Lorcaserin (Belviq®): From Rational Design to the Market

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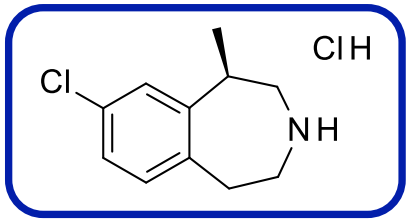
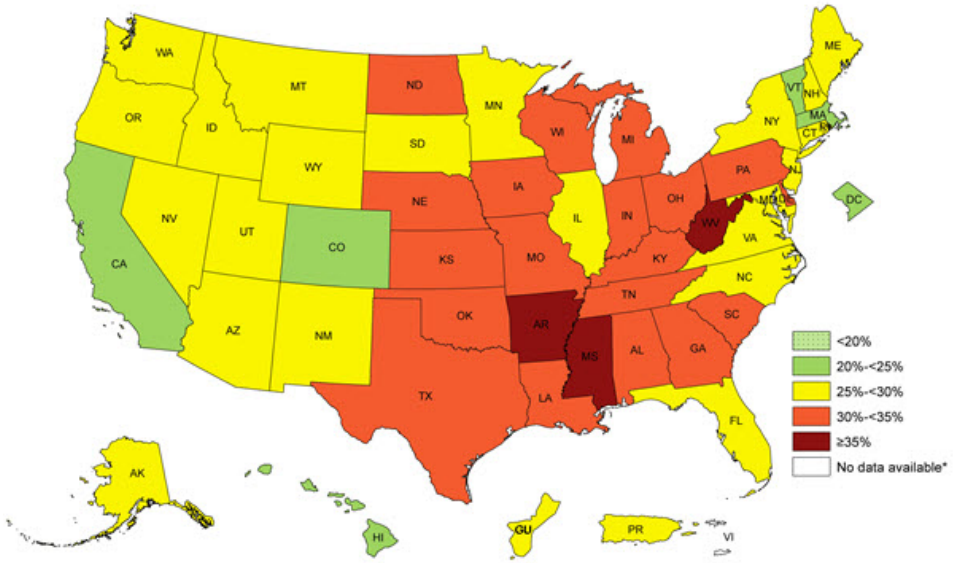
Drug Summary



- Working name: APD-356
- Chemical name: (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride
- Generic name: Lorcaserin hydrochloride
- Drug name: Belviq®
- Phase: Launched in USA (June-2013)
- Company: - Discovered and patented by Arena Pharmaceuticals
  - Commercial agreement with Eisai (July-2010)
- Indication: Chronic weight management as adjunct to lifestyle changes
- Pharmacology: Selective 5-HT_{2C} Agonist
- Receptor type: G-Protein Coupled Receptor (GPCR)
- Route administration: Oral, blue film-coated tablet (10 mg)

Obesity Trends Among US Adults (2014)

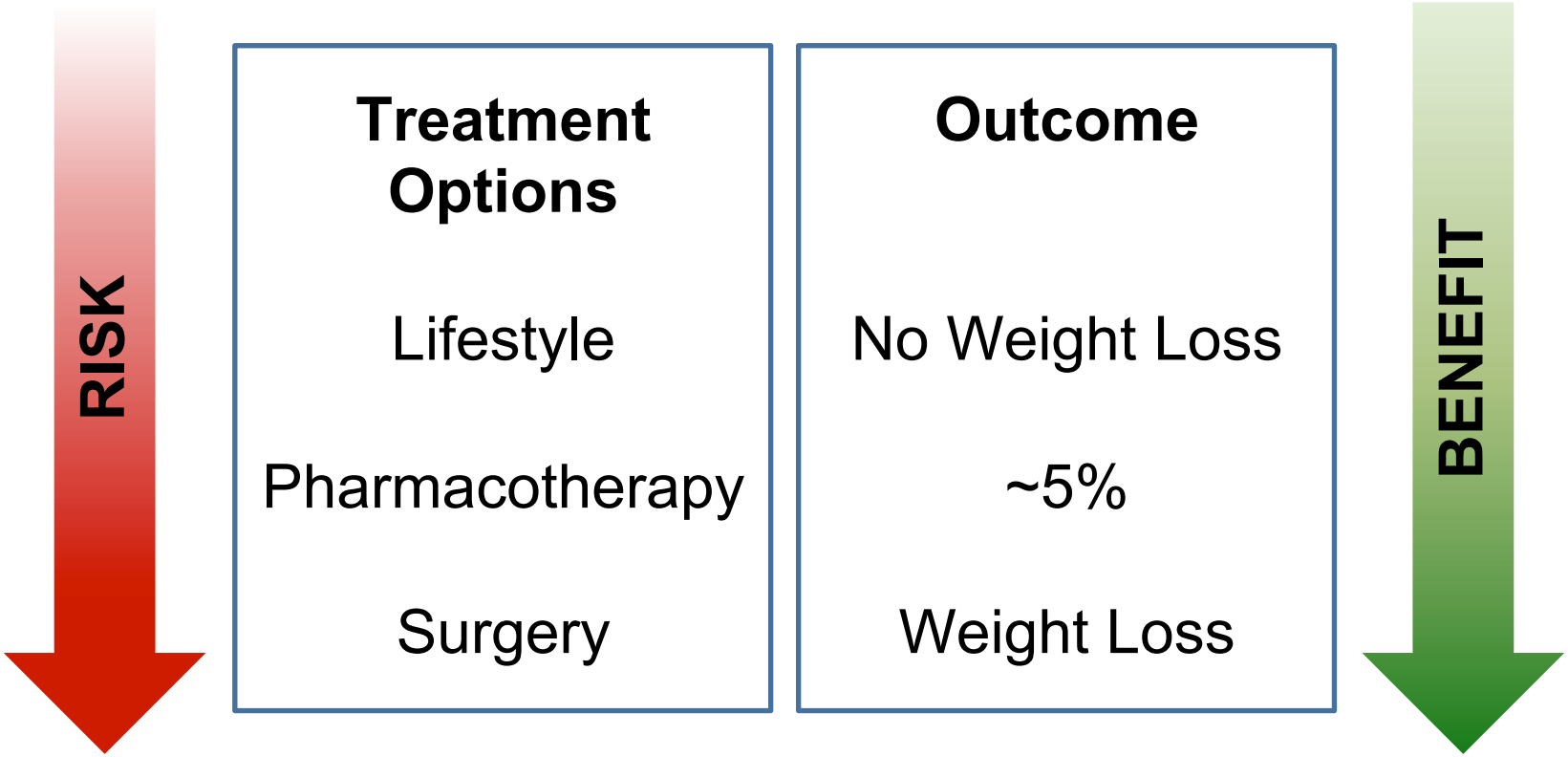
Percentage of people with BMI ≥ 30 Kg/m^2



BMI (Body Mass Index) = Weight (Kg) / Height Squared (m^2)

BMI (Kg/m^2)	Category
Below 18.5	Underweight
18.5 - 24.9	Normal Weight
25.0 - 29.9	Overweight
30 or higher	Obese

Risk-Benefit for Obesity Treatments



Weight Loss Efficacy of Antiobesity Agents

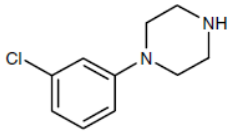
Treatment	Dose	Effect (52 weeks)	Placebo (52 weeks)
Orlistat	120 mg, TID (po)	-6.1 Kg	-2.6 Kg
Sibutramine	15 mg, QD (po)	-6.4 Kg	-1.6 Kg
Qnexa (phentermine/ topiramate)	15/92 mg, QD (po)	-10.6 Kg	-1.7 Kg
NB32 (naltrexone/ bupropion)	32/360 mg, QD (po)	-6.1 Kg	-1.4 Kg
Lorcaserin	10 mg, BID (po)	-5.8 Kg	-2.5 Kg
Liraglutide	3 mg, QD (sc)	-8 Kg	-2.6 Kg

TID = Three times a day; BID = Twice a day; QD = Once a day

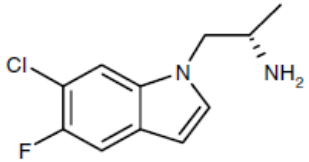
- Orlistat has unpleasant side effects
- Sibutramine was withdrawn from the market in 2010
- Qnexa, NB32 and Liraglutide were approved later than Lorcaserin

Target Validation for Obesity previous to Lorcaserin

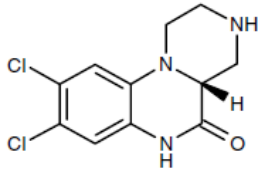
- Since the discovery of fenfluramine, the role of 5-HT in the control of food intake has been established (*Curr. Drug Targets* **2005**, *6,* 201-213).
- Multiple 5-HT_{2C} agonists decrease feeding and regulate weight in DIO or fasted rat models: m-CPP, Ro-600175, WAY-161503, WAY-163909, IL639, etc



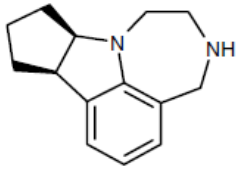
m-CPP



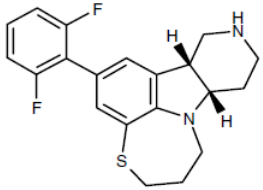
Ro-600175



WAY-161503



WAY-163909



IL639

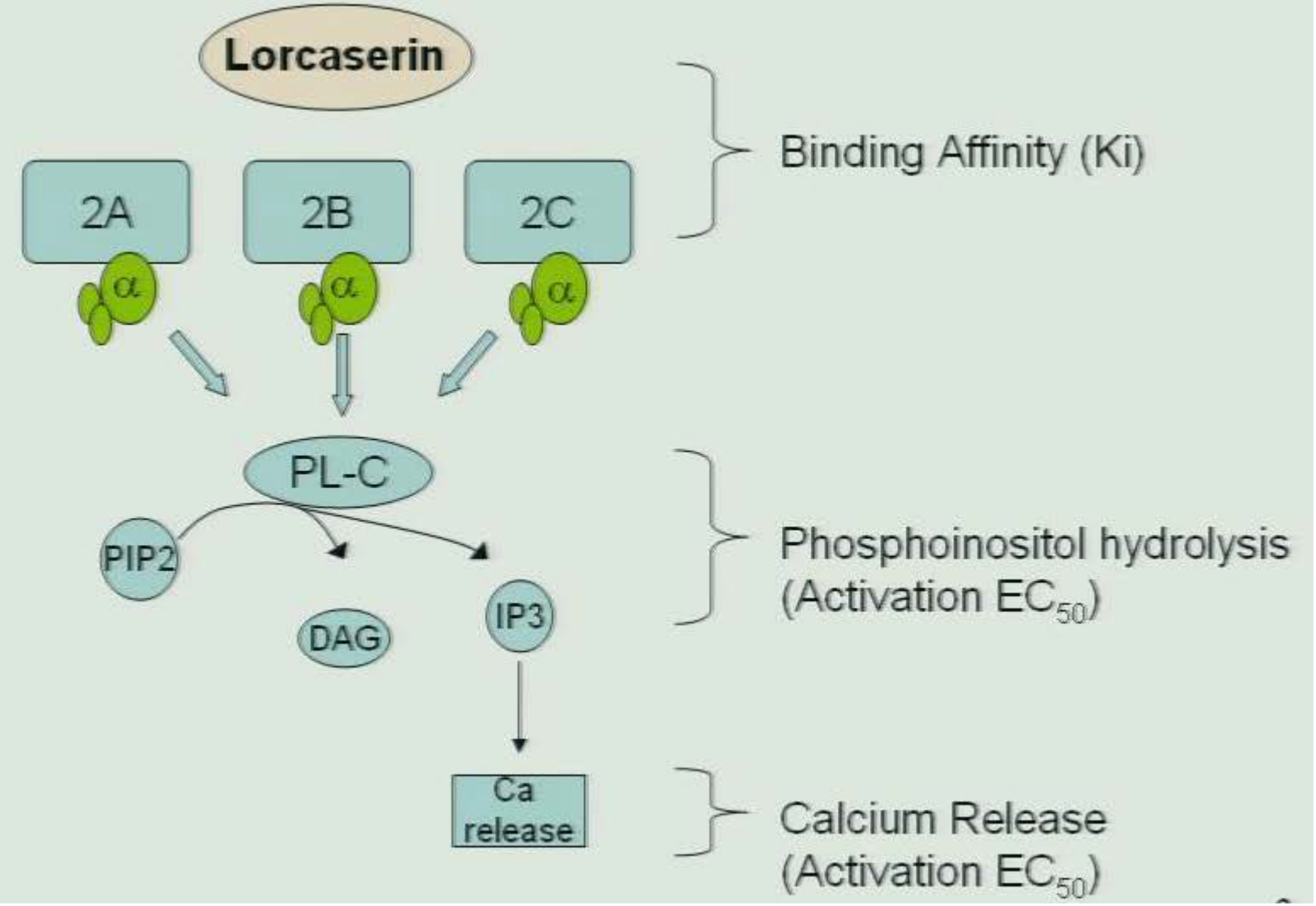
- Feeding reduction is blocked by co-administration of a 5-HT_{2C} antagonist (*Neuropharmacology* **2001**, *41*, 200; *Curr. Top Med. Chem.* **2003**, *3,* 885).
- 5-HT_{2C} receptor knockout mice show excess weight gain relative to wild type (*Nature* **1995**, *374*, 542-546; *Psychopharmacology* **1999**, *143,* 309-314).
- A small study with m-CPP in 18 healthy volunteers resulted in weight loss (0.75 Kg) after 2 week treatment (*Psychopharmacology* **1997**, *133*, 309-12).

Selectivity: The challenge of 5-HT_{2C} Agonists

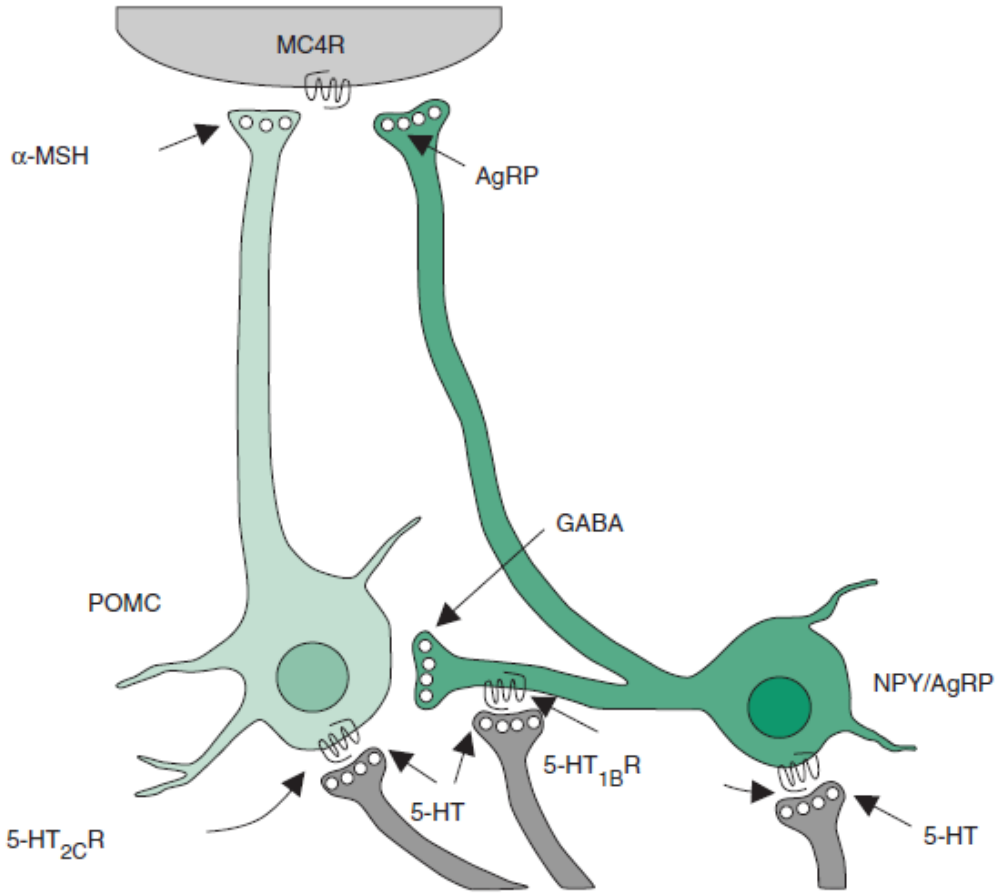
5-HT_2 Receptors	CNS Function	Periphery Function
5-HT_{2A}	**Drug-induced hallucinogenic responses**	Vasoactive (pulmonary/coronary vessels), adipocyte differentiation, platelet aggregation
5-HT_{2B}	Motor behavior, anxiety, cerebrovascular tone	**Drug-induced valvulopathy** **Pulmonary vascular hypertension**
5-HT_{2C}	**Appetite suppression** Anxiety, stress response	Limited expression

- 5-HT_{2C} agonists must be free of liability to induce heart valve disease and pulmonary hypertension due to 5-HT_{2B} agonism.
- Psychoactive properties associated with some 5-HT_{2A} agonism must also be absent.
- The three 5-HT_2 receptors share high homology (80%) in their sequence.
- In addition, selectivity over the other serotonin receptors is required: 5-HT_1 (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}), 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7.

Potency and Selectivity: In vitro assessment



Pharmacological Action of 5-HT_{2C} Agonists

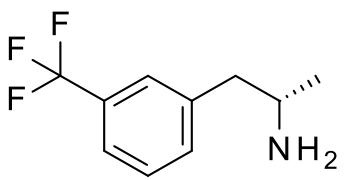


Science **2002**, *297,* 609-611

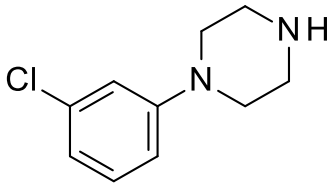
- Activation of 5-HT_{2C} receptors on pro-opiomelanocortin (POMC) neurons in the hypothalamus releases α-melanocortin-stimulating hormone (α-MSH).
- This mechanism is thought to decreases food consumption and promote satiety.

Drugs **2007**, *67,* 27-55

Lorcaserin: Rational Design and SAR

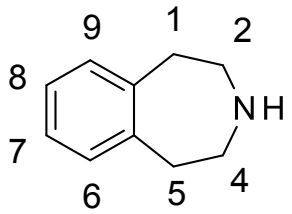


nor-Dexfenfluramine



mCPP

Non-selective 5-HT_{2C} agonists



Benzazepines

Selective 5-HT_{2C} agonists

Constraining the arylethylamine motif into a bicyclic system reduced the number of conformations, leading to compounds with improved 5-HT_{2C} selectivity *vs* 5-HT_{2A} and 5-HT_{2B} receptors.

Position-substituent	EC_{50} (nM)		
	5-HT_{2C}	5-HT_{2A}	5-HT_{2B}
1-Me, 7-MeO, 8-Br	5	80	100
1-Me, 7-MeO, 8-Cl	11	80	140
1-Me, 7-MeO, 8-I	2	61	64
1-Me, 8-Cl	11	260	1100
1-Me, 8-Cl (R)	11	190	1000
1-Me, 8-Cl (S)	16	265	1400
1-Me, 8-CF_3	7	100	380
1-Me, 7,8-DiCl	4	16	78
1-Me, 8,9-DiCl	6	220	1800
1-Me, 8,9-DiCl (S)	3	135	25 at 10 μM
1-Me, 8-Cl, 7-F	7	72	360
1-Me, 8-Cl, 9-F	22	840	> 10,000

Bioorg. Med. Chem. Lett. **2005**, *15*, 1467-1470; *J. Med. Chem.* **2008**, *51*, 305-313

Lorcaserin: In vitro Data

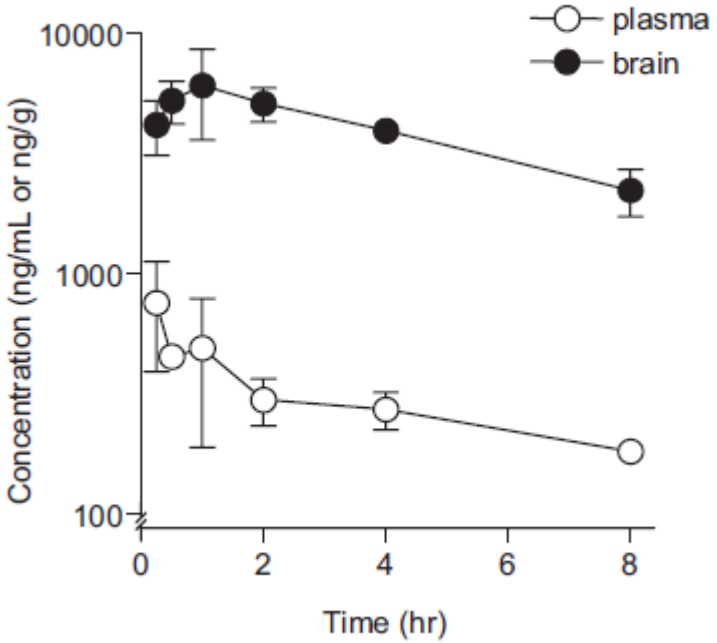
	Binding Assay	Functional Assay*	
Receptor	**Ki (nM)**	**EC_{50} (nM)**	**Emax (%)**
Human 5-HT_{2C}	15 ± 1 (n=28)	9 ± 0.5 (n=40)	100
Human 5-HT_{2A}	112 ± 7 (n=25)	168 ± 11 (n=34)	75
Human 5-HT_{2B}	174 ± 32 (n=18)	943 ± 90 (n=35)	100
Rat 5-HT_{2C}	29 ± 7 (n=7)	193 ± 12 (n=4)	100
Rat 5-HT_{2A}	159 ± 27 (n=14)	676 ± 129 (n=3)	100
Rat 5-HT_{2B}	190 ± 5 (n=3)	272 ± 87 (n=4)	100

*IP3 accumulation assay

- Selectivity based in the functional assay (15-fold for 5-HT_{2A} and 100-fold for 5-HT_{2B})
- No significant binding activity at 1 μM in a panel of 63 other receptors, ion channels and transporters

J. Pharmacol. Exp. Ther. **2008**, *325*, 577-587

Brain and Plasma Pharmacokinetics in Rats



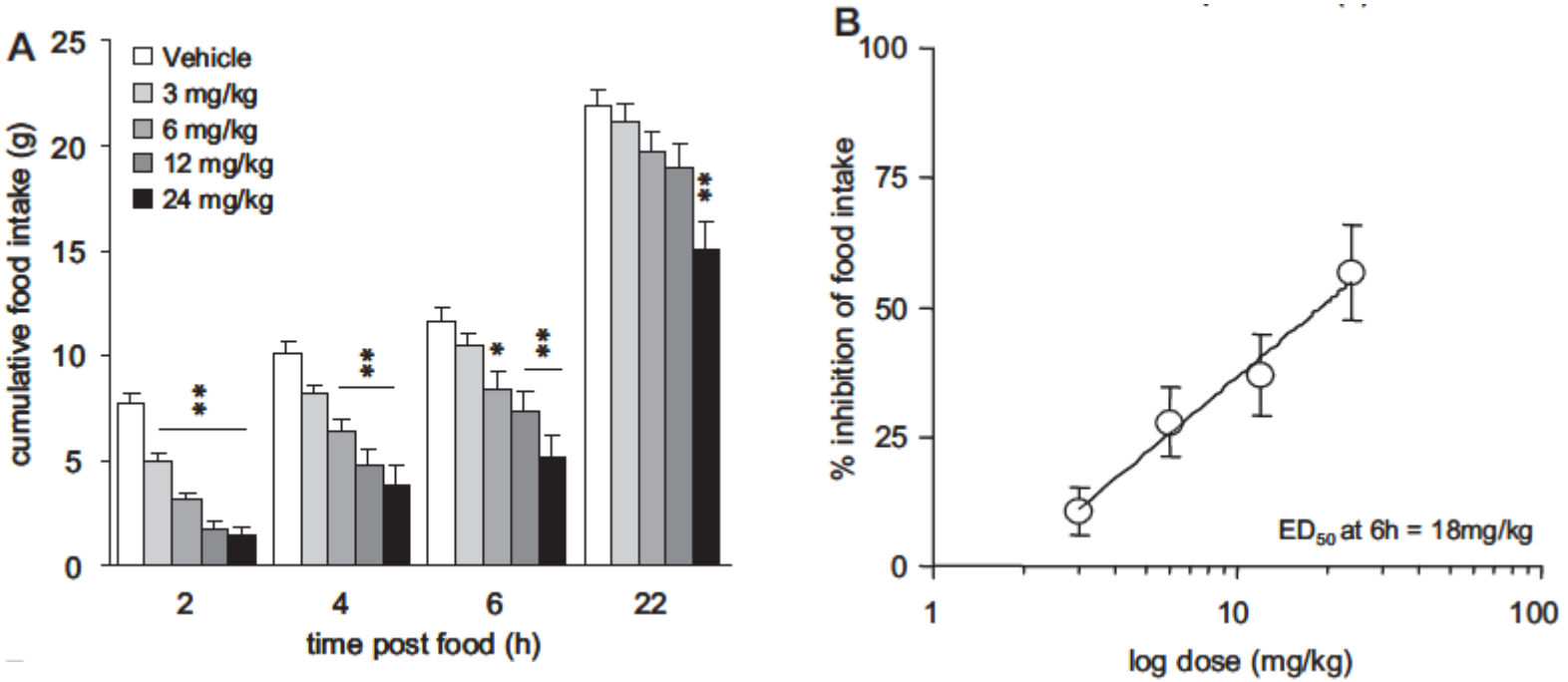
Parameter	Plasma	Brain
AUC (h·μg/mL)	3322	44132
$t_{1/2}$ (h)	4.9	4.7
C_{max} (ng/mL)	760	6110
T_{max} (h)	0.25	1
Residence time (h)	5.4	6.1

Single oral administration of 10 mg/Kg in SD rats

- Lorcaserin is rapidly absorbed and demonstrates favorable PK parameters in rat, dog and monkeys with projections of once or twice daily dosing in humans.
- Lorcaserin demonstrates brain levels exceeding plasma levels
- Rat bioavailability: F = 94%
- Monkey bioavailability: F = 49%

J. Pharmacol. Exp. Ther. **2008**, *325*, 577-587

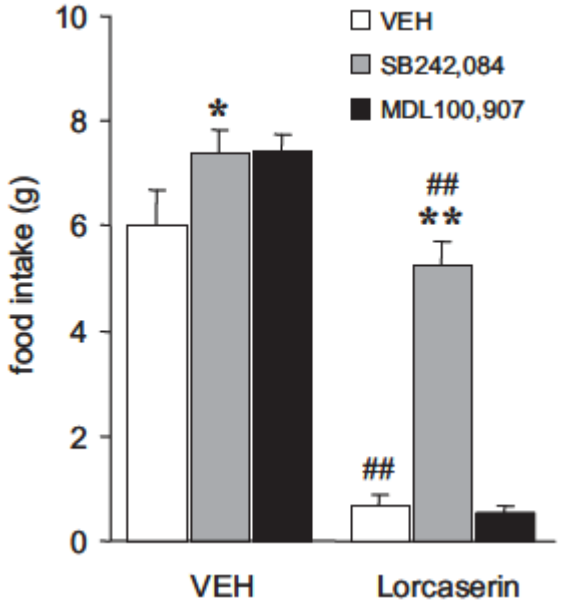
Acute Reduction of Food Intake in non-Obese Rats



- Lorcaserin was administered 30 min before food was presented.
- Lorcaserin decreased cumulative food intake at 2, 4, 6, 22 h.
- A single dose ED_{50} of 18 mg/Kg was derived at the 6 h time point.

J. Pharmacol. Exp. Ther. **2008**, *325*, 577-587

Target Engagement

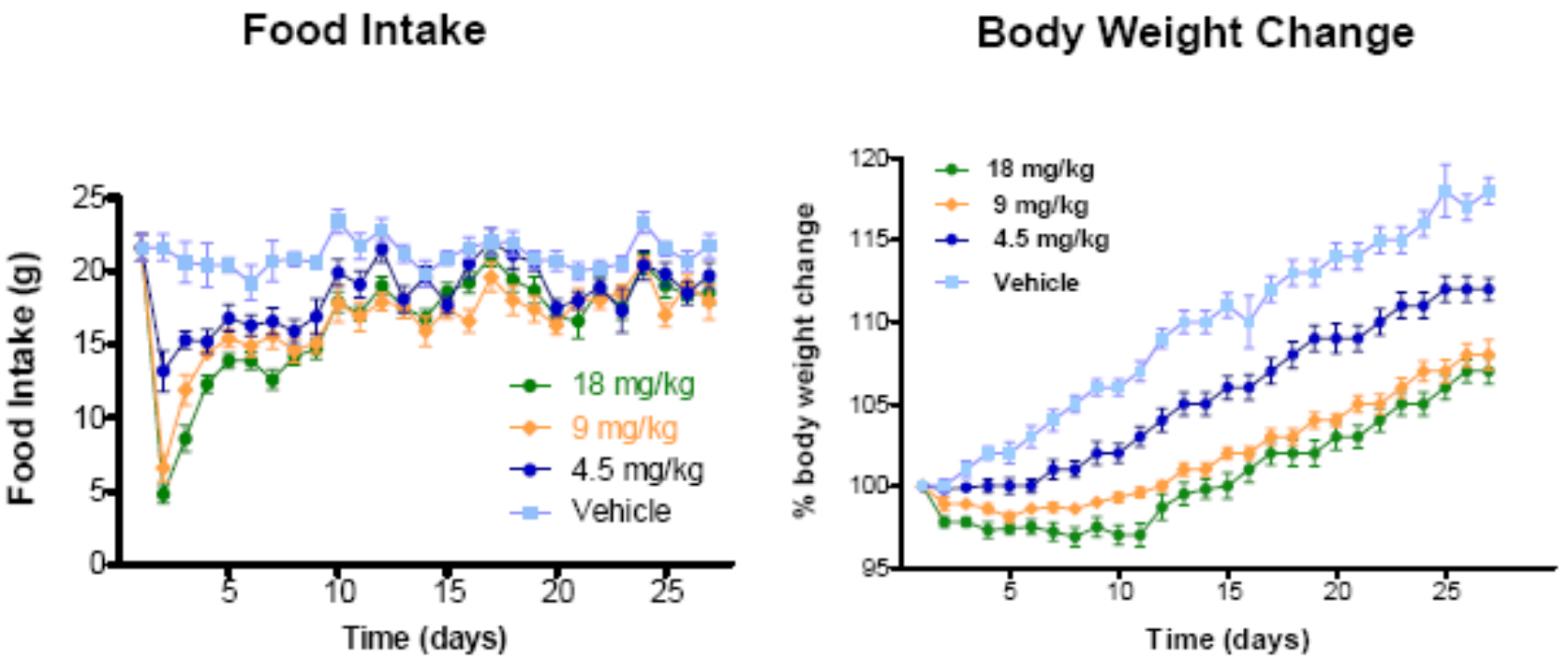


- Inhibition of lorcaserin-induced hypophagia with SB141084 (5-HT2C antagonist) but not with MDL100907 (5-HT2A antagonist).
- Rats were pretreated with SB242084 (1 mg/Kg) or MDL100907 (0.5 mg/Kg) 15 min before oral administration of lorcaserin (18 mg/Kg) or vehicle
- Food intake was measured 60 min later

- SB242084 and MDL100907 were tested for their ability to inhibit lorcaserin-induced reductions in food intake.
- SB242084 attenuates the food intake reduction induced by lorcaserin but MDL100907 does not.
- Food intake reduction induced by lorcaserin is mediated by 5-HT_{2C} but not 5-HT_{2A}

J. Pharmacol. Exp. Ther. **2008**, *325*, 577-587

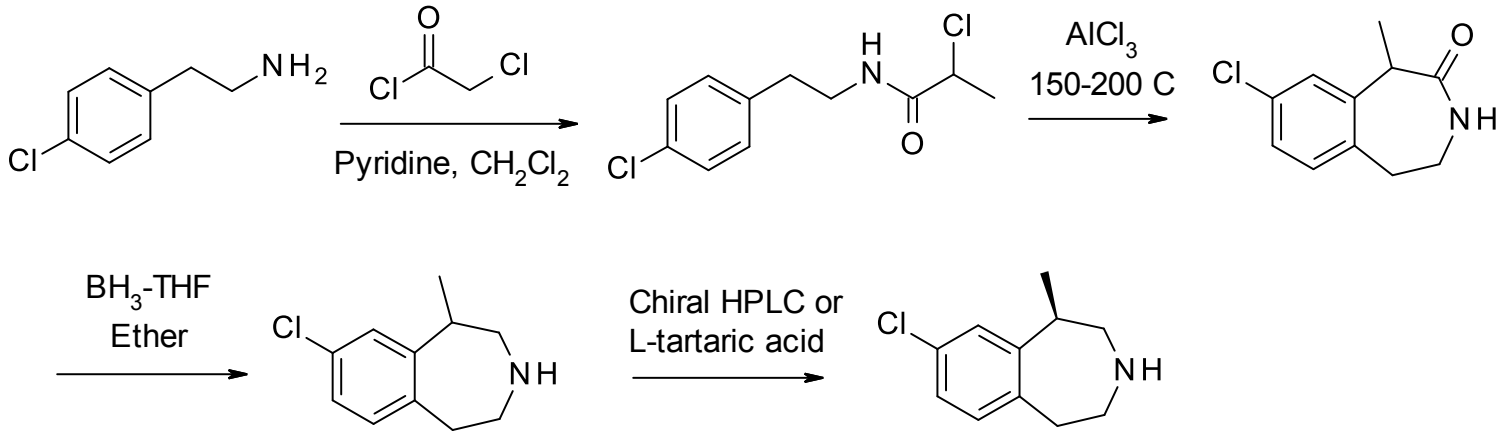
Food Intake and Body Weight Change in DIO Rats



- Arena has reported preclinical data in several obesity models
- After 13 days of dosing, there was a progressive loss in food intake reduction
- Lorcaserin shows dose-dependent reduction in body weight attributable to selective effects on fat mass but not in lean mass

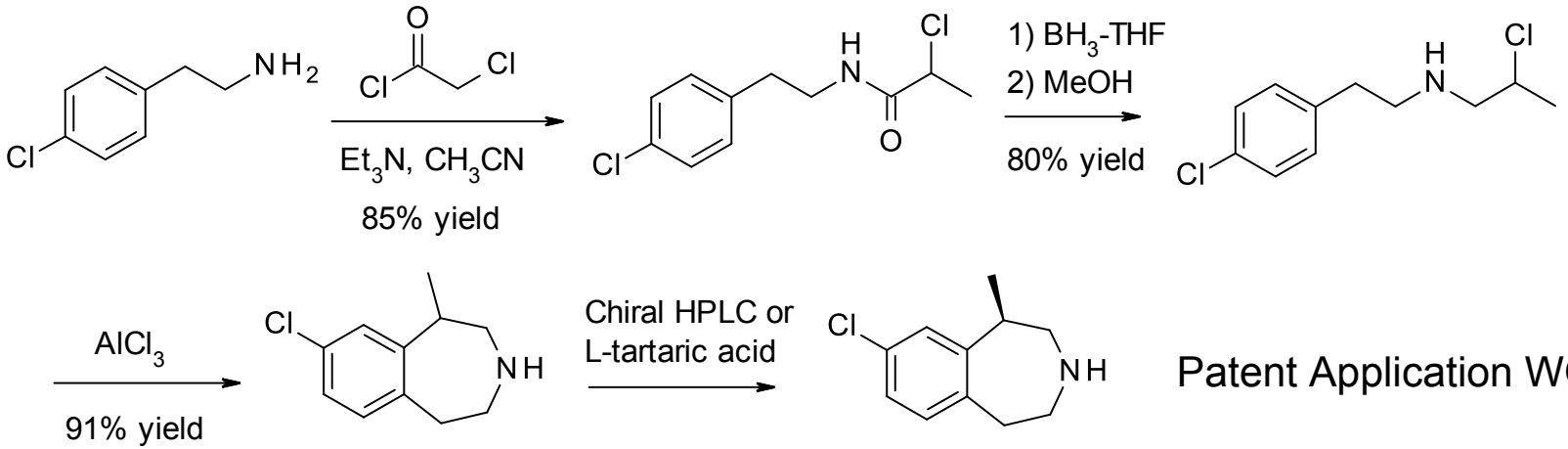
J. Pharmacol. Exp. Ther. **2008**, *325*, 577-587

Initial Synthesis of Lorcaserin



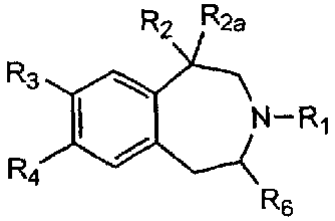
Bioorg. Med. Chem. Lett. **2005**, *15*, 1467-1470

Large Scale Synthesis Optimization

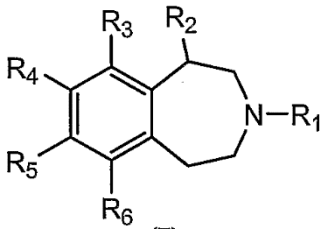


Patent Application WO05019179

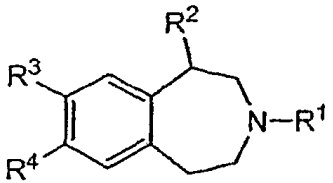
Patent Summary



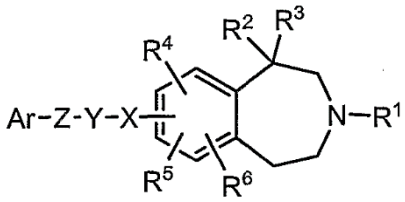
WO03086306



WO05003096



WO05042490



WO05042491

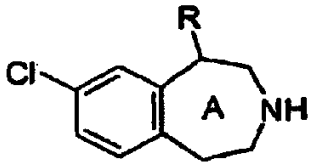
WO05019179: Large scale synthesis of benzazepines

WO07120517: Large scale synthesis of Lorcaserin

WO08070111: Large scale synthesis of Lorcaserin

WO06069363: Crystalline forms of Lorcaserin

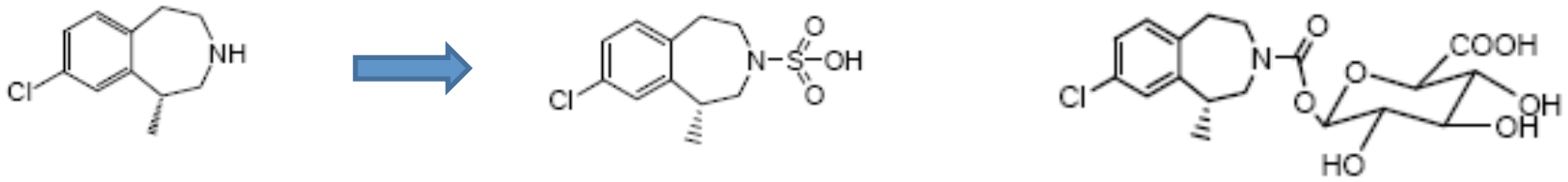
WO06071740: Composition (5-HT_{2C} agonist + Phentermine) and methods of use



WO09051747: Deuterated Lorcaserin

Patent expiration is 2023 in most jurisdictions

Lorcaserin: *in vivo* Metabolites



Lorcaserin

M1
Lorcaserin sulfamate

M5
N-Carbamoyl glucoronide
of Lorcaserin

- Lorcaserin is primarily excreted by the kidney
- M1 is the major circulating metabolite in rats, mice, monkeys and humans
- M5 is observed in all of these species and is the major metabolite in monkey and human urine
- Neither of these metabolites had significant binding at a large panel of receptors
- Lorcaserin does not undergo chiral conversion *in vivo*. Lorcaserin enantiomer is a low-level impurity (<1%) in the lorcaserin API

NDA 22-529, briefing document for FDA Advisory Committee

Lorcaserin: Potential for Drug-drug Interactions

- Lorcaserin is a weak CYP2D6 inhibitor (IC_{50} = 4.0 μM)
- It may increase the concentration of co-administered CYP2D6 substrates
- Arena conducted a clinical drug-drug interaction study in combination with dextromethoraphan (generic antitussive, CYP2D6 substrate). Lorcaserin increased dextromethoraphan exposure two-fold, suggesting that lorcaserin mininally inhibits dextromethoraphan metabolism and showing very low safety concerns.
- The safety of other medications with concurrent lorcaserin therapy has not been systematically evaluated.
- In addition, there is low probability of drug-drug interactions in which lorcaserin concentrations are affected because of its metabolism through multiple CYP P450s.

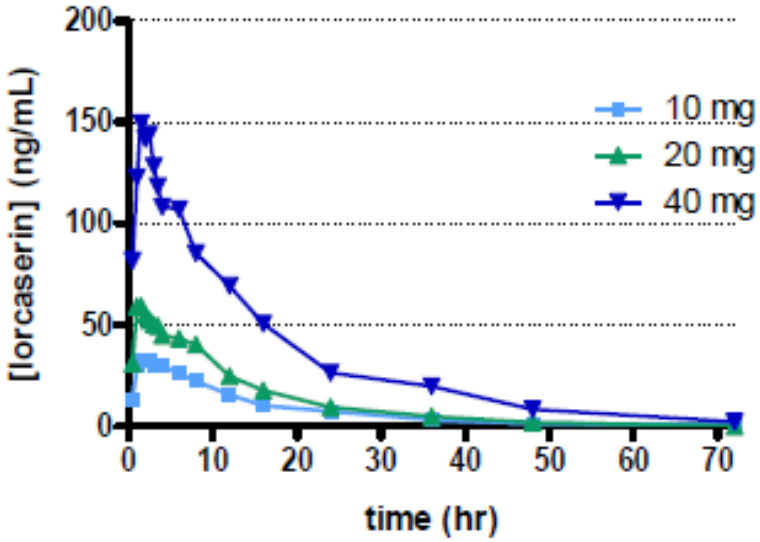
GLP Tox Studies

- Roedor species for general toxicity studies = Mouse and Rat
- Large animal specie for general toxicity studies = Monkey
- Monkey was selected as the most relevant specie due to the similar receptor distribution in monkey and human.
- General toxicity studies were conducted at doses that produced very high exposure multiples relative to the human maximum recommended dose.
- Lorcaserin was well tolerated at doses below MTD in mice, rats and monkeys with no adverse findings of direct relevance to humans at therapeutic doses.
- MTDs were defined by mortality in mice and rats and by emesis in monkeys.
- Extensive histopathological analysis showed no effects on heart valves, other cardiac tissues or the pulmonary vasculature after 2 years in rats/mice and 1 year in monkeys.

MTD = Maximum tolerated dose

NDA 22-529, briefing document for FDA Advisory Committee

Lorcaserin Clinical Trials: Phase 1 (July-2004)

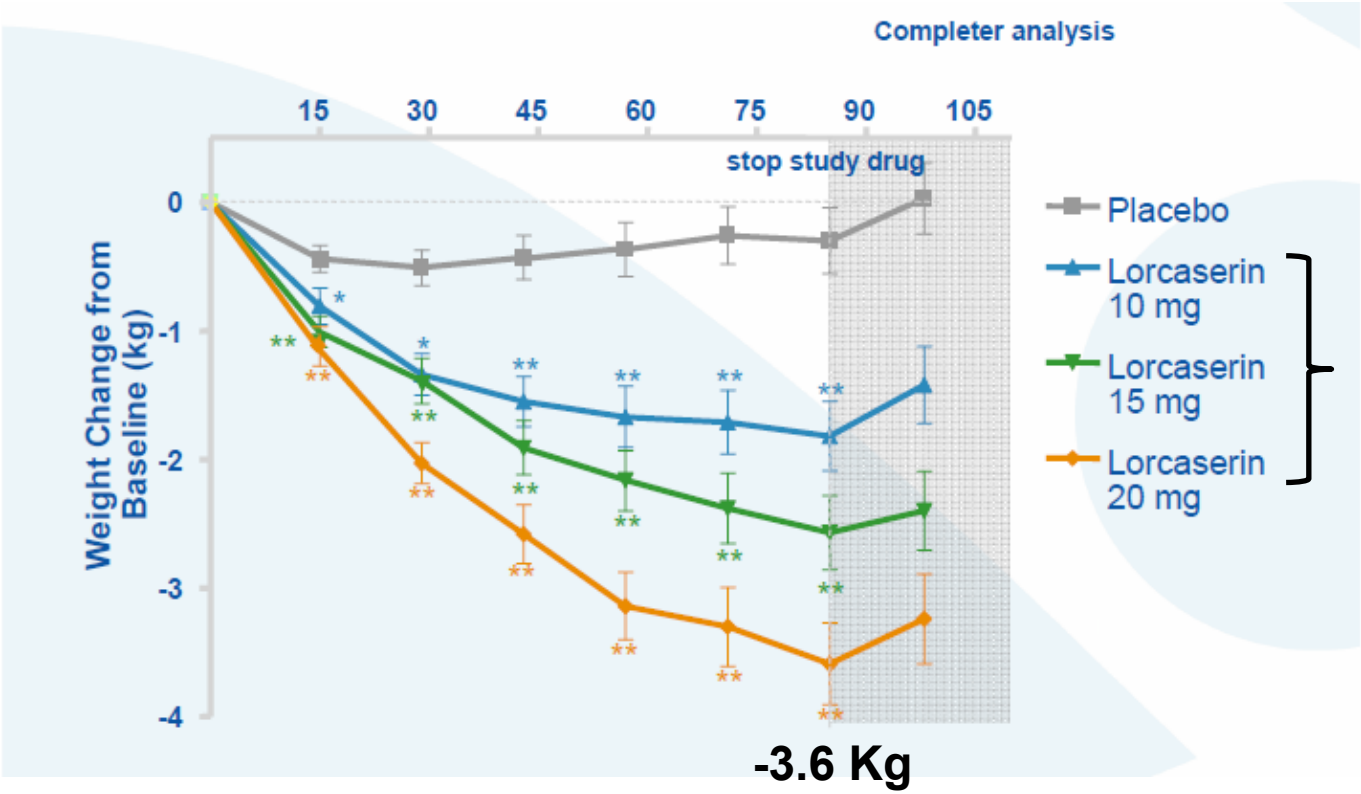


Concentration vs. time plot for single dose lorcaserin in healthy subjects

- In single and multiple dose studies, lorcaserin C_{max} and AUC increased proportionally with dose, with no change in T_{max}.
- Formal clinical studies evaluated the effects of age, race, gender, renal function and hepatic function on the PK properties of lorcaserin.
- Gender, age and race did not affect clearance or volume of distribution.
- Patients with lower body weight are predicted to have slightly higher lorcaserin exposure as compared with higher body weight.

NDA 22-529, briefing document for FDA Advisory Committee

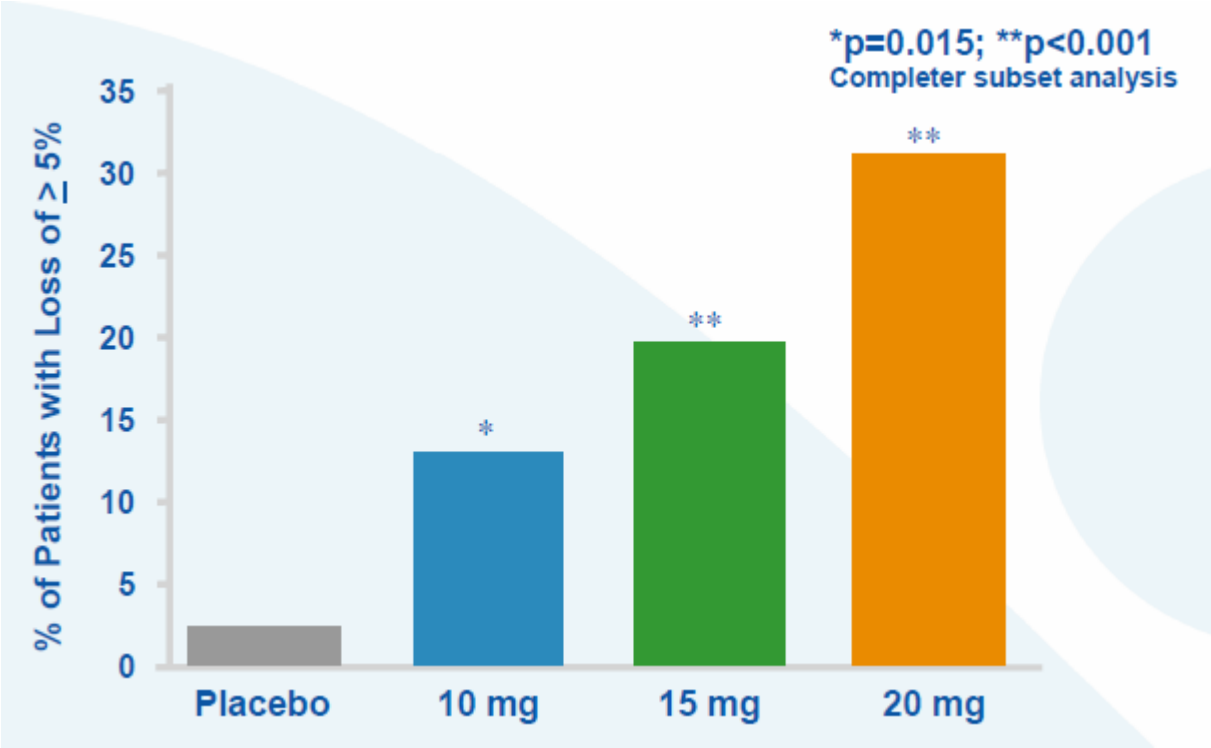
Lorcaserin Clinical Trials: Phase 2b (Dec-2005)



- Lorcaserin Phase 2b demonstrated a dose-dependent and progressive weight loss with significant reduction in waist circumference
- Well tolerated with no effects on heart valves or pulmonary hypertension

Obesity **2008**, *17*, 494-503

Lorcaserin Clinical Trials: Phase 2b (Dec-2005)



32% of patients lost ≥5% of weight from baseline

Obesity **2008**, *17*, 494-503

Lorcaserin: Phase 2b

Adverse Event	Placebo	10 mg	15 mg	20 mg
Headache	17.8	29.9	32.2	26.7
Nausea	3.4	8.5	9.3	11.2
Dizziness	0	6.0	7.6	7.8
URI	9.3	1.7	3.4	3.4
Nasopharyngitis	8.5	5.1	5.9	6.0
Dry Mouth	0	1.7	1.7	6.0
Diarrhea	5.9	0.9	4.2	3.4
Fatigue	2.5	4.3	5.9	4.3
Vomiting	0.8	1.7	1.7	5.2
UTI	4.2	2.6	5.1	5.2
Dyspepsia	5.1	3.4	1.7	3.4

Lorcaserin was generally well tolerated at doses investigated

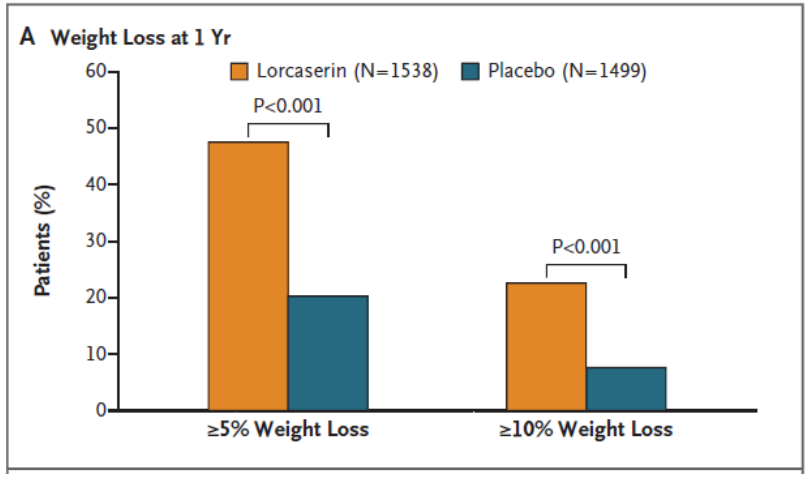
Obesity **2008**, *17*, 494-503

Lorcaserin: Phase 3 Summary

TRIAL	BLOOM	BLOSSOM	BLOOM-DM
Start	September 2006	December 2007	December 2007
Patients	3182 enrolled	4008 enrolled	604 enrolled
Duration	2 years	1 year	1 year
Daily dosing vs placebo	20 mg (10 mg BID)	10 mg & 20 mg (10 mg BID)	10 mg & 20 mg (10 mg BID)
Echo monitoring	Screening, 6, 12, 18, 24 months	Entry, 6, 12 months	Entry, 6, 12 months
Efficacy endpoints	Weight loss at 1 and 2 year. Maintenance of weight loss	Weight loss at 1 year	Weight loss at 1 year

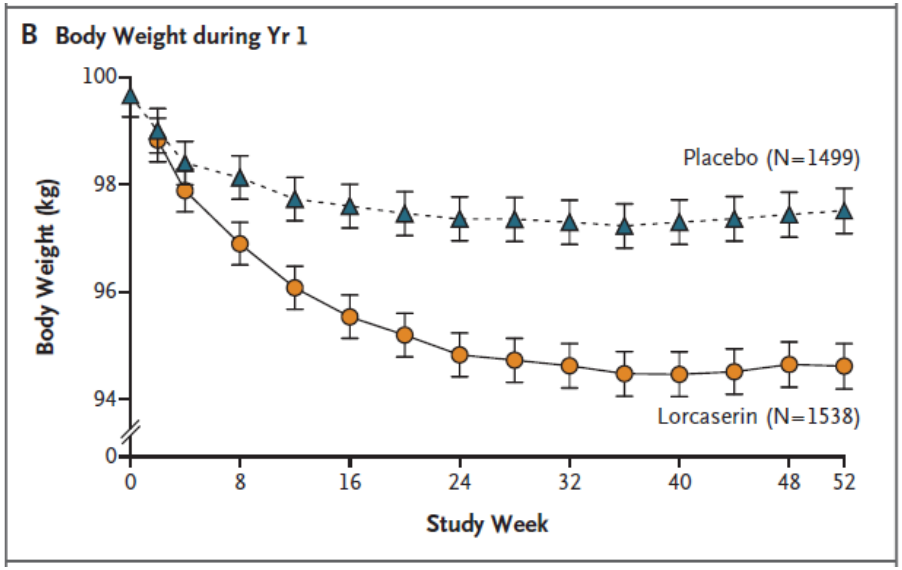
BLOOM = Behavioral modification of Lorcaserin for Overweight and Obesity Management
BLOSSOM = Behavioral modification of Lorcaserin Second Study for Obesity Management
BLOOM-DM = Behavioral modification of Lorcaserin for Overweight and Obesity Management in Diabetes Mellitus.

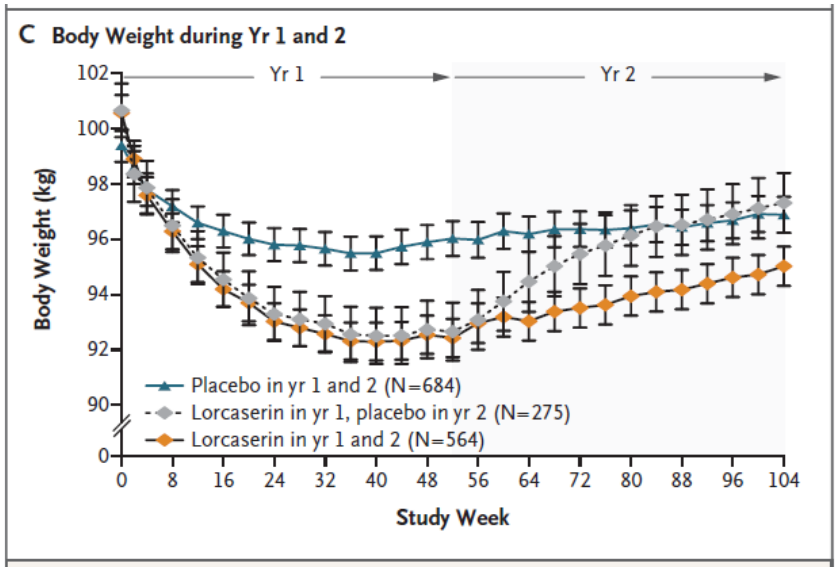
Lorcaserin: BLOOM Weight Loss at Week 52 and 104



Weight Loss	% of Patients	Group
5%	**48%**	**Lorcaserin**
	20%	Placebo
10%	**22%**	**Lorcaserin**
	8%	Placebo

Strong efficacy in patients who completed 1 year



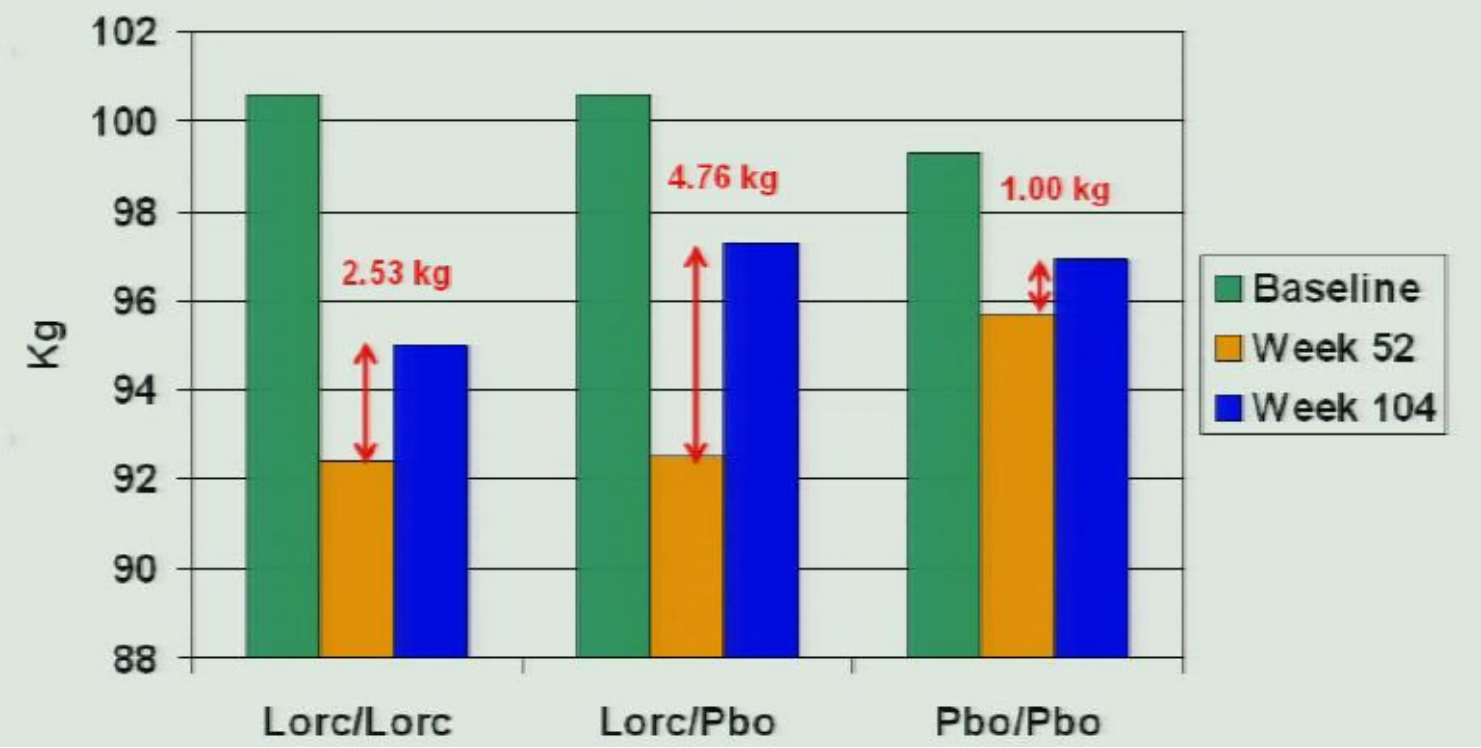


Year 1: Weight loss

Year 2: Weight was regained in all groups

New Engl. J. Med. **2010**, *363*, 245-256

Year 2 Efficacy: BLOOM Mean Weight over Time



- All appetite suppressants have a rebound effect
- Weight was regained in all treatment groups in Year 2 of BLOOM study, with the greatest weight regain in Lorc/Pbo

New Engl. J. Med. **2010**, *363*, 245-256

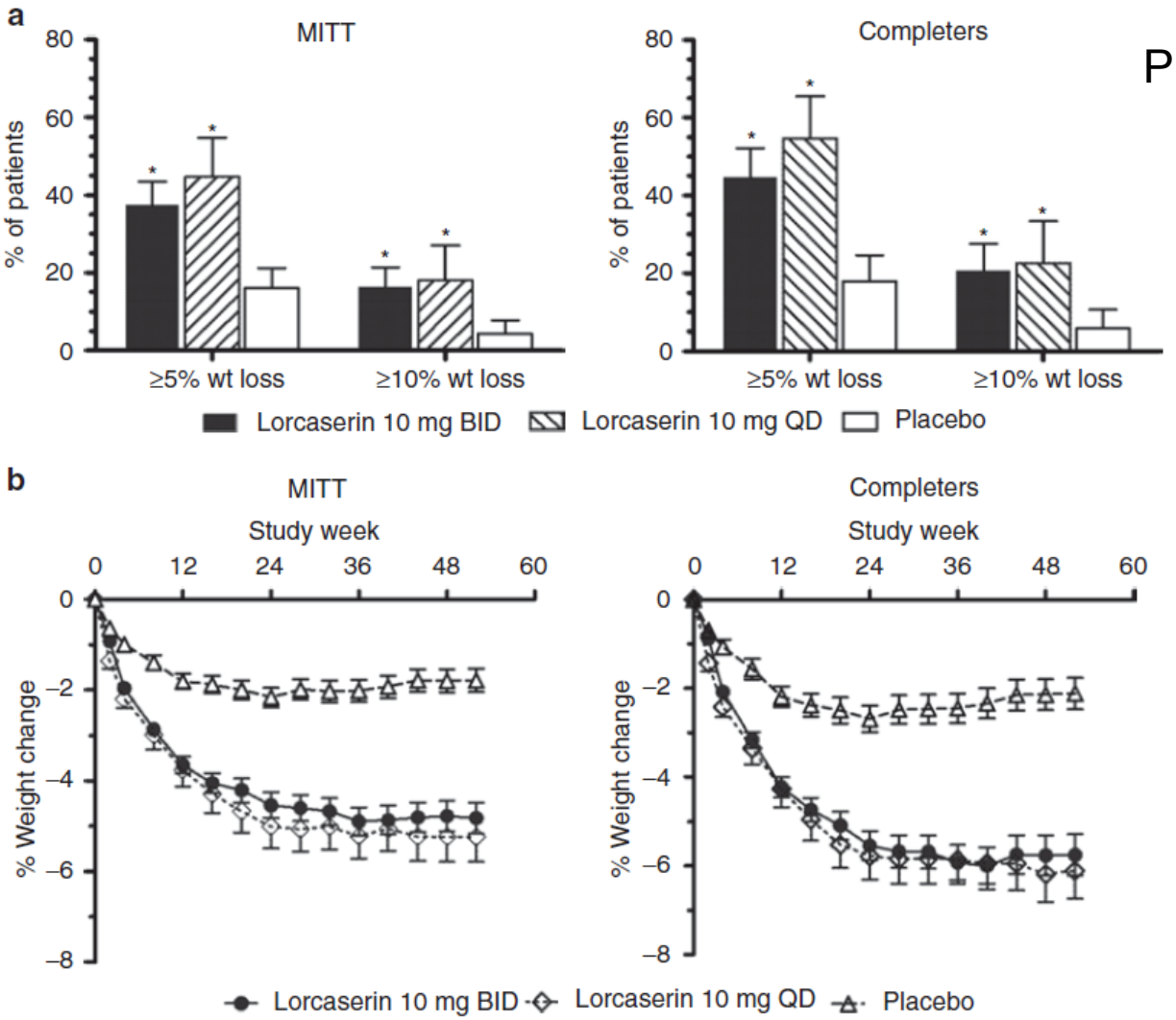
Lorcaserin: BLOOM vs. BLOSSOM

	Treatment group	Baseline mean wt (kg)	Adjusted mean % wt change from baseline	Diff in adjusted mean % change (95% CI)	p-value
BLOOM	Placebo	99.7	-2.2	--	
	Lorc 10 BID	100.4	-5.9	-3.7 (-4.1, -3.3)	< 0.001
BLOSSOM	Placebo	100.8	-2.8	--	
	Lorc 10 QD	100.1	-4.7	-1.9 (-2.5, -1.4)	< 0.001
	Lorc 10 BID	100.3	-5.8	-3.0 (-3.4, -2.6)	<0.001

- Patients treated with lorcaserin 10 mg BID lost -5.8% of baseline body weight
- 10 mg BID was selected as the appropriate dosing regimen for marketing

J. Clin. Endocrinol. Metab. **2011**, *96*, 3067-3077

Lorcaserin: BLOOM-DM Study



Primary endpoint: Weight loss in obese/overweight type 2 diabetics (604 patients)

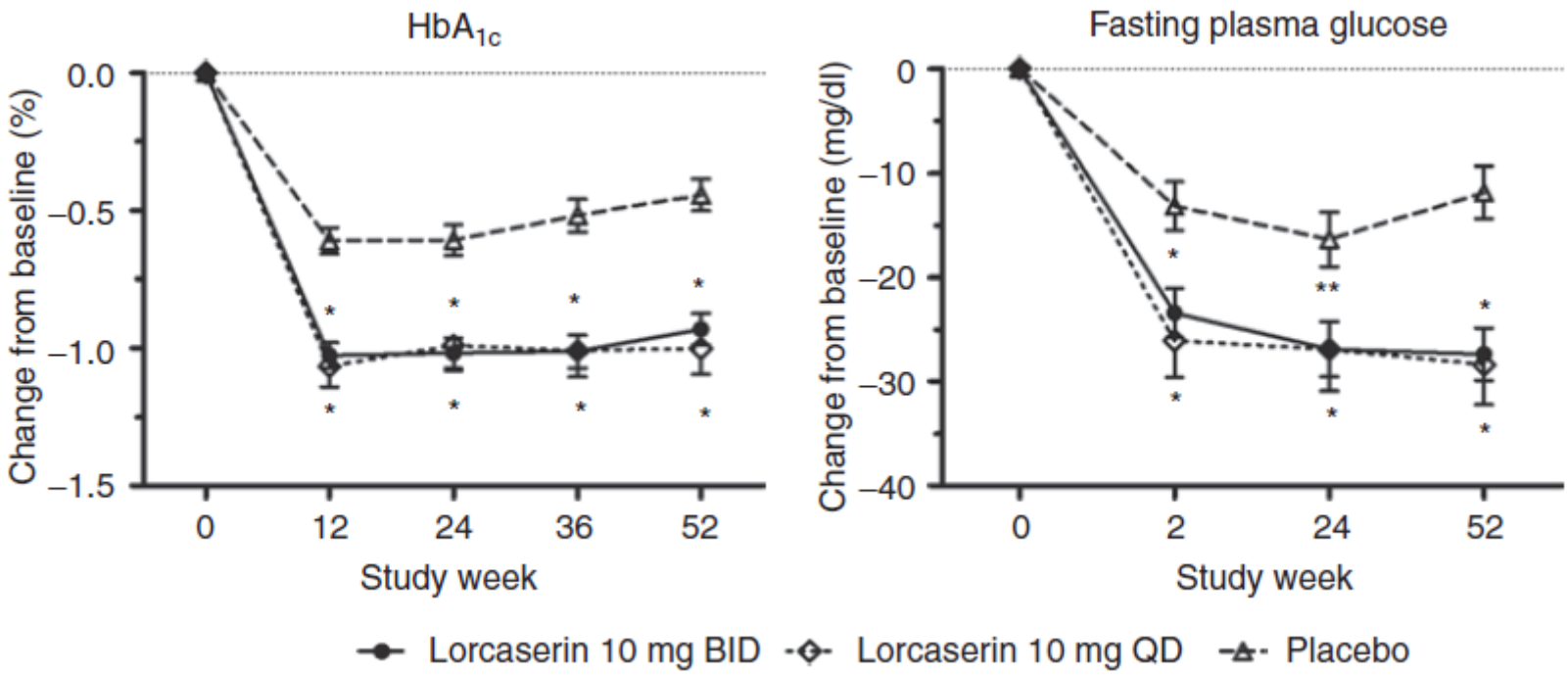
Analysis of body weight change

Percent change in body weight from baseline by study week

Obesity **2012**, *20*, 1426-1436

Lorcaserin: BLOOM-DM Study

- Secondary endpoint: Evaluation of glycemic control
- Patients were treated with metformin, a sulfonylurea or both



Change in glycemic parameters by study week

Obesity **2012**, *20*, 1426-1436

Lorcaserin Timelines

- **April-2003**: International Filing Date of Patent Application WO03086306
- **January-2004**: Phase 1a trial
- **July-2004**: Phase 1b trial
- **December-2004**: Phase 2a trial
- **December-2005**: Phase 2b trial completed
- **September-2006**: Phase 3 BLOOM trial (2 years)
- **December-2007**: Phase 3 BLOSSOM and BLOOM-DM trials (1 year each)
- **June-2009**: Presentation of Phase 3 BLOOM Data at the ADA meeting
- **December-2009**: Submitted NDA (New Drug Application) to the FDA
- **July-2010**: Agreement with Esai for commercialization in USA
- **October-2010**: First Advisory Committee meeting by FDA. Additional information requested to Arena.
- **May-2012**: Second Advisory Committee meeting by FDA
- **June-2012**: FDA approval
- **June-2013**: Belviq® launched in USA