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ORIGINAL ARTICLE

Effect of lorcaserin in different age groups: a post hoc analysis of patients from the BLOOM, BLOSSOM and BLOOM-DM studies

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Summary

Introduction

The elderly population is projected to be the fastest growing group of individuals with obesity group in the United States. As such, there is merit in examining factors that contribute to healthy aging and weight management. The effects of newer weight loss medications approved after 2013 have been studied but are not often assessed specifically in older persons.

Methods

This post hoc analysis evaluated the magnitude of weight loss in adults across age quartiles with lorcaserin, a serotonin (5-HT) 2C receptor agonist indicated as an adjunct to a reduced-caloric diet and increased physical activity for chronic weight management. Data from three lorcaserin pivotal phase 3 studies were used in this analysis. Data for patients with overweight/obesity without type 2 diabetes (T2D; BLOOM/BLOSSOM; body mass index [BMI] 27.0–29.9 kg/m^2 and ≥1 comorbidity or BMI 30.0–45.0 kg/m^2) and patients with overweight/obesity with T2D (BLOOM-DM; BMI 27.0–45.0 kg/m^2) were used. Patients were randomized to receive lorcaserin 10 mg twice daily or placebo in addition to diet and exercise for 52 weeks. Age quartiles between the studies differed as the T2D population was on average, 9 years older.

Results

This analysis shows that lorcaserin was associated with improved weight loss relative to placebo regardless of age. Importantly, these results were consistent for patients with and without T2D. Interestingly, the magnitude of weight loss for lorcaserin appeared to increase with increasing age. In patients without T2D, odds of achieving ≥5% and ≥10% reduction in body weight at 52 weeks were significantly higher for patients >36 years. Lorcaserin was well tolerated in all patients across all quartiles including the oldest quartile.

Conclusions

In summary, this post hoc analysis demonstrates that lorcaserin treatment in patients with and without T2D was safe and effective at reducing weight across all age groups analysed. Weight loss appeared to be greater for older patients; additional analyses are warranted to confirm these findings and to better understand the factors for improved weight loss.

Keywords: Aging, Cardiometabolic, Functionality, Weight loss.

Introduction

Obesity is associated with significant health risks and impacts individuals of all age groups (1,2). The prevalence of obesity among U.S. adults was 39.8%, with 35.7% of adults aged 20–39, 42.8% of adults aged 40–59, and 41.0% of adults over the age of 60 considered obese (1). Projections show a steady increase in obesity rates

until at least 2030, with obesity levels in the United States expected to be 47% of the population by 2030 (3). Obesity in older adults (>60 years) is a particular concern, as they are projected to be the fastest growing obesity group in the United States (3–6). Projected rates of obesity for the population aged 65 years and over in 2050 are 83.7 million, an almost twofold increase in the estimated population of 43.1 million people reported in 2012 (3).

Lorcaserin is a selective serotonin 2C (5-HT2C) receptor agonist indicated as a treatment for chronic weight management in combinations with a reduced calorie diet and increased physical activity for in adults with an initial body mass index (BMI) of ≥30 kg m^2 (obese) or BMI ≥ 27 kg m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g. hypertension, dyslipidaemia or type 2 diabetes [T2D]) (7). The mechanism of the 5-HT2C receptor in appetite regulation is mediated via the hypothalamic melanocortin system and has been demonstrated to induce hypophagia by increasing within meal satiation and post meal satiety (8). The 5-HT2C receptor agonist does not increase blood pressure or induce cardiac events and is not highly expressed in heart valve tissue as compared with the older agents fenfluramine and dexfenfluramine which were 5-HT2B receptor agonists. (9)

Lorcaserin has been evaluated clinically for weight loss in three randomized controlled pivotal trials, the BLOOM, BLOSSOM and BLOOM DM studies, that included over 6,000 patients (10–14). Given the impact of obesity on health risks across the age spectrum, the objective of this retrospective subgroup analysis was to evaluate the effect of lorcaserin on weight loss in patients from various age groups from the database of the phase 3 studies and to evaluate if lorcaserin was effective for reducing weight across all age groups for with or without T2D.

Materials and methods

Study design and treatments

This post hoc analysis was performed on the three phase 3 studies in patients with overweight or obesity: BLOOM/BLOSSOM (patients without T2D) and BLOOM-DM (patients with T2D) (10–14). The detailed design of BLOOM (NCT00395135, ClinicalTrials.gov), BLOSSOM (NCT00603902, ClinicalTrials.gov) and BLOOM-DM (NCT00603291, ClinicalTrials.gov), the study-specific efficacy and safety end points, study procedures and the inclusion and exclusion criteria have been published previously (12–14). Briefly, the three trials included in this analysis were phase 3, randomized and double-blind and placebo-controlled clinical trials designed to evaluate the efficacy and safety of lorcaserin in overweight and obese patients. Unlike BLOOM and BLOSSOM, BLOOM-DM was specific for patients with T2D mellitus. BLOOM was a 2-year trial, whereas BLOSSOM and BLOOM-DM were 1-year studies. The BLOOM and BLOSSOM studies were combined because they have very similar patient populations, whereas the BLOOM-DM was analysed separately due to the different patient population relative to BLOOM/BLOSSOM studies (i.e. T2D, older population [average age of 53 years vs. 44 years], and different gender profile [54% women vs. 82% women]) (10–14).

Patients included in this analysis were randomized to treatment with lorcaserin 10 mg twice daily (BID) in addition to diet and exercise, or placebo plus diet and exercise. The studies were conducted at academic and private research sites in the United States under the guidelines of the Declaration of Helsinki. Institutional review boards reviewed and approved the protocols for each research site. All patients provided written informed consent before participation in the trials.

Analyses presented herein evaluated the impact of age on weight loss associated with lorcaserin (10 mg BID) versus placebo in pooled data from the BLOOM and BLOSSOM, as well as the BLOOM-DM trial, collected through week 52. The working hypothesis for this analysis was that lorcaserin-associated weight loss would not change significantly based on age for either patients with or without T2D.

Endpoints and statistical analyses

Primary endpoints for these analyses follow the key efficacy endpoint in the pivotal studies, including proportion of patients with a reduction in the baseline body weight of 5% or more at the end of year 1, change in weight between baseline and the end of year 1 and proportion of patients with a reduction in the baseline body weight of 10% or more at the end of year 1. Additional endpoints analysed included standard safety assessments. Baseline demographics and clinical characteristics were summarized across four age quartiles for patients with and without TDM; no formal statistical comparisons were made. Adverse events and discontinuation rates were summarized descriptively across the age groups.

For the analyses, comparison were planned among the age subgroups as well as between the two treatment conditions (with or without T2D). Age quartiles were generated from pooled BLOOM and BLOSSOM studies, and BLOOM-DM, respectively. To generate the quartiles, data were ranked by age, and the data set was divided into four equal groups. A modified intention-to-treat analysis was used and defined as all patients who

received at least one dose of study medication and had at least one post-baseline body weight assessment. Last observation carried forward was employed for missing data. The safety population includes all randomized patients who received at least one dose of the study medication.

A logistic regression model was used for the proportion of patients who lost ≥5% or ≥10% of body weight. The BLOOM/BLOSSOM studies used the model which included effects for treatment, study and baseline body weight (kg). The BLOOM-DM study included within the model effects the same as for BLOOM/BLOSSOM in addition to baseline antihyperglycemic treatment stratum (metformin or sulfonylurea [+/− metformin]), and baseline glycated haemoglobin (A1C) stratum (<9% or ≥9%).

Change in weight was analysed using analysis of covariance models. The model used for the BLOOM/BLOSSOM studies included treatment and study as factors and baseline body weight (kg) as a covariate. The model for the BLOOM-DM study included treatment, baseline antihyperglycemic treatment stratum (metformin or sulfonylurea [+/− metformin]), and baseline A1C stratum (<9% or ≥9%) as factors, and baseline body weight (kg) as a covariate. The randomization was stratified by antihyperglycemic treatment and baseline A1C stratums. Baseline weight was included to adjust as part of the covariance model.

Results

Demographic and baseline characteristics

Demographic and baseline characteristics for patients without T2D and with T2D are presented in Tables 1 and 2, respectively. There were a total of 6,136 and 499 patients included in this analysis in the pooled BLOOM/BLOSSOM (without T2D) and BLOOM-DM (with T2D) populations. The age quartiles for BLOOM/BLOSSOM were: ≤36 years, >36 to ≤45 years, >45 to ≤53 years and >53 years. BLOOM-DM age quartiles were ≤47 years, >47 to ≤54 years, >54 to ≤60 years and >60 years. The patient populations in BLOOM and BLOSSOM consisted of men and women aged 18–66 years who were categorized as having obesity with a BMI of 30 to 45 kg/m^2 with or without a co-morbid condition, or who were overweight as defined with a BMI of 27 to 29.9 kg/m^2 and at least one co-morbidity. A summary of oral antidiabetic medication use by age quartile for patients with T2D (BLOOM-DM) is presented in Table 3. The distribution of oral antidiabetic medication (metformin

Table 1 Demographic and baseline characteristics by age quartile for patients without T2D (BLOOM/BLOSSOM)

	≤36 Years		>36 to ≤45 Years		>45 to ≤53 Years		>53 Years	
Demographic/baseline characteristic	Lorcaserin (*N* = 856)	Placebo (*N* = 803)	Lorcaserin (*N* = 770)	Placebo (*N* = 784)	Lorcaserin (*N* = 735)	Placebo (*N* = 704)	Lorcaserin (*N* = 737)	Placebo (*N* = 747)
Age (years)								
Mean (SD)	29.3 (5.1)	29.4 (4.8)	41.2 (2.6)	41.2 (2.6)	49.6 (2.3)	49.5 (2.3)	58.6 (3.3)	58.7 (3.3)
Gender, *N* (%)								
Male	134 (15.7)	125 (15.6)	110 (14.3)	126 (16.1)	134 (18.2)	141 (20.0)	187 (25.4)	185 (24.8)
Female	722 (84.3)	678 (84.4)	660 (85.7)	658 (83.9)	601 (81.8)	563 (80.0)	550 (74.6)	562 (75.2)
Race, *N* (%)								
Caucasian	477 (55.7)	443 (55.2)	476 (61.8)	472 (60.2)	529 (72.0)	503 (71.4)	629 (85.3)	628 (84.1)
African American	195 (22.8)	183 (22.8)	179 (23.2)	188 (24.0)	134 (18.2)	126 (17.9)	68 (9.2)	70 (9.4)
Hispanic	160 (18.7)	152 (18.9)	94 (12.2)	108 (13.8)	57 (7.8)	66 (9.4)	28 (3.8)	41 (5.5)
Asian	6 (0.7)	7 (0.9)	7 (0.9)	4 (0.5)	6 (0.8)	4 (0.6)	5 (0.7)	3 (0.4)
Other	18 (2.1)	18 (2.2)	14 (1.8)	12 (1.5)	9 (1.2)	5 (0.7)	7 (0.9)	5 (0.7)
BMI (kg/m^2)								
Mean (SD)	36.9 (4.2)	36.8 (4.2)	36.5 (4.2)	36.1 (4.2)	35.6 (4.2)	35.9 (4.1)	35.3 (4.3)	35.4 (4.1)
BMI group, *N* (%)								
<30	18 (2.1)	17 (2.1)	19 (2.5)	33 (4.2)	45 (6.1)	27 (3.8)	62 (8.4)	45 (6.0)
30 to <35	300 (35.0)	285 (35.5)	282 (36.6)	317 (40.4)	309 (42.0)	296 (42.0)	314 (42.6)	337 (45.1)
35 to <40	320 (37.4)	298 (37.1)	278 (36.1)	263 (33.5)	251 (34.1)	257 (36.5)	243 (33.0)	242 (32.4)
40 to <45	206 (24.1)	186 (23.2)	184 (23.9)	164 (20.9)	126 (17.1)	116 (16.5)	109 (14.8)	115 (15.4)
≥45	12 (1.4)	17 (2.1)	7 (0.9)	7 (0.9)	4 (0.5)	8 (1.1)	9 (1.2)	8 (1.1)

Modified intent-to-treat population with last observation carried forward. BMI, body mass index; lorcaserin 10 mg BID; SD, standard deviation; T2D, type 2 diabetes.

Table 2 Demographic and baseline characteristics by age quartile for patients with T2D (BLOOM-DM)

	≤47 Years		>47 to ≤54 Years		>54 to ≤60 Years		>60 Years	
Demographic/baseline characteristic	Lorcaserin (*N* = 62)	Placebo (*N* = 74)	Lorcaserin (*N* = 57)	Placebo (*N* = 68)	Lorcaserin (*N* = 79)	Placebo (*N* = 48)	Lorcaserin (*N* = 53)	Placebo (*N* = 58)
Age (years)								
Mean (SD)	41.5 (4.7)	40.6 (5.6)	50.5 (2.0)	51.2 (2.2)	57.4 (1.7)	57.8 (1.7)	62.9 (1.5)	63.2 (1.5)
Gender, *N* (%)								
Male	27 (43.5)	34 (45.9)	24 (42.1)	28 (41.2)	38 (48.1)	23 (47.9)	27 (50.9)	28 (48.3)
Female	35 (56.5)	40 (54.1)	33 (57.9)	40 (58.8)	41 (51.9)	25 (52.1)	26 (49.1)	30 (51.7)
Race, *N* (%)								
Caucasian	28 (45.2)	44 (59.5)	28 (49.1)	42 (61.8)	52 (65.8)	35 (72.9)	40 (75.5)	44 (75.9)
African American	15 (24.2)	12 (16.2)	15 (26.3)	15 (22.1)	16 (20.3)	6 (12.5)	8 (15.1)	10 (17.2)
Hispanic	15 (24.2)	12 (16.2)	10 (17.5)	8 (11.8)	9 (11.4)	4 (8.3)	4 (7.5)	2 (3.4)
Asian	4 (6.5)	2 (2.7)	4 (7.0)	2 (2.9)	2 (2.5)	2 (4.2)	0	2 (3.4)
Other	0	4 (5.4)	0	1 (1.5)	0	1 (2.1)	1 (1.9)	0
BMI (kg/m^2)								
Mean (SD)	36.9 (4.4)	36.3 (4.4)	36.1 (4.2)	36.2 (4.7)	36.2 (4.5)	35.6 (4.5)	35.3 (4.7)	34.9 (4.3)
BMI group, *N* (%)								
<30	6 (9.7)	6 (8.1)	3 (5.3)	7 (10.3)	5 (6.3)	6 (12.5)	7 (13.2)	5 (8.6)
30 to <35	11 (17.7)	24 (32.4)	19 (33.3)	20 (29.4)	28 (35.4)	15 (31.3)	21 (39.6)	27 (46.6)
35 to <40	27 (43.5)	27 (36.5)	24 (42.1)	24 (35.3)	26 (32.9)	17 (35.4)	14 (26.4)	18 (31.0)
40 to <45	18 (29.0)	17 (23.0)	11 (19.3)	17 (25.0)	20 (25.3)	10 (20.8)	11 (20.8)	7 (12.1)
≥45	0	0	0	0	0	0	0	1 (1.7)

Modified intent-to-treat population with last observation carried forward. BMI, body mass index; lorcaserin 10 mg BID; SD, standard deviation; T2D, type 2 diabetes.

Table 3 Oral antidiabetic medication use by age quartile for patients with T2D (BLOOM-DM)

	≤47 Years		>47 to ≤ 54 Years		>54 to ≤ 60 Years		>60 Years	
Oral antidiabetic medications used, *N* (%)	Lorcaserin (*N* = 62)	Placebo (*N* = 74)	Lorcaserin (*N* = 57)	Placebo (*N* = 68)	Lorcaserin (*N* = 79)	Placebo (*N* = 48)	Lorcaserin (*N* = 53)	Placebo (*N* = 58)
Metformin[a]	58 (93.5)	67 (90.5)	51 (89.5)	60 (88.2)	75 (94.9)	47 (97.9)	48 (90.6)	52 (89.7)
SFU	4 (6.5)	7 (9.5)	6 (10.5)	8 (11.8)	4 (5.1)	1 (2.1)	5 (9.4)	6 (10.3)

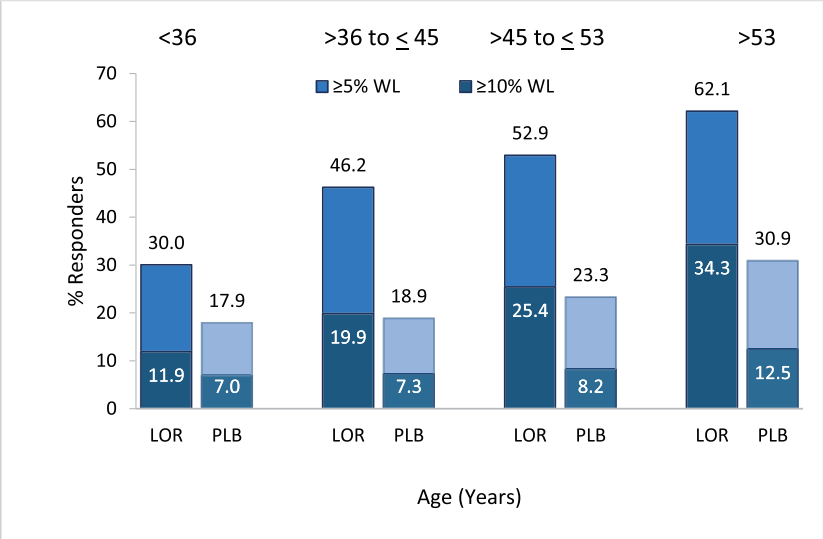
[a]Includes patients taking metformin with or without SFU. Modified intent-to-treat population with last observation carried forward. Lorcaserin 10 mg BID; SFU, sulfonylurea; T2D, type 2 diabetes.

and sulfonylureas) use in patients with T2D was consistent across age quartiles.

Weight loss efficacy

The results in patients without T2D (BLOOM/BLOSSOM) achieving ≥5% and ≥10% weight loss are shown in Figure 1. In each age quartile, the percentage of patients without T2D achieving ≥5% weight loss with lorcaserin treatment was higher compared to that observed in the placebo groups (≤36: LOR = 30.0% vs. PLB = 17.9; >36 to ≤45: 46.2% vs. 18.9%; >45 to ≤53: 52.9% vs. 23.3%; >53: 62.1% vs. 30.9%). Likewise, the percentage of patients without T2D (BLOOM/BLOSSOM) achieving ≥10% weight loss with lorcaserin treatment was also higher compared to that observed in the placebo groups (≤36: LOR = 11.9% vs. PLB = 7.0; >36 to ≤45: 19.9% vs. 7.3%; >45 to ≤53: 25.4% vs. 8.2%; >53: 34.3% vs. 12.5%). The magnitude of weight loss with lorcaserin increased with increasing age for each successive group for both ≥5% and ≥10% weight loss (Figure 1) ($p \leq 0.005$).

The ≥5% weight loss odds ratios for patients without T2D were 2 (CI: 1.6, 2.5), 3.7 (3.0, 4.7), 3.7 (3.0, 4.6) and 3.7 (3.0, 4.6) for the ≤36, >36 to ≤45, >45 to ≤53 and >53 groups, respectively. Likewise, for the ≥10% weight loss analysis, the odds ratios for patients without diabetes were 1.8 (CI: 1.3, 2.6), 3.2 (2.3, 4.4), 3.8 (2.8, 5.2) and 3.7 (2.8, 4.8) for the ≤36, >36 to ≤45, >45 to ≤53 and



Age (Years)	≤36		>36 to ≤ 45		>45 to ≤ 53		>53	
N (Total)	856	803	770	784	735	704	737	747
N, 5% WL	257	144	356	148	389	164	458	231
N, 10% WL	102	56	153	57	187	58	253	93

Figure 1 Patients without T2D (BLOOM/BLOSSOM) achieving ≥5% and ≥10% weight loss by age quartile. *P*-value for treatment by age quartile interaction <0.001. *P*-value for treatment by age quartile interaction = 0.005. Modified intent-to-treat population with last observation carried forward. CI, confidence interval; LOR, lorcaserin 10 mg BID; PLB, placebo; T2D, type 2 diabetes; WL, weight loss.

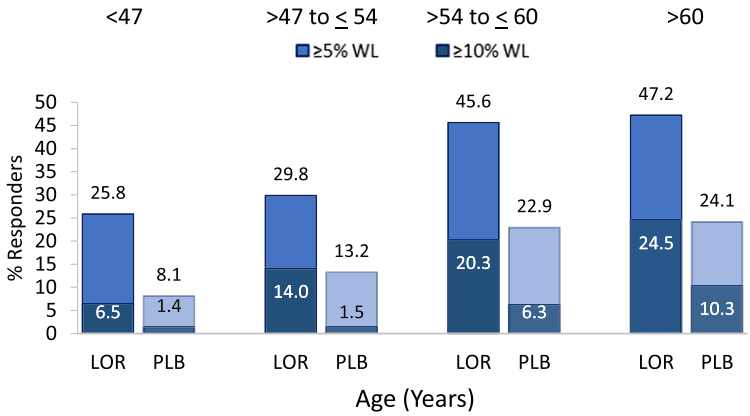
>53 groups, respectively. In patients without T2D, the odds of achieving ≥5% reduction in body weight at week 52 are significantly higher for patients >36 years ($p < 0.0001$). Similar results were observed in lorcaserin-treated patients achieving ≥10% body weight reduction and absolute weight loss.

Table 4 shows data for absolute weight loss by age quartile in patients without T2D. All patients in the lorcaserin groups had significant reductions in weight loss compared to placebo. The LS mean difference compared with placebo was −1.9, −3.3, −4.0 and −4.1 for the ≤36, >36 to ≤45, >45 to ≤53 and >53 age groups, respectively. The results in patients with T2D achieving ≥5% and ≥10% weight loss are shown in Figure 2. In each age quartile, the percentage of patients with T2D achieving ≥5% weight loss with lorcaserin treatment was higher

Table 4 Absolute (kg) weight loss by age quartile in patients without T2D (BLOOM/BLOSSOM)

				Comparison with placebo	
Treatment	Number of patients	LS mean (SE)	95% CI	Difference in LS means	(95% CI)
≤36 Years					
Lorcaserin	856	−3.6 (0.2)	(−4.0, −3.2)	−1.9	(−2.4, −1.3)
Placebo	803	−1.7 (0.2)	(−2.1, −1.3)	---	---
>36 to ≤45 Years					
Lorcaserin	770	−5.3 (0.2)	(−5.7, −4.9)	−3.3	(−3.9, −2.8)
Placebo	784	−2.0 (0.2)	(−2.4, −1.6)	---	---
>45 to ≤53 Years					
Lorcaserin	735	−6.6 (0.2)	(−7.1, −6.2)	−4.0	(−4.6, −3.3)
Placebo	704	−2.7 (0.2)	(−3.1, −2.2)	---	---
>53 Years					
Lorcaserin	737	−7.9 (0.2)	(−8.3, −7.4)	−4.1	(−4.8, −3.5)
Placebo	747	−3.7 (0.2)	(−4.2, −3.3)	---	---

P-value for treatment by subgroup interaction is <0.001. Modified intent-to treat population with last observation carried forward. CI, confidence interval; lorcaserin 10 mg BID; LS, least squares; SE, standard error; T2D, type 2 diabetes.



Age (Years)	≤47		>47 to ≤ 54		>54 to ≤ 60		>60	
N (Total)	62	74	57	68	79	48	53	58
N, 5% WL	16	6	17	9	36	11	25	14
N, 10% WL	4	1	8	1	16	3	13	6

Figure 2 Patients with T2D (BLOOM-DM) achieving ≥5% and ≥ 10% weight loss by age quartile. *P*-value for treatment by age quartile interaction = 0.920. *P*-value for treatment by age quartile interaction = 0.707. Modified intent-to-treat population with last observation carried forward. CI, confidence interval; lorcaserin 10 mg BID; PLB, placebo; T2D, type 2 diabetes; WL, weight loss.

compared to that observed in the placebo groups (≤47: LOR = 25.8% vs. PLB = 8.1%; >47 to ≤54: 29.8% vs. 13.2%; >54 to ≤60: 45.6% vs. 22.9%; >60: 47.2% vs. 24.1%). Likewise, the percentage of patients with T2D achieving ≥10% weight loss with lorcaserin treatment was also higher compared to that observed in the placebo groups (≤47: LOR = 6.5% vs. PLB = 1.4; >47 to ≤54: 14.0% vs. 1.5%; >54 to ≤60: 20.3% vs. 6.3%; >60: 24.5% vs. 10.3%).

For patients with T2D, no clear trend across age quartiles was observed. The ≥5% weight loss odds ratios for patients with T2D were 4.4 (CI: 1.6, 12.4), 3.1 (1.2, 7.9), 2.8 (1.3, 6.3) and 2.8 (1.2, 6.2) for the ≤47, >47 to ≤54, >54 to ≤60 and >60 groups, respectively. For the ≥10% weight loss analysis, the odds ratios for patients with T2D were 5.3 (CI: 0.5, 52.2), 12.0 (1.4, 102.5), 4.1 (1.1, 15.1) and 2.8 (1.0, 8.2) for the ≤47, >47 to ≤54, >54 to ≤60 and >60 groups, respectively.

Table 5 shows data for absolute weight loss by age quartile in patients withT2D. All patients in the lorcaserin groups had significant reductions in weight loss compared to placebo. The LS mean difference compared with placebo was −2.7, −2.3, −3.2 and −3.2 for the ≤47, >47 to ≤54, >54 to ≤60 and >60 age groups, respectively.

Table 5 Absolute (kg) weight loss by age quartile in patients with T2D (BLOOM-DM)

				Comparison with placebo	
Treatment	Number of patients	LS mean (SE)	95% CI	Difference in LS means	(95% CI)
≤47 Years					
Lorcaserin	62	−3.5 (0.5)	(−4.5, −2.5)	−2.7	(−3.9, −1.5)
Placebo	74	−0.8 (0.5)	(−1.7, 0.1)	---	---
>47 to ≤54 Years					
Lorcaserin	57	−3.4 (0.6)	(−4.6, −2.1)	−2.3	(−3.9, −0.8)
Placebo	68	−1.0 (0.6)	(−2.2, 0.2)	---	---
>54 to ≤60 Years					
Lorcaserin	79	−4.9 (0.9)	(−6.6, −3.2)	−3.2	(−5.4, −0.9)
Placebo	48	−1.8 (1.0)	(−3.8, 0.3)	---	---
>60 Years					
Lorcaserin	53	−7.9 (1.0)	(−10.0, −5.9)	−3.2	(−5.2, −1.2)
Placebo	58	−4.7 (1.0)	(−6.7, −2.7)	---	---

P-value for treatment by subgroup interaction – 0.833. Modified intent-to-treat population with last observation carried forward. CI, confidence interval; lorcaserin 10 mg BID; LS, least squares; SE, standard error; T2D, type 2 diabetes.

Safety

Overall results for adverse events during the studies is summarized in Tables 6 and 7. Frequency of adverse events and related adverse events were similar for lorcaserin relative to placebo for all age groups in patients with and without T2D. No deaths occurred during these studies for any age group in the lorcaserin groups, and

Table 6 Adverse event (AE) summary by age quartile in patients without T2D (BLOOM/BLOSSOM) in the safety population

	≤36 Years		>36 to ≤45 Years		>45 to ≤53 Years		>53 Years	
Event no. of patients (%)	Lorcaserin (*N* = 904)	Placebo (*N* = 870)	Lorcaserin (*N* = 793)	Placebo (*N* = 828)	Lorcaserin (*N* = 754)	Placebo (*N* = 728)	Lorcaserin (*N* = 744)	Placebo (*N* = 759)
All AE	683 (75.6)	611 (70.2)	655 (82.6)	602 (72.7)	646 (85.7)	564 (77.5)	661 (88.8)	629 (82.9)
All related AE	320 (35.4)	214 (24.6)	296 (37.3)	202 (24.4)	275 (36.5)	190 (26.1)	295 (39.7)	193 (25.4)
Serious AE	15 (1.7)	19 (2.2)	23 (2.9)	15 (1.8)	23 (3.1)	14 (1.9)	26 (3.5)	25 (3.3)
Related serious AE	3 (0.3)	2 (0.2)	3 (0.4)	2 (0.1)	1 (0.1)	0	2 (0.3)	2 (0.3)
Occurring in >5% in any quartile								
Headache	167 (18.5)	92 (10.6)	142 (17.9)	98 (11.8)	122 (16.2)	75 (10.3)	106 (14.2)	56 (7.4)
Upper respiratory tract infection	107 (11.8)	114 (13.1)	122 (15.4)	92 (11.1)	117 (15.5)	85 (11.7)	93 (12.5)	100 (13.2)
Nasopharyngitis	100 (11.1)	81 (9.3)	109 (13.7)	87 (10.5)	99 (13.1)	104 (14.3)	106 (14.2)	109 (14.4)
Nausea	76 (8.4)	57 (6.6)	65 (8.2)	44 (5.3)	66 (8.8)	25 (3.4)	57 (7.7)	44 (5.8)
Urinary tract infection	63 (7.0)	52 (6.0)	48 (6.1)	43 (5.2)	46 (6.1)	33 (4.5)	50 (6.7)	43 (5.7)
Dizziness	63 (7.0)	30 (3.4)	65 (8.2)	31 (3.7)	74 (9.8)	30 (4.1)	68 (9.1)	31 (4.1)
Back pain	48 (5.3)	37 (4.3)	44 (5.5)	44 (5.3)	56 (7.4)	47 (6.5)	53 (7.1)	50 (6.6)
Fatigue	45 (5.0)	34 (3.9)	65 (8.2)	30 (3.6)	54 (7.2)	18 (2.5)	65 (8.7)	32 (4.2)
Sinusitis	41 (4.5)	50 (5.7)	64 (8.1)	60 (7.2)	71 (9.4)	64 (8.8)	60 (8.1)	71 (9.4)
Diarrhoea	44 (4.9)	46 (5.3)	50 (6.3)	42 (5.1)	56 (7.4)	47 (6.5)	57 (7.7)	44 (5.8)
Dry mouth	33 (3.7)	18 (2.1)	40 (5.0)	20 (2.4)	45 (6.0)	19 (2.6)	51 (6.9)	17 (2.2)
Constipation	28 (3.1)	23 (2.6)	40 (5.0)	25 (3.0)	53 (7.0)	36 (4.9)	65 (8.7)	41 (5.4)
Arthralgia	14 (1.5)	16 (1.8)	37 (4.7)	29 (3.5)	53 (7.0)	47 (6.5)	45 (6.0)	58 (7.6)

Table 7 Adverse event (AE) summary by age quartile in patients with T2D (BLOOM-DM)

	≤47 Years		>47 to ≤54 Years		>54 to ≤60 Years		>60 Years	
Event no. of patients (%)	Lorcaserin (*N* = 62)	Placebo (*N* = 76)	Lorcaserin (*N* = 57)	Placebo (*N* = 70)	Lorcaserin (*N* = 82)	Placebo (*N* = 48)	Lorcaserin (*N* = 55)	Placebo (*N* = 58)
All AE	58 (93.5)	60 (78.9)	52 (91.2)	60 (85.7)	76 (92.7)	41 (85.4)	50 (90.9)	52 (89.7)
All related AE	23 (37.1)	18 (23.7)	28 (49.1)	21 (30.0)	32 (39.0)	11 (22.9)	25 (45.5)	18 (31.0)
Serious AE	3 (4.8)	4 (5.3)	5 (8.8)	4 (5.7)	5 (6.1)	3 (6.3)	3 (5.5)	6 (10.3)
Related serious AE	0	1 (1.3)	0	2 (2.9)	0	0	0	0
Occurring in >5% in any quartile								
Hypoglycaemia	23 (37.1)	12 (15.8)	11 (19.3)	12 (17.1)	24 (29.3)	12 (25.0)	17 (30.9)	17 (29.3)
Headache	13 (21.0)	6 (7.9)	10 (17.5)	5 (7.1)	8 (9.8)	4 (8.3)	6 (10.9)	3 (5.2)
Upper respiratory tract infection	11 (17.7)	7 (9.2)	8 (14.0)	10 (14.3)	8 (9.8)	10 (20.8)	8 (14.5)	10 (17.2)
Back pain	8 (12.9)	10 (13.2)	10 (17.5)	3 (4.3)	5 (6.1)	4 (8.3)	7 (12.7)	3 (5.2)
Nasopharyngitis	8 (12.9)	7 (9.2)	10 (17.5)	9 (12.9)	8 (9.8)	5 (10.4)	3 (5.5)	4 (6.9)
Oropharyngeal pain	7 (11.3)	4 (5.3)	2 (3.5)	2 (2.9)	2 (2.4)	2 (4.2)	0 (0.0)	4 (6.9)
Nausea	6 (9.7)	9 (11.8)	3 (5.3)	5 (7.1)	8 (9.8)	2 (4.2)	7 (12.7)	4 (6.9)
Urinary tract infection	4 (6.5)	4 (5.3)	6 (10.5)	7 (10.0)	8 (9.8)	3 (6.3)	5 (9.1)	1 (1.7)
Fatigue	2 (3.2)	1 (1.3)	3 (5.3)	4 (5.7)	11 (13.4)	1 (2.1)	3 (5.5)	4 (6.9)
Gastroenteritis viral	2 (3.2)	4 (5.3)	3 (5.3)	2 (2.9)	9 (11.0)	2 (4.2)	4 (7.3)	3 (5.2)
Cough	2 (3.2)	4 (5.3)	5 (8.8)	4 (5.7)	9 (11.0)	1 (2.1)	5 (9.1)	2 (3.4)
Procedural pain	2 (3.2)	1 (1.3)	2 (3.5)	1 (1.4)	3 (3.7)	3 (6.3)	6 (10.9)	0 (0.0)
Muscle strain	0 (0.0)	3 (3.9)	6 (10.5)	3 (4.3)	2 (2.4)	1 (1.3)	2 (3.6)	2 (3.4)

the frequency of serious AEs was low and generally comparable to placebo. AEs occurring at ≥5% for patients without T2D and ≥10% in patients with T2D in any quartile are also presented in Tables 6 and 7, respectively. The three most common AEs occurring at ≥5% in any quartile associated with lorcaserin treatment in patients without T2D were headache, upper respiratory tract infection and nasopharyngitis (Table 6). Overall, the most common AEs in patients with T2D across all ages was hypoglycaemia (defined as patient-reported suspected hypoglycaemia or "low blood glucose" and included all events regardless of documented low glucose, and with or without symptoms), headache and upper respiratory infection (Table 7). The most common AEs with lorcaserin treatment were consistent across age quartiles in patients without T2D, whereas there was some variation in most common AEs across age groups in patients with T2D, with no clear pattern relative to the age groups.

Results for the discontinuations from these studies for patients without and with T2D are depicted in Figures 3 and 4, respectively. Across all age groups, discontinuation rates for lorcaserin-treated groups were similar or lower relative to placebo-treated groups for patients with and without T2D. The percentage of patients without T2D who discontinued for any reason decreased with decreasing age (Figure 3). Rates of discontinuation due to adverse events were low and consistent across the age groups. Discontinuation rates for any reason for patients with T2D were largely consistent across the age groups and ranged for the lorcaserin groups from 26% to 40% (Figure 4). Similar to patients without T2D, rates of discontinuation due to adverse events were low and consistent across the age groups.

Discussion

The phase 3 weight loss studies, BLOOM, BLOSSOM and BLOOM DM were among the first clinical investigations assessing the effects of lorcaserin, a 5-HT2C agonist taken BID with diet and exercise for weight management in patients with overweight or obesity/diabetes with T2D (BLOOM DM) and at least one comorbid condition (hypertension, dyslipidaemia, cardiovascular disease, glucose intolerance or sleep apnoea). This analysis shows that lorcaserin was associated with improved weight loss relative to placebo regardless of age. Importantly, these results were consistent for patient with and without T2D. Interestingly, the magnitude of weight loss for lorcaserin appeared to increase with increasing age.

Slowing age related declines in health is an important public health concern, and therefore, the observation of larger weight loss with increasing age in this analysis may be particularly relevant for older patients. For example, in this analysis, patients in the oldest quartile (age 53 and older) had twice as many responders as the group less than 36 years of age. From this analysis, it is not clear what factors would be responsible for driving greater weight loss in older patients. Notably, overall discontinuation results appeared to be lower for older patients in this analysis and therefore one could speculate that improved adherence could lead to improved weight loss outcomes (15–18). Improved weight loss outcomes for older patients has been noted previously in the literature (15–18). For example, a systematic meta-analysis of randomized controlled trials evaluating weight loss interventions found some evidence that participants aged 60 or over lost more weight than younger participants (15). Likewise,

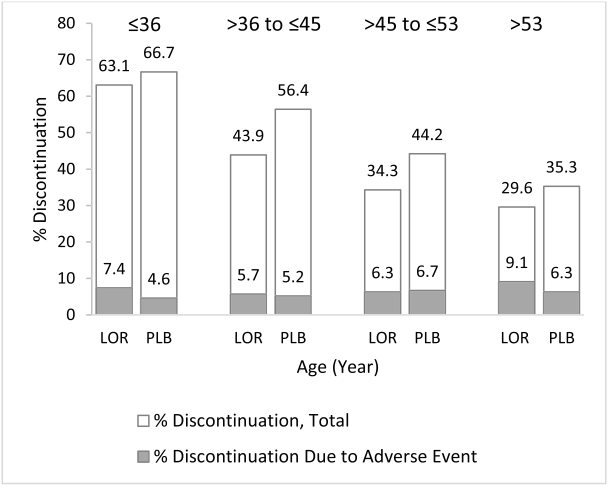


Figure 3 Percent discontinuation by age quartile in patients without T2D (BLOOM/BLOSSOM). All randomized patients. Lorcaserin 10 mg BID; PLB, placebo; T2D, type 2 diabetes.

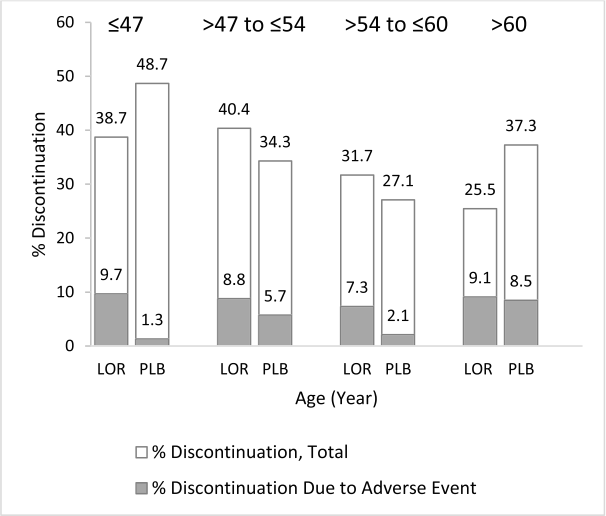


Figure 4 Percent discontinuation by age quartile in patients with T2D (BLOOM-DM). All randomized patients. Lorcaserin 10 mg BID; PLB, placebo; T2D, type 2 diabetes

in the Look AHEAD study, a randomized controlled trial that evaluated an intensive lifestyle intervention (ILI) on physical function found the ILI was actually more effective for the older volunteers (>65 years) than for younger ones (16–18). The authors of the Look AHEAD study also noted that age was not a negative factor with regard to behavioural change and that the findings may be because they were more compliant with diet and physical activity guidelines, including opting for more meal replacements and they came to meetings more regularly.

The safety results in this analysis are consistent with the known safety profile of lorcaserin in this patient population (10–14). This study demonstrates that treatment-related adverse events were largely consistent across age groups, did not increase in older patients relative to younger age groups and were comparable to placebo. Serious AEs and discontinuations due to AEs were low for all age ranges evaluated. There were no deaths in the lorcaserin groups during the course of these studies. These safety findings are particularly important in these patient populations, who are seeking to lose body weight but also have comorbid CV-related disease. In patients with T2D, the most common AEs across all age quartiles with lorcaserin treatment was hypoglycaemia via self-report, which did not necessitate an emergency department visit. Although there was an increase in hypoglycaemia for lorcaserin versus placebo, there were no increases in hypoglycaemia in the older quartiles versus the younger quartiles. Hypoglycaemia can be a common problem when patients with T2D lose weight, and their hyperglycemic medications are not lowered, as weight loss improves glucose control. Hypoglycaemia was not more prevalent in the older age group.

The cumulative impact of diet and lifestyle impacts healthy aging. The metabolic benefit of weight loss and fat mass reduction is the goal of weight management at any age and older persons have an opportunity to reduce cardiometabolic risk attributable to obesity and overweight. As noted in previous lorcaserin studies, the loss of 5% to 10% of body weight can have beneficial effects on hypertension, dyslipidaemia, diabetes mellitus, arthritis and sleep apnoea and can also help prevent the development of T2D and heart disease (19–22). Accordingly, lorcaserin weight loss was associated with improvements in serum lipid levels, insulin resistance and blood pressure as well as decreased waist circumference and decreased levels of markers of inflammation (23–27).

As the prevalence of obesity and obesity related morbidity continues to grow, individuals of all ages are advised to lower excess body weight to reduce the onset of disease, or disease severity. As moderate amounts of weight loss can produce cardiometabolic benefits, weight loss and weight maintenance medications like lorcaserin, in tandem with diet and increased physical activity, provide safe, effective and viable methods to lower body weight and improve cardiometabolic variables and functionality in adults across all age groups. Taken together, this post hoc analysis demonstrates that lorcaserin treatment in patients with and without T2D was safe and effective at reducing weight across all age groups analysed. Weight loss appeared to be greater for older patients; additional analyses are

warranted to confirm these findings and to better understand the factors for improved weight loss.

Conflict of Interest Statement

No conflict of interest was declared.

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