT_{2C} receptors by serotonin (in response to food intake) or 5-HT_{2C} receptor agonists modulates firing of pro-opiomelanocortin neurons (POMC) in the arcuate nucleus of the hypothalamus. Anorectic POMC neurons expressing 5-HT_{2C} receptors depolarize when activated and release α -melanocyte-stimulating hormone (α -MSH) leading to downstream activation of melanocortin 4 receptors in the paraventricular hypothalamus. These anorectic signals in the CNS promote satiety and decrease food intake (11, 12).

SEROTONERGIC DRUGS FOR WEIGHT MANAGEMENT

Over the past 40 years, several serotonergic drugs have been developed for weight loss. It has been through the successes and failures of these compounds that the serotonergic receptors responsible for regulation of satiety and food intake were identified and more sophisticated compounds with greater selectivity for the 5-HT_{2C} receptor are being developed and tested in preclinical and clinical trials (13). Currently orlistat (Xenical®) is the only drug approved by the U.S. FDA for weight loss. Until October 2010, the list of approved agents also included sibutramine (Meridia®), a serotonergic drug; however, given its association with cardiovascular events and stroke, sibutramine was withdrawn from the market. Phentermine, an adrenergic reuptake inhibitor is also approved but only for short-term use. In the mid-1990s this list also included fenfluramine and dexfenfluramine; however, given increasing safety concerns both compounds were withdrawn from the market in 1997. Other tested serotonergic compounds showing efficacy for weight loss include fluoxetine and m-chlorophenylpiperazine (mCPP).

Sibutramine

Sibutramine is a serotonergic, noradrenaline and dopamine reuptake inhibitor, enhancing serotonergic, adrenergic and dopaminergic signaling in the brain (14). Initially developed to treat depression, sibutramine was first demonstrated to stimulate thermogenesis (15, 16) and later convincing evidence suggested that sibutramine exerted a more profound effect on reducing food intake and appetite (17, 18). Treatment with sibutramine at the normal dose (10–15 mg/day) produces a weight loss of 5–8% over 1 year in comparison to 2–4% with placebo (19, 20). Sibutramine was approved for short-term (12 months) use by the U.S. FDA in 1997. However, due to the transient increases in heart rate and blood pressure associated with ongoing administration (21) and the increased incidence of cardiovascular events and stroke (22), the drug was withdrawn from the market in the U.S., the E.U. and Japan in October 2010.

Fenfluramine and dexfenfluramine

Fenfluramine was developed in the 1960s and was released on the U.S. market as an antiobesity agent in 1973 (23). Fenfluramine and its biologically active enantiomer, dexfenfluramine, are monoamine secretagogues. These drugs act to cause reversal and blockade of the serotonin transporter, thereby increasing the availability of serotonin at serotonergic synapses. Extensive pharmacological studies and genetic studies using the 5-HT_{2C} knockout mice demonstrated that the anorectic action of fenfluramine and dexfenfluramine occurs via interaction with the 5-HT_{2C} (24, 25) and 5-HT_{1B} (26) receptors. Furthermore, the major metabolite of fenfluramine, norfenfluramine, is a 5-HT_{2C} receptor agonist (27). With regard to food intake, a single dose of fenfluramine could reduce food intake by ~25% accompanied by decreased subjective ratings of appetite and increasing pre-meal satiety (28). Collectively, several studies demonstrated the efficacy of dexfenfluramine in both short- and long-term paradigms on food intake (29–32). In a meta-analysis of 14 studies of fenfluramine for weight loss, individuals treated with fenfluramine at varying doses (30–120 mg/day) had on average a 2.5 kg weight loss over individuals treated with placebo (33). More impressive were the weight loss effects of dexfenfluramine. A multicenter, randomized, double-blind placebo-controlled trial (INDEX) in more than 800 obese individuals found that treatment with dexfenfluramine (15 mg b.i.d.) for 12 months resulted in significantly greater weight loss compared to placebo (10.3 vs. 7.1%, respectively) and more than half of the individuals receiving dexfenfluramine lost more than 10% of their baseline body weight (34).

In the early 1990s fenfluramine was combined with an adrenergic agonist, phentermine, with more marked effects on weight loss (35). This combination known as “fen-phen” or “phen-fen” saw widespread use after the FDA approved dexfenfluramine for weight loss in 1996. The following year, in 1997, more than two decades after the approval of fenfluramine, high rates of cardiac valvular pathologies were being reported in patients prescribed these agents (36) and both fenfluramine and dexfenfluramine were withdrawn from the market. Several years later it was learned that valvular heart disease observed with fenfluramine and dexfenfluramine use was due to the nonselective stimulation of 5-HT_{2B} receptors in cardiac interstitial cells. This important discovery then led the way for development of new antiobesity targets that were selective for the 5-HT_{2C} receptor (13). Phentermine is still approved but only for short-term treatment of obesity.

Fluoxetine

Fluoxetine is a selective serotonin reuptake inhibitor that in rodents leads to a consistent reduction in food intake probably through the interaction with 5-HT₁, and 5-HT₂ receptor families (37, 38). Furthermore, body weight loss is sustained during fluoxetine treatment. The data in humans suggest a tolerance to fluoxetine-induced hypophagia ensues with continued use (39, 40). Consistent reports indicate that fluoxetine has the capacity to decrease food intake and perceived hunger with the initiation of treatment; however, the effect dissipates compared to placebo when treatment is continued long term. Similarly, increased weight loss is reported with fluoxetine treatment (3.3 kg difference compared with placebo) during a 6-month period (33); however, an intolerance to weight also develops with long-term treatment (1 year) (41, 42).

mCPP

mCPP is a preferential agonist of the 5-HT_{1B} and 5-HT_{2C} receptors and has been demonstrated in humans to decrease food intake and pre-meal ratings of hunger (43). A 2-week treatment with mCPP in obese men and women showed promising effects on weight loss with treatment resulting in almost a 1 kg difference in weight change from baseline compared to placebo (44). Unfortunately, mCPP also has a track record for significant reporting of adverse effects compared to placebo, including nausea, lightheadedness and anxiety (43).

LORCASERIN

Lorcaserin (8-chloro-1(*R*)-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride), formerly known as APD-365, is a novel selective 5-HT_{2C} receptor agonist (Fig. 1) synthesized by Arena Pharmaceuticals for weight loss therapy (13). Preclinical and clinical studies (Table I) indicate that lorcaserin is well tolerated and not associated with cardiac valvulopathy or pulmonary hypertension. Furthermore, lorcaserin demonstrated efficacy for decreasing food intake and body weight.

Preclinical studies

Pharmacology—The binding affinity of lorcaserin (K_i) for recombinant human 5-HT_{2C} receptors was 7.5-fold higher than for 5-HT_{2A} receptors and 11.6-fold higher than for 5-HT_{2B} receptors (45). Compared to serotonin, lorcaserin induces full agonistic activity at 5-HT_{2C} and 5-HT_{2B} receptors, partial activity at 5-HT_{2A} receptors and no activity at the other 75 serotonin receptor subtypes except for antagonism at 5-HT_{1A} (45). The accumulation of inositol phosphate in HEK-293 cells expressing recombinant human 5-HT₂ receptors showed that lorcaserin induces agonist activity at all three human 5-HT₂ receptor subtypes, although lorcaserin exhibited a higher potency for the 5-HT_{2C} receptor subtype (45). The EC₅₀ of lorcaserin at human 5-HT_{2C} receptors is 9 ± 0.5 nM, which was 18 times more

potent than at 5-HT_{2A} receptors ($EC_{50} = 168 \pm 11$ nM) and 104 times more potent than at 5-HT_{2B} receptors ($EC_{50} = 943 \pm 90$ nM).

Pharmacokinetics—The pharmacokinetics of lorcaserin was evaluated following a single 10 mg/kg dose in male Sprague-Dawley rats. Lorcaserin was rapidly absorbed resulting in a maximum concentration (C_{max}) of 0.76 μ g/mL after 15 minutes and has a moderate clearance rate ($t_{1/2}$ 4.9 h) (45).

Efficacy—In an acute study, food intake was measured in Sprague-Dawley rats following a single oral dose of lorcaserin (3, 6, 12 and 24 mg/kg) at 2, 4, 6 and 22 hours after food exposure. Cumulative food intake over the 22-hour study was significantly inhibited by lorcaserin (13, 45). Statistical analysis indicated that the cumulative decrease in food intake was accounted for by a significant reduction in the first 2 hours only (3 mg/kg: $34 \pm 3\%$, 24 mg/kg: $82 \pm 6\%$). Administration of lorcaserin (18 mg/kg) in conjunction with either a selective 5-HT_{2C} antagonist (SB-242084) or selective 5-HT_{2A} antagonist (MDL-100907) demonstrated that lorcaserin-mediated hypophagia was attenuated with SB-242084, whereas there was no effect of MDL-100907, indicating that the reduction in food intake with lorcaserin is mediated by 5-HT_{2C} receptors and not 5-HT_{2A} receptors (45). To test the efficacy of lorcaserin to reduce body weight, lorcaserin (4, 5, 9 or 18 mg/kg) or placebo was administered to diet-induced obese rats for 28 days. Lorcaserin significantly decreased food intake and body weight gain over the 4-week study, an effect which was most apparent with the 9 and 18 mg/kg groups. Body composition analysis showed that the reduction in body weight was attributed to a significant reduction in fat mass and not fat-free mass. Withdrawal from 18 mg/kg b.i.d. lorcaserin reversed the effect on weight loss and food intake; after 4 weeks body weight was equivalent to that of the vehicle-treated animals (45).

Phase I clinical studies

Safety—A placebo-controlled study conducted in 45 healthy men and women tested the safety and tolerability of single doses of lorcaserin (10, 20 and 40 mg). At 10 and 20 mg, lorcaserin was tolerated, with the high dose (40 mg) being associated with central nervous system side effects (46). In a phase Ib trial, 27 individuals (BMI: 31 ± 6 kg/m²) received either 3, 10 or 20 mg lorcaserin daily for 14 days. There were no serious adverse events reported at these three doses (46).

Pharmacokinetics—The single-dose (10 mg) phase I studies of lorcaserin showed that the plasma half-life was 11 hours, indicative of the suitability for once-daily dosing in patients. The maximum drug levels achieved with a 10-mg dose were 20 times higher than the in vitro EC_{50} for 5-HT_{2C} receptors (46). In a repeat-dose study, t_{max} was reached after 2 hours and plasma half-life was 10 hours. Steady-state levels were attained by the 5th day of dosing. Pharmacokinetic studies in humans showed that the maximum concentration (C_{max}) after ingestion of a single 10-mg dose was 158 ± 56 nmol/L and the minimum concentration (C_{min}) was 131 ± 78 nmol/L (47). Lorcaserin reaches steady state in serum after approximately 4 days of treatment.

Efficacy—Using a randomized, double-blind, four-period crossover study, the effect of a single dose of lorcaserin on food intake was measured (48). Over a period of 4 weeks, 20 males received placebo or 0.1, 1 or 10 mg of lorcaserin at weekly intervals and food intake during a test meal was measured 2 hours postdosing. Data from all subjects showed a 6.5% reduction in food intake with 10 mg of lorcaserin (not significant); however, with a single outlier removed from the dataset, food intake was significantly reduced by 10.7% with a single 10-mg dose of lorcaserin compared to placebo (48).

Phase II clinical studies

The main phase II clinical study was a double-blind, randomized, placebo-controlled, parallel-arm study designed to test the hypothesis that lorcaserin administration will lead to weight loss in healthy obese adults (47). In this 12-week study, 469 obese (BMI: 30–45 kg/m²) men and women were randomized across 42 clinical centers to receive placebo or lorcaserin 10 mg q.d., lorcaserin 15 mg q.d. or lorcaserin 10 mg b.i.d. Subjects were instructed to maintain their habitual diet and exercise habits throughout the study and no lifestyle modification program was implemented. Extensive echocardiography was performed to test the secondary hypothesis that lorcaserin use is not associated with changes in heart valve insufficiency or increased pulmonary artery pressure (PAP).

The primary outcome was change in body weight from baseline to day 85 and the proportion of subjects who lost 5% or more of their baseline body weight (Table I). Secondary outcomes included changes from baseline in BMI, waist circumference and serum lipid profiles (Table I).

Lorcaserin treatment produced weight loss in a dose-dependent manner seen with each dose of lorcaserin after 30 days of treatment (47). Lorcaserin at each dose produced a significant reduction in body weight compared to placebo after 85 days of treatment (placebo: -0.3 ± 2.4 , 10 mg q.d.: -1.8 ± 2.5 , 15 mg q.d.: -2.6 ± 2.6 , 10 mg b.i.d.: -3.6 ± 2.8 kg). The proportion of subjects who had 5% or greater weight loss at 85 days was dose-dependently and significantly increased by lorcaserin treatment. That is, 12.8% of subjects had 5% or more weight loss with 10 mg q.d. lorcaserin compared to 19.5% with 15 mg q.d. and 31.2% with 10 mg b.i.d. (47).

With regard to secondary outcomes, weight loss with lorcaserin treatment was associated with dose-related reductions in waist circumference and BMI. In addition, lorcaserin at 10 mg b.i.d. was associated with a significant decrease in total cholesterol and fasting glucose (47).

Phase III clinical studies

The main phase III study, BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obese Management), was a double-blind, randomized, placebo-controlled clinical study designed to determine the efficacy and safety of lorcaserin for weight loss and maintenance of weight loss in conjunction with a lifestyle modification program (49). A total of 3,182 adults from 98 clinical trial sites were enrolled in the 2-year study. During year 1, subjects were randomly assigned to receive either lorcaserin (10 mg) or placebo, twice daily (once before breakfast and once before dinner) for 52 weeks. During year 2, subjects assigned to placebo continued to receive placebo treatment, whereas subjects in the lorcaserin group were randomly reassigned to receive either lorcaserin or placebo.

The primary endpoints were weight loss at the end of year 1 (proportion of subjects with a reduction in body weight from baseline of 5 or 10% or greater) and maintenance of weight loss (the proportion of subjects with a reduction in body weight of 5% or more from baseline at the end of year 1 who maintained the weight loss at the end of year 2) (Table I). Secondary outcomes included changes in blood lipid profiles, glycemic profiles (HbA_{1c}, fasting glucose), insulin resistance (HOMA-IR), inflammatory markers and quality of life (Table I).

In comparison to 20% of subjects receiving placebo treatment, almost half (47.5%) of the subjects treated with lorcaserin lost 5% or more of their baseline body weight (weight loss -2.2 ± 0.1 versus -5.8 ± 0.2 kg, respectively) after 1 year (49). There was also a significantly greater proportion of subjects treated with lorcaserin (22.6%) who lost 10% or

more of their baseline body weight compared with placebo (7.7%). Lorcaserin treatment in the second year also showed efficacy for weight loss maintenance. For those subjects in the lorcaserin-treated group with weight loss of 5% or more at the end of year 1, the weight loss was maintained in a significantly greater proportion of subjects with continued lorcaserin treatment in year 2 (67.9%), compared to subjects who were reassigned to placebo (50.3%) in the second year (49).

Compared to placebo treatment, treatment with lorcaserin for 1 year led to significant reductions in waist circumference, blood pressure (systolic and diastolic), total cholesterol, LDL-cholesterol and triglycerides (49). In addition, 1 year of lorcaserin treatment induced significant reductions in glycated hemoglobin, fasting glucose and insulin and therefore a significant improvement in insulin sensitivity as measured by HOMA-IR. Inflammatory markers, high-sensitivity C-reactive protein and fibrinogen were also significantly reduced by 1 year of lorcaserin treatment compared to placebo (49).

The phase III clinical study showed that lorcaserin was associated with significant weight loss compared to placebo when administered in conjunction with a lifestyle modification program (nutrition modification and increased physical activity). Weight loss after 1 year of lorcaserin treatment led to improvements in waist circumference, blood pressure, serum lipids and inflammatory markers and insulin resistance.

Mechanism of action study

Clinical Trials.gov Identifier NCT00829140 was an investigator-initiated, double-blind, randomized, placebo-controlled study designed to determine the effect of lorcaserin on energy intake, appetite ratings and energy expenditure in overweight and obese individuals (50). Fifty-seven participants at a single site were randomized to receive either placebo ($n = 28$) or lorcaserin ($n = 29$; 10 mg b.i.d.) for 56 days. The study was implemented in two phases, a 7-day weight maintenance phase followed by a 7-week lifestyle modification program. Study endpoints were evaluated during weight maintenance (day 7) and after weight loss (day 56).

The primary endpoints were changes in 24-hour energy metabolism (expenditure and substrate oxidation) and food intake and ratings of appetite and satiety. Secondary outcomes included changes in body weight and body composition and blood lipid profiles.

After 7 days of treatment during weight maintenance, energy intake (measured during lunch and dinner) was significantly ($P < 0.01$) reduced with lorcaserin but not placebo (mean $\pm$ SE; lorcaserin: -286 ± 86 kcal, placebo: -147 ± 89 kcal). After 56 days of treatment, a significantly larger weight loss was observed with lorcaserin treatment (lorcaserin: -3.8 ± 0.4 kg, placebo: -2.2 ± 0.5 kg, $P < 0.01$) in association with a significant reduction in energy intake (lorcaserin: -470 ± 87 kcal; placebo: -205 ± 91 kcal, $P < 0.05$) and appetite ratings compared to placebo (50). Energy expenditure measured over 24 hours or during sleep was significantly reduced by weight loss with both lorcaserin and placebo treatment (50). Even after adjusting the change in energy expenditure for the change in body weight and body composition, energy expenditure was still significantly different from baseline in both treatment groups, indicating a metabolic adaptation (lorcaserin: -105.9 kcal/24 h; placebo: -86.1 kcal/24 h, $P < 0.05$). Energy expenditure, however, was not different between lorcaserin and placebo at any time point. After 56 days, there was a significant reduction in total cholesterol (lorcaserin: $-9.8 \pm 1.7\%$, placebo: $-4.4 \pm 2.7\%$, $P < 0.01$), HDL cholesterol (lorcaserin: $-0.5 \pm 1.8\%$, placebo: $-4.4 \pm 1.9\%$, $P < 0.01$) and LDL-cholesterol (lorcaserin: $-13.8 \pm 2.0\%$, placebo: $-4.4 \pm 3.7\%$, $P < 0.001$) in lorcaserin compared to placebo (50). There was no change in serum triglycerides.

Safety

Activation of 5-HT_{2B} receptors in cardiac interstitial cells is believed to be associated with cardiac valvular insufficiency and pulmonary hypertension (51, 52). Careful monitoring of changes in cardiac and pulmonary pathology therefore is essential for evaluating the safety of lorcaserin for obesity treatment. The phase II clinical studies indicated that there was no apparent effect of lorcaserin on heart valve function or PAP. Echocardiograms were performed at screening and after 84 days of treatment with lorcaserin at three different study doses: 10 mg q.d., 15 mg q.d. and 10 mg b.i.d. Estimated mean PAP was not different between the treatment groups at screening or following treatment and overall there was no significant change in PAP from baseline in any treatment group (47). Examination of the proportion of subjects with an increase in PAP of 5 mmHg or more indicated no difference between treatment groups (placebo: 13.2%, 10 mg q.d.: 10.9%, 15 mg q.d.: 11.4%, 10 mg b.i.d.: 15.1%). There were only seven cases of an increase in PAP of 10 mmHg or more, with four cases in the 10-mg q.d. lorcaserin group, one case in the placebo group, one case in the 15-mg q.d. and one case in the 10-mg b.i.d. lorcaserin groups (47). With regard to cardiac valvulopathy, the proportion of subjects with increased valvular regurgitation (mitral valve, aortic valve or tricuspid valve) compared to those with decreased valvular regurgitation (or no change in valvular regurgitation) was not significantly different between treatment groups.

In the phase III studies, echocardiography was performed at screening and during weeks 24, 52, 76 and 104 of the study (49). The incidence of FDA-defined valvulopathy after 1 year was 2.3% in the placebo group compared with 2.7% in the lorcaserin group. In agreement with the phase II study (47), there was no difference in the incidence of cardiac valvulopathy between placebo and lorcaserin 10 mg b.i.d. ($P=0.70$). During the second year of treatment, the incidence of valvulopathy was unchanged from year 1 and was not different between the two treatment groups (placebo: 2.7%, lorcaserin: 2.6%).

Activation of central 5-HT_{2A} receptors by nonselective serotonergic drugs is a cause for concern as interaction with central 5-HT_{2A} receptors can lead to hallucinations and changes in perception (7). As reported (49), the incidence of depression (including depressive symptoms, depressed mood or depression) was not different between lorcaserin and placebo in year 1 (placebo: 2.2%, lorcaserin: 2.5%) or year 2 (placebo: 3.0%, lorcaserin: 2.0%). The Beck Depression Inventory II (BDI-II) indicated that the incidence of suicidal thoughts was 1.3% in both treatment groups. There was no difference in the overall BDI-II score between lorcaserin and placebo at baseline.

Similarly, during the 8-week proof-of-concept study (50), there were no apparent negative treatment-related effects on clinical labs, vital signs or cardiac valvulopathy. Furthermore, lorcaserin 10 mg b.i.d. did not increase depressive symptoms as measured by the BDI-II.

Tolerability

In the phase II studies lorcaserin treatment was associated with increased incidence of headache, nausea and dizziness (47). Headaches were reported in 29.6% of lorcaserin-treated patients (17.8% in placebo) and generally occurred on day 1 and resolved within hours. Nausea was reported in 9.7% of lorcaserin-treated patients and was also reported early in the study and typically lasted 1–2 days (47).

In the phase III study (49), 2 years of treatment (either lorcaserin 10 mg b.i.d. or placebo; year 1 plus year 2) the most commonly reported adverse events were (in order) upper respiratory infections, nasopharyngitis, sinusitis, arthralgia, influenza, urinary tract infection and headache (Table I). The incidence of nausea and dizziness, which were commonly

reported in the phase II study, was higher with placebo in the 2-year study compared to treatment with lorcaserin (Table I).

During the 8-week proof-of-concept study, lorcaserin was generally well tolerated (50). The most common adverse event reported was headache followed by dizziness (Table I). Most adverse events were reported as mild and resolved without any action. A total of six adverse events were reported among four subjects to be of severe intensity; five were considered not related or unlikely related to the study drug. A single event, vertigo, was considered possibly related to the study drug and resolved by the next day with no action taken (50).

CONCLUSIONS

In 2006 the annual cost of obesity in the U.S. was estimated to be USD 147 million and with the most recent statistics from the Centers for Disease Control indicating that obesity is rising, obesity-related medical expenses have reached approximately 10% of all medical spending. Given that the average American is 23 pounds over-weight there is an urgent need for pharmacotherapy. The phase II and phase III studies of lorcaserin for the treatment of obesity indicate weight loss both alone and in combination with a lifestyle modification (targeting a 600 kcal/day caloric deficit) program. Lorcaserin acts to alter energy balance through a reduction in energy intake and without an increase in energy expenditure. Importantly, and in agreement with the preclinical data, treatment with lorcaserin (10 mg b.i.d.) for up to 2 years was not associated with cardiac valvulopathy or pulmonary hypertension or changes in depression, indicating that lorcaserin is a selective 5-HT_{2C} receptor agonist and has little or no activation of the 5-HT_{2B} and 5-HT_{2A} receptors. Therefore, given that the problem with the early serotonergic weight loss drugs were nonselectivity, lorcaserin would appear to be a good candidate for combination therapy. In September 2010, the meeting of the U.S. FDA Endocrinologic and Metabolic Drugs Advisory Committee voted 9 to 5 that the presented data do not adequately demonstrate that the efficacy of lorcaserin outweighs potential risks. The FDA did not approve the use of lorcaserin in its present form, although it is expected that a revised submission addressing their concerns will be forthcoming. There is still hope that lorcaserin will become an available pharmaceutical therapy for weight loss.

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Figure 1.
Chemical structures of serotonin and lorcaserin.

Table 1

Summary of the safety, tolerability and efficacy of lorcaserin in clinical studies.

	Phase II ^a 12 weeks Mean ± SEM		Phase III ^b 2 years Mean ± SEM		Mechanism of action 8 weeks Mean ± SEM	
	Placebo	10 mg b.i.d.	Placebo	10 mg b.i.d.	Placebo	10 mg b.i.d.
N	88	77	697	564	28	29
Baseline BMI (kg/m ²)	36.4 ± 0.4	36.2 ± 0.4	35.8 ± 0.2	36.1 ± 0.2	35.9 ± 4.6	35.2 ± 5.0
Weight change (kg)	-0.3 ± 0.3	-3.6 ± 0.3	-2.4 ± 0.3	-5.6 ± 0.3	-2.2 ± 0.5	-3.8 ± 0.5
> 5% (% of subjects)	2.3	31.2	29.8	50.2	-	-
Safety						
Pulmonary artery pressure (mmHg)	0.03 ± 0.53	1.0 ± 0.48	-0.94 ± 0.32	-1.61 ± 0.31	-	-
Other parameters						
Waist circumference (cm)	-2.1 ± 0.6	-4.6 ± 0.6	-2.4 ± 0.3	-5.6 ± 0.4	-4.9 ± 0.8	-4.6 ± 0.5
BMI (kg/m ²)	-0.09 ± 0.1	-1.31 ± 0.1	-0.88 ± 0.1	-2.01 ± 0.1	-0.66 ± 0.2	-1.37 ± 0.2
Systolic BP (mmHg)	-0.6 ± 1.2	-1.6 ± 1.4	-1.5 ± 0.5	-2.5 ± 0.5	-1.2 ± 1.9	-3.8 ± 2.0
Diastolic BP (mmHg)	-1.2 ± 0.9	-1.2 ± 0.9	-0.7 ± 0.3	-1.7 ± 0.4	-4.0 ± 1.5	-4.7 ± 1.7
Total cholesterol (mg/dL)	1.3 ± 2.0	-7.0 ± 2.3	1.6 ± 1.1	-0.27 ± 1.1	-9.8 ± 3.3	-23.3 ± 3.3
LDL cholesterol (mg/dL)	1.3 ± 1.8	-3.2 ± 2.2	5.6 ± 0.9	4.3 ± 1.0	-6.3 ± 2.7	-19.8 ± 2.6
HDL cholesterol (mg/dL)	0.1 ± 0.6	-1.6 ± 0.7	-1.9 ± 0.3	-0.9 ± 0.3	-2.6 ± 0.9	-4.9 ± 0.8
Triglycerides (mg/dL)	-3.4 ± 0.1	-14.3 ± 2.9	-9.1 ± 3.6	-18.9 ± 2.5	-5.6 ± 6.7	7.1 ± 6.4
Fasting glucose (mg/dL)	0.2 ± 0.2	-2.9 ± 1.2	2.2 ± 0.4	0.6 ± 0.5	-1.7 ± 1.2	0.3 ± 1.6
HbA _{1c} (%)	0.05 ± 0.03	0.03 ± 0.03	-0.09 ± 0.01	-0.17 ± 0.01	-	-
HOMA-IR	-	-	-0.37 ± 0.04	-0.45 ± 0.05	-	-
Adverse events, n (%)						
Headache	21 (17.8)	31 (26.7)	30 (4.3)	41 (7.2)	9 (32.1)	11 (37.9)
Dizziness	0	9 (7.8)	17 (2.4)	10 (1.7)	1 (3.6)	3 (10.3)
Nasopharyngitis	10 (8.5)	7 (6.0)	88 (12.6)	94 (16.4)	3 (10.7)	1 (3.4)
Sinusitis	4 (3.4)	4 (3.4)	48 (6.9)	49 (8.6)	1 (3.6)	1 (3.4)
Nausea	4 (3.4)	13 (11.2)	29 (4.2)	20 (3.5)	1 (3.6)	2 (6.9)
Diarrhea	7 (5.9)	4 (3.4)	30 (4.3)	34 (5.9)	1 (3.6)	2 (6.9)

^aResults are presented as completer analysis from baseline to day 85;

^b Results are presented as change from baseline after 2 years using intent-to-treat; last observation carried forward analysis; – data not reported.