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TWO NEW DRUGS FOR OBESITY: A REVIEW

Erika Fant, Pharm.D. Candidate

Estimates by the World Health Organization in 2008 revealed more than 1.4 billion adults worldwide were overweight, with over 200 million men and 300 million women classified as obese.[1] Obesity is defined as a body mass index (BMI) of ≥ 30 kg/m^2 and overweight as a BMI of 25-29.9 kg/m^2.[2] In 2009-2010, more than one-third of adults within the United States were classified as obese.[3] Geographically, the incidence of obesity is the highest among the Southern states (29.4% of adults) and lowest in the West (24.1%). Patients identifying themselves as non-Hispanic blacks had the highest rate of obesity (44.1%), followed by Mexican Americans, Hispanics, and non-Hispanic whites (32.6%). Socioeconomic differences also account for changes in prevalence of obesity, with lower-income individuals (especially women) more likely to be obese than women with higher incomes.[4]

From a public health perspective, obesity is one of the largest monetary drains on the healthcare system costing nearly $150 billion in 2008.[4] Obesity is associated with a number of comorbid conditions, including heart disease, type 2 diabetes (T2DM), hypertension (HTN), sleep apnea, dyslipidemia, osteoarthritis, and certain cancers. Obese patients are often victims of social stigma and discrimination, adding a mental health burden onto patients already suffering from multiple health issues.[1] Research shows that a decrease of 5% body weight (BW) can lead to significant improvements in these conditions.[5,6]

The National Institutes of Health National Heart, Lung, and Blood Institute released treatment guidelines in 2008 for primary care-based approaches to managing and treating obese patients.[1] The traditional and most widespread approach is combination dietary therapy and exercise, beginning with a 500-1,000 kcal/day dietary deficit for an average daily intake limit of 1,000-1,200 kcal/day for women and 1,200-1,500 kcal/day for men in combination with a sustained exercise regimen of at least 30 minutes most days of the week.[1]

Past pharmacological options for weight loss included combination fenfluramine-phentermine (Fen-Phen®), removed from the market due to increased risk of valvulopathy associated with serotonin subtype 2B receptor (5-HT$_{2B}$) agonism, and sibutramine (Meridia®), removed for increased risk of cardiovascular disease.[7] Currently, the only prescription weight-loss agent on the market is orlistat (Xenical®), an oral lipase inhibitor, but adverse effects and low efficacy drive the need for more acceptable options. In Phase III development, a combination treatment of bupropion SR-naltrexone SR (Contrave®) is hypothesized to work synergistically to mediate food intake by affecting dopamine areas of the brain.[8,9] Surgical interventions are gaining in popularity among the most severely obese patients (BMI ≥ 40 kg/m^2), including Lap-Band® surgery and gastric bypass; however, all procedures are associated with significant increased risk of complications.[10]

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This summer, two new weight-loss drugs were approved by the Food and Drug Administration (FDA). Lorcaserin (Belviq ®), a 5-HT_{2C} selective receptor agonist developed by Arena Pharmaceuticals and marketed jointly with Eisai Inc. It was approved in late June 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with a BMI of > 30k g/m^2 or > 27 kg/m^2 with at least one weight-related comorbid condition (eg HTN, dyslipidemia, T2DM).[11] The combination drug phentermine-topiramate ER (Qsymia®), by VIVUS, Inc., was approved in July, 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with at least one weight-related comorbidity (e.g. HTN, T2DM, or dyslipidemia).[12] This article will offer an introduction and discussion of each of these new weight-loss drugs and their potential place in therapy.

Pharmacology

Each drug has a separate mechanism to augment weight loss. Lorcaserin is a selective 5-HT_{2C} agonist that decreases food intake and promotes satiety through stimulation of the hypothalamic melanocortin system.[5,13,14] While this mechanism is not novel (previously exploited by fenfluramine and dexfenfluramine), the selectivity for the 5-HT_{2C} receptor is intended to reduce the incidence of valvulopathy associated with the 5-HT_{2B} receptor agonism that plagued fenfluramine.[13] Phentermine-topiramate ER (phen-top ER) also works centrally through the hypothalamus to promote release of norepinephrine via the phentermine component; while the topiramate ER component is hypothesized from animal studies to increase energy expenditure, decrease energy efficiency, and decrease caloric intake.[6,15,16]

Pharmacokinetics

Lorcaserin and phen-top ER are orally administered drugs that can be taken without regard to food. Lorcaserin is largely metabolized by the liver, while phen-top ER is primarily excreted unchanged by the kidneys (**Table 1**).[11,12]

Table 1 | Pharmacokinetic Profiles of Lorcaserin and Phen-top ER

	Lorcaserin[11]	Phen-top ER[12]
Absorption	Time to Cmax: 1.5-2 hrs; T 1/2: 11 hrs; Little food effect (< 10% effect on Cmax or AUC, 1 hr delay in Tmax)	*Phentermine:* Time to Cmax: 6 hrs; T 1/2: 20 hrs; No effect of food on absorption *Topiramate:* Time to Cmax: 9 hrs; T 1/2: 65 hrs; No effect of food on absorption
Distribution	Plasma protein binding: 70%	*Phentermine:* Plasma protein binding: 17.5% *Topiramate:* Plasma protein binding: 15-41%
Metabolism	Mixed hepatic (glucuronidation, conjugation)	*Phentermine:* CYP 3A4 metabolism *Topiramate:* No significant metabolism
Elimination	92.5% renal elimination of metabolites 2.2% eliminated fecally	*Phentermine:* 80% excreted unchanged in urine Estimated clearance of oral doses: 8.79 L/hr *Topiramate:* 70% excreted unchanged in urine Estimated clearance of oral doses: 1.17 L/hr
Special Populations	*Renal Impairment:* No dose adjustment necessary in mild renal impairment; use caution in moderate renal impairment. Not recommended for CrCl < 30 mL/min or ESRD *Hepatic Impairment:* No dose adjustment for mild-moderate hepatic impairment (Child-Pugh score 5-9); Use with caution in severe hepatic impairment *Heart Failure:* Use with caution due to possible upregulation of 5-HT_{2B} receptors Avoid in *Cardiac valvular disease*	*Renal Impairment:* No dose adjustments in patients with mild renal impairment. Do not exceed 7.5mg/46mg QD in moderate (CrCl = 30-50 ml/min) to severe (CrCl = < 30 mL/min) impairment. No studies in patients with ESRD *Hepatic Impairment:* No dose adjustments in patients with mild hepatic impairment. In moderate hepatic impairment, do not exceed 7.5mg/46mg QD. 60% increase in AUC of phentermine in moderate (Child-Pugh 7-9) liver impairment. Avoid in severe hepatic impairment *Women of Childbearing Potential:* REMS requirement for negative pregnancy test before beginning therapy and each month therafter. Avoid in *Glaucoma, Hyperthyroidism, Recent (<6months) or unstable heart disease or stroke*

5-HT = serotonin, AUC = area under the curve, Cmax = peak plasma concentration, CrCl = creatinine clearance, CYP = hepatic Cytochrome P450 enzyme, ESRD = end stage renal disease, hr = hour, QD = every day, Phen-top ER = phentermine/topiramate extended release, REMS = risk evaluation and mitigation strategy, T 1/2 = half life, Tmax = time to maximum concentration

Drug Interactions

There are a number of important drug interactions to watch for with each of these agents. Lorcaserin inhibits hepatic enzyme cytochrome P450 (CYP) subtype 2D6, and may increase exposure to drugs extensively metabolized through this pathway, such as opioids, selective-serotonin reuptake inhibitors (SSRIs), and dextromethorphan.[11,17] Additionally, as a serotonin agonist, there is some risk of serotonin syndrome with other serotonergic or dopamine agonists.[7,11]

The components of phen-top ER have each been extensively studied, and drug-drug interactions seen with each agent are also of concern with the combination product. Phentermine is not recommended for use with tricyclic antidepressants or SSRIs, and use of phentermine within 14 days of a monoamine oxidase inhibitor is an absolute contraindication due to the increased risk for hypertensive crisis.[18] Topiramate is a mild inhibitor of CYP 2C19 and a mild inducer of CYP 3A4. Topiramate, like other anticonvulsants, has documented proof of decreasing the effectiveness of oral contraceptives. It may also increase exposure to citalopram, increasing the risk of QT prolongation, and increase the risk of lactic acidosis with metformin.[19]

Review of Major Clinical Trials

The Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) and BLOOM in Type 2 Diabetes Mellitus (BLOOM-DM) as well as the One Year Randomized Trial of Lorcaserin for Weight Loss in Obese and Overweight Adults (BLOSSOM) trial evaluated the safety and efficacy of lorcaserin in obese and overweight adults. The coprimary end points for each study included: proportion of patients with ≥ 5% weight loss (WL), proportion of patients with ≥ 10% WL, and change in BW. Secondary end points include changes from baseline for: lipids, glycemic variables, physical measures, blood pressure, inflammatory cardiac biomarkers, and quality of life (QOL).[5,13,14]

BLOOM, a two-year, multicenter, placebo-controlled trial enrolled 3182 patients 18-65 years old with BMI of 30-45 kg/m^2 or 27-45 kg/m^2 with at least one weight-related comorbidity (HTN, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea) (**Table 2**).[13] Patients were randomly assigned in a 1:1 ratio to placebo or lorcaserin 10 mg twice daily (BID). In the second year, patients in the placebo group continued to receive placebo while those in the lorcaserin 10 mg twice daily group were randomly assigned in a 2:1 ratio to continue to receive lorcaserin or to placebo. At year one, 47.5% of patients receiving lorcaserin had lost 5% or more of their baseline BW, as compared with 20.3% of patients receiving only placebo (p<0.001). Additionally,

Table 2 | Overview of Major Clinical Trials for Lorcaserin

	Treatment Groups	No. of Patients	Inclusion Criteria	Results
BLOOM[13] 2 year trial	1:1 ratio PL L 10mg BID	3182	18-65 years of age BMI 30-45 kg/m2 OR BMI 27-45 kg/m2 with ≥1 coexisting weight-related comorbidity	**Year 1**: 47.5% of pts in L groups had lost ≥ 5% of their BBW, vs. 20.3% of pts in PL. 22.6% of pts in L vs. 7.7% in PL lost 10% of BW. **Year 2**: sustained WL of ≥ 5% was maintained in more pts on L vs. PL (67.9% vs. 50.3%, p<0.001). Improvement in 2° outcomes returned toward baseline for pts without sustained WL in year two
BLOOM-DM[14] 1 year trial	1:1:1 ratio PL L 10mg QD L 10mg BID	604	18-65 years of age T2DM treated with MET and/or SU HbA1c 7-10% at screening BMI 27-45 kg/m^2 Moderate exercise program	Significant differences in PL vs. L groups in terms of WL, FPG and HbA1c (p<0.001 for all except p<0.015 for FPG in L QD) Non-significant effects on other 2° outcomes
BLOSSOM[5] 1 year trial	2:1:2 ratio L 10mg BID L 10mg QD PL	4008	18-65 years of age BMI 30-45 kg/m2 or 27-29.9 kg/m2 with ≥1 coexisting weight-related comorbidity Moderate exercise program	Significantly more WL of ≥ 5% with L (47.2 and 40.2% respectively for L 10mg BID and 10 mg QD vs. 25% in PL, p<0.0001). L BID associated with significantly more WL than L QD (p<0.01).

2° = secondary, BBW = baseline body weight, BID = twice daily, BMI = body mass indexBW = body weight, FPG = fasting plasma glucose, L = lorcaserin, MET = metformin, PL = placebo, Pts = patients QD = every day, SU = sulfonylurea, T2DM = type two diabetes mellitus, WL = weight loss

22.6% of patients in the lorcaserin group compared to 7.7% in the placebo group lost ≥ 10% of baseline BW (p<0.001). Through the second year, sustained weight loss of ≥ 5% was maintained in more patients who continued in the lorcaserin group versus those who changed to placebo (67.9% vs. 50.3%, p<0.001). A modest improvement in secondary outcomes were seen after one year, but tended to return to baseline for patients who did not sustain weight loss in year two. Most patients in the BLOOM trial were Caucasian females in their mid-forties, and high attrition gave a final power of only 60% to the study results.[13]

BLOOM-DM had a similar procedure to BLOOM, but was a one-year trial with randomization to placebo, lorcaserin 10 mg once daily (QD) or lorcaserin 10 mg BID in a 1:1:1 ratio.[14] All patients had T2DM treated with metformin and/or a sulfonylurea with a hemoglobin A1c (HbA1c) of 7-10% and the same BMI requirements as BLOOM. Exclusion criteria were much more stringent, including use of any other antidiabetic medications. In BLOOM-DM there was no significant dose-dependent effect on weight loss between the QD and BID dosing of lorcaserin. However, there were significant effects seen between the placebo group and each treatment group (QD and BID) in terms of weight loss, fasting plasma glucose, and HbA1c (p<0.015 for fasting plasma glucose in the lorcaserin QD group, p<0.001 for all other outcomes) with non-significant effects on lipids, blood pressure, or other secondary outcomes. Negligible blood pressure differences could be attributed to patient blood pressure being managed pharmacologically through outside physicians. BLOOM -DM was a much smaller trial than BLOOM, with only 604 patients, most of which were elderly white patients with mild diabetes.[14]

BLOSSOM, a 52-week randomized, double-blind, placebo-controlled study assessed lorcaserin at 10 mg BID versus 10 mg QD versus placebo in a 2:1:2 ratio. With a similar patient population to the BLOOM study (**Table 2**), BLOSSOM found similar results: significantly more patients assigned to lorcaserin therapy losing at least 5% of baseline BW (47.2 and 40.2% respectively for lorcaserin 10 mg BID and 10 mg QD groups versus 25% in placebo, p<0.0001).[5] At the end of this study, investigators concluded that lorcaserin BID was associated with significantly more weight loss than lorcaserin QD (p<0.01). [5] There were no significant improvements in metabolic variables, other than those seen in high-density lipoprotein (3.7% change vs. 1.3% with placebo, p<0.001), triglycerides (-4.3% change vs. -0.9% with placebo, p<0.02), and apolipoprotein B (-2.9% change vs. 1.4% with placebo, p<0.001). There was also a significant difference in the short form of the Impact of Weight on Quality of Life survey (IWQOL-LITE) showing improved quality of life for patients in the lorcaserin treatment groups versus placebo (p<0.001).[5]

The three major studies involved in the approval of phen-top ER were the Controlled-Release Phentermine/Topiramate in Severely Obese Adults (EQUIP), Effects of low-dose controlled-release phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER), and Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL). SEQUEL was a 1-year extension of the 1-year CONQUER trial (**Table 3**). Each randomized controlled trial studied the effects of multiple doses of phen-top ER in overweight and obese patients, with shared coprimary end points of percent of patients achieving ≥5% weight loss and percent change in BW, and secondary end points assessing metabolic variables.[6,15,16]

EQUIP, a 56-week trial, randomized 1267 patients to placebo, phen-top ER 3.75mg/23mg, or phen-top ER 15mg/92mg in a 2:1:2 ratio.[15] Significant weight loss versus placebo was seen in both phen-top ER treatment groups, but weight loss in the 15mg/92mg group was significant over that in the 3.75mg/23mg group (p<0.0001 for all). Nearly one-third of patients in the 15mg/92mg group lost ≥ 15% of BW. Percent weight loss did not significantly differ between baseline BMI readings. Most secondary outcome measures, such as fasting serum glucose, triglycerides and blood pressure (p<0.001 for all) were significantly improved in patients in the 15mg/92mg group, but not the 3.75mg/23mg group.[15]

CONQUER and its extension study SEQUEL were each 1 year randomized trials assessing the safety and effectiveness of two doses of phen-top ER versus placebo. In CONQUER, patients were assigned in a 2:1:2 ratio to placebo, phen-top ER 7.5mg/46mg, or phen-top ER 15mg/92mg.[6] SEQUEL was a continuation trial of CONQUER, with patients volunteering to continue receiving their originally assigned doses of placebo or phen-top ER during CONGQUER.[16]

In the CONQUER study, both treatment groups had significantly more weight loss of ≥ 5% compared to placebo (p<0.001 for both), though there was a higher percentage of patients achieving that benchmark in the 15mg/92mg group than the 7.5mg/46mg group (70% vs. 62% respectively). SEQUEL found similar results, and weight loss was largely sustained through year two of the study in phen-top ER groups compared with placebo (p<0.0001 for both groups). Patients with the highest baseline BMI (40-45 kg/m^2) had greater weight loss on the 15mg/92mg dose of phen-

Table 3 | Overview of Major Clinical Trials for Phen-Top ER

	Treatment Groups	Inclusion Criteria	Results
EQUIP[15] 1 year trial n = 1267	2:1:2 ratio PL, Phen-top ER 3.75mg/ 23mg, Phen-top ER 15mg/92mg	18-70 years of age BMI ≥ 35 kg/m^2	Phen-top ER 15mg/92mg had sig. > WL vs. 3.75mg/23mg, who lost sig. > PL (p<0.0001 for all) 2º end points sig. improved in only 15mg/92mg pts
CONQUER[6] 1 year trial n = 2847	2:1:2 ratio PL Phen-top ER 7.5mg/46mg Phen-top ER 15mg/92mg	BMI 27-45 kg/ m2 AND ≥ 2 weight -related comorbidities (ie. HTN, DM, dyslipidemia)	Phen-top ER 15mg/92mg pts had the highest rate of >= 5% WL over PL (70% vs. 21% PL) Phen-top ER 7.5mg/46mg also had sig. >WL vs. PL, though < 15mg/92mg (62% vs. 21% PL) Most sig. improvements in 2º end points in pts with pre-existing comorbidities
SEQUEL[16] 1 year trial (extension) n = 676			Sustained WL over 108 wks seen in both phen-top ER groups over PL (p<0.0001) Both doses had similar effects in low BMI Phen-top ER 15mg/92mg showed sig. improved WL in severely obese patients (p<0.0016 vs. 7.5mg/46mg)

> = more than, < = less than, 2º = secondary, BMI = body mass index, DM = diabetes mellitus, HTN = hypertension, n = sample size, Phen-top ER = phentermine-topiramate ER, PL = placebo, Sig. = significantly, wk = week(s), WL = weight loss

top ER, while there was no significant difference between doses in patients with lower baseline BMI (p=0.0016 vs. 7.5mg/46mg group). However, enrollment was voluntary in the extension trial, so the results may be confounded by the fact that patients satisfied with their weight loss were more likely to continue the trial.[16]

Adverse Effects

Lorcaserin and phen-top ER have each been associated with the potential of severe adverse effects. Echoes of fenfluramine have given rise to concern for the development of valvulopathy with lorcaserin despite its selectivity for the 5-HT$_{2C}$ receptor.[5,11,13,14] Five patients taking lorcaserin 10 mg BID in the BLOOM-DM study developed new echocardiographic valvulopathy at week 24 compared with four patients on placebo (2.5% vs. 1.9%, p=0.750) and three patients on lorcaserin 10 mg QD (3.9% , p=0.395 vs. placebo) (**Table 4**).[14] In the BLOOM study, 2.7% of patients taking lorcaserin 10 mg BID developed FDA-defined valvulopathy versus 2.3% of patients in the placebo group (p=0.70).[13] Similar results were found in the BLOSSOM study, with new echocardiographic findings indicating valvulopathy developed in 2.0% of patients taking lorcaserin 10 mg BID, 1.4% of patients taking lorcaserin 10 mg QD, and 2.0% of patients in the placebo group.[5]

Phen-top ER was previously denied FDA approval under the brand name Qnexa® due to safety concerns for teratogenic effects and increased heart rate. A small increase in mean heart rate of 1.7 beats per minute (P<0.0001 vs. placebo) was seen in the 15mg/92mg phen-top ER group in the CONQUER study, while nonsignificant effects were seen in lower dose phen-top ER and placebo (**Table 5**).[6] Heart rate also increased nonsignificantly in the 15mg/92mg phen-top ER group of the EQUIP study, with nonsignificant mean decreases in heart rate in the 3.75mg/23mg phen-top ER group and the placebo group.[15] In addition to cardiovascular concerns, topiramate has been associated with mental status changes.[19] Each study used regular assessments with the nine item Patient Health Questionnaire depression

Table 4 | Most common Adverse Events for Lorcaserin therapy vs. Placebo, year 1 [5,13]

	Placebo (%)	Lorcaserin 10 mg BID (%)
Headache	9.2-11	15.6-18.0
UR symptoms	11.9-12.6	12.7-14.8
Dizziness	3.8-3.9	8.2-8.7
Nausea	5.3-5.4	7.5-9.1
Sinusitis	7.3-8.2	7.2-7.6
UTI	4.8-6.1	6.7
Constipation	3.8-4.0	5.0-6.7
Fatigue	3.0-4.1	6.0-8.4
Dry mouth	2.3	5.2-5.4
Reported in >=5% patients in the BLOOM-DM study:[14]		
HTN	3.2	5.1
Symptomatic hypoglycemia	6.3	7.4
Cough	4.4	8.2

HTN = hypertension, UR = upper respiratory, UTI = urinary tract infection

Table 5 | Most Common Adverse Events for Phen-top ER vs. Placebo [6,15,16]

	Placebo (%)	Phen-top ER 7.5mg/46mg (%)	Phen-top ER 15mg/92mg (%)
Paresthesia	1.9-2.6	13.7-14.0	18.8-21.0
Dry mouth	2.0-3.7	13.0-13.7	17.0-21.0
Constipation	6.0-7.1	15-16.3	14.1-21.0
URTI	10.9-20.7	12.0-15.0	12.3-18.6
Headache	9.0-10.1	5.2-7.0	9.5-11.9
Dysgeusia	1.0-1.8	7.0-11.8	8.4-13.2
Insomnia	4.9-6.6	6.0-7.8	7.8-10.0
Nausea	4.0-5.7	3.3-4.0	6.4-7.2
Sinusitis	5.5-8.4	7.0-11.1	7.2-13.2
Dizziness	2.6-4.1	5.9-7.0	5.7-10.0

Phen-top ER = phentermine-topiramate extended release, URTI = upper respiratory tract infection

scale (PHQ-9) and/or the Columbia Suicide Severity Rating Scale (C-SSRS), with no significant increase in suicidality in any study.[6,15,16] Patients taking 15mg/92mg phen-top ER in the EQUIP trial had a significant increase in both anxiety and irritability, which occurred mainly in the early phase of treatment, and resolved on drug discontinuation.[15] Concerns for teratogenicity (cleft palate) with topiramate have been addressed by FDA Risk Evaluation and Mitigation Strategies (REMS) regulations.[19,20]

Dosage and Cost

Dosing and titration differ for phen-top ER and lorcaserin (**Table 6**). Phen-top ER will only be available by mail order through specially certified pharmacies.[21] Insurance coverage for either product is unlikely and the bulk of prescription costs is likely to fall solely on the patient.[22,23]

The FDA has required postmarketing surveillance for each drug. Lorcaserin was approved with requirements to complete six postmarketing surveillance studies, including a long-term cardiovascular outcomes trial to assess for heart attack and stroke. Phen-top ER was approved with a REMS program, comprising a Medication Guide that must be distributed to each patient as well as prescriber training and pharmacy certification.[21] The manufacturer of phen-top ER is also required to complete ten postmarketing trials, including a long-term cardiovascular outcomes trial and one in pediatric patients to assess for heart attack and stroke.[20]

Summary

Lorcaserin and phen-top ER are the first new weight loss drugs approved by the FDA in over a decade.[24] Each were shown to significantly induce weight loss of 5-10% from baseline BW as adjunct therapy in patients with elevated BMI. In the BLOOM, BLOOM-DM, and BLOSSOM trials, lorcaserin significantly im-

Table 6 | Dosage and Administration of lorcaserin and phen-top ER [11,12, 22, 23]

	Lorcaserin	Phen-top ER
Dosage and Administration	1 tablet (10 mg) BID	Initial: 3.75mg/23mg QAM x 14 days Titrate up: 7.5mg/46mg QAM Severe renal or moderate hepatic impairment: do not exceed 7.5mg/46mg QD Avoid evening dose to prevent insomnia Titrate off slowly to prevent possible seizure
Monitoring	Percent weight loss D/c if 5% WL not achieved by week 12	Percent weight loss D/c if 3% WL not achieved after 12 weeks at 7.5mg/46mg or if 5% WL is not achieved after 12 weeks at 15mg/92mg Pregnancy test at baseline then monthly
Cost*	Estimated at $4 per day[23]	Estimated at $6 per pill[23]

BID = twice daily, D/c = discontinue, phen-top ER = phentermine-topiramate extended release, QAM = every morning, QD = every day, WL = weight loss. *As neither drug is commercially available at this time, costs are speculated

proved the percentage of patients achieving 5% loss of baseline BW modestly sustained through the second year of therapy.[5,13,14] Dosed twice daily, lorcaserin has not been shown to have the same valvulopathy association as fenfluramine due to its improved 5-HT_{2C} selectivity.[5,13] EQUIP, CONQUER, and SEQUEL demonstrated the weight loss effects of phen-top ER with significant proportions of patients achieving 5- and 10% weight loss compared to placebo, with sustained weight loss through year two.[6,15,16] However, phen-top ER is associated with more side effects than placebo, including paresthesia, and is approved with a REMS program for women of childbearing potential.[6,20] Phen-top ER will only be available through specially licensed mail-order pharmacies.[21] Finally, pricing may be an issue for patients as insurance companies are unlikely to cover therapy and costs are speculated to be as high as $2 per pill for lorcaserin and $6 per pill for phen-top ER.[22,23]

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Clinical Trial Update

Risk of diabetes with statins: an update— Recent concerns surrounding statins and the risk of incident diabetes has led the FDA to update the labeling of all statins to indicate an increased risk for developing diabetes. Much of the concern stems from the JUPITER trial[1] in which patients receiving rosuvastatin 20 mg daily were found to have a 27% increased risk for physician diagnosed diabetes compared to placebo. The long-term consequences of the apparent increased risk for diabetes and whether the benefits of statin therapy outweigh the risks is unknown.

As the JUPITER trial was the centerpiece elucidating the increased risk of diabetes Ridker and colleagues, the original authors of JUPITER, re-analyzed data from JUPITER to determine if the benefits of statin therapy were outweighed by the risk of incident diabetes.[2]

Briefly, JUPITER[1] was a prospective randomized trial comparing rosuvastatin 20 mg daily and placebo in patients without cardiovascular disease who had a baseline low-density lipoprotein (LDL) less than 130 mg/dL and a high-sensitivity c-reactive protein (hsCRP) greater than 2 mg/L; diabetes (fasting blood glucose > 126 mg/dL) was a prespecified exclusion criteria. The primary outcome was a composite of major cardiovascular (CV) events which included non-fatal myocardial infarction (MI) or stroke, hospitalization for unstable angina, revascularization procedure, or CV death. After a median follow-up of 1.9 years the study was prematurely discontinued as rosuvastatin reduced the risk for the primary outcome by 44% compared to placebo (HR 0.56, p<0.00001). In the rosuvastatin group 270 subjects were diagnosed with diabetes compared to 216 subjects receiving placebo. The differences in the median hemoblogin A1c (HbA1c) values for rosuvastatin and placebo were not clinically different (5.9% vs. 5.8%, respectively), but the difference was found to be statistically significant (p=0.001).

In the present analysis of the JUPITER results Ridker and colleagues conducted a post-hoc literature search and identified four major risk factors for diabetes: metabolic syndrome, impaired fasting glucose (fasting glucose 100-125 mg/dL), HbA1c greater than 6%, or a body-mass index (BMI) of 30 kg/m^2 or more at baseline. In total 17,603 subjects were included in the analysis: 6095 had no major risk factors and 11,508 had one or more major risk factors.

To address the CV and diabetes hazards or therapy with rosuvastatin Cox proportional hazard regression models were used to calculate the first major CV event or death and for incident diabetes. As a conservative measure all cases of physician diagnosed diabetes were included whether or not the results were confirmed by formal laboratory testing.

For subjects with at least one major risk factor for diabetes treatment with rosuvastatin reduced the risk for the primary endpoint by 39% (HR 0.61, 95% confidence interval [CI] 0.47-0.79, p=0.0001) and increased the risk for diabetes by 28% (HR 1.28, 95% CI 1.07-1.54, p=0.01). Treatment with rosuvastatin prevented 134 CV events or deaths while 54 cases of diabetes were newly diagnosed, suggested the CV benefits outweigh the risks for incident diabetes. For subjects without a major risk factor for diabetes treatment reduced the primary endpoint by 52% (HR 0.48, 95% CI 0.33-.068, p=0.0001) without increasing the risk for diabetes (HR 0.99, p=0.99). Rosuvastatin did not lead to any new cases of diabetes while 86 CV events or deaths were prevented in these subjects, again confirming the positive benefit-to-risk ratio for treatment with rosuvatatin.

Notably, the risk for diabetes did not differ substantially based on the number of major risk factors present. In subjects with one risk factor the HR for development of physician diagnosed diabetes was 1.2 while the HR was 1.4 for those subjects with all four major risk factors. Treatment with rosuvastatin did shorten the average time to diagnosis of diabetes by 5.4 weeks (84.3 weeks in subjects receiving rosuvastatin compared to 89.7 weeks for subjects receiving placebo).

Echoing the current recommendations of the FDA he authors conclude that rosuvastatin does appear to increase the risk of physician diagnosed diabetes when compared to placebo. However, this increased risk for diabetes is not outweighed by the CV benefits provided over a median follow-up of two years and therefore statins should remain a cornerstone therapy for CV risk reduction.

1. Ridker PM, et al. New Engl J Med 2008;359:2195-207.
2. Ridker PM, et al. Lancet 2012;380:565-71.

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