

Protocol

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Protocol for: Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 2010;363:245-56.

CLINICAL PROTOCOL

APD356-009

Protocol Title: Behavioral modification and Lorcaserin for Overweight and Obesity Management (BLOOM)
A 104-Week, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Safety and Efficacy of Lorcaserin Hydrochloride in Obese Patients

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ARENA PHARMACEUTICALS PROTOCOL SIGNATURE PAGE

Protocol Title: Behavioral modification and Lorcaserin for Overweight and Obesity Management (BLOOM)

A 104-Week, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Safety and Efficacy of Lorcaserin Hydrochloride in Obese Patients.

This study will be conducted in accordance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) (E6), applicable Food and Drug Administration (FDA) guidelines, and the ethical principles that have their origins in the Declaration of Helsinki (1996 Version).

Protocol Number: APD356-009, Amendment 03

Arena Signatures:

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NATIONAL CO-PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

Protocol Title: Behavioral modification and Lorcaserin for Overweight and Obesity Management (BLOOM)

A 104-Week, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Safety and Efficacy of Lorcaserin Hydrochloride in Obese Patients.

Protocol Number: APD356-009, Amendment 03

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SIGNATURES ON FILE

LIST OF ABBREVIATIONS

5-HT	Serotonin
A-DIS	Abbreviated Diagnostic Interview Schedule
AE	adverse event
ALT	alanine aminotransferase
AM	ante meridiem
ANOVA	analysis of variance
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma concentration - time curve
AUC _{inf}	area under the plasma concentration - time curve from time zero to infinity
AUC ₀₋₂₄	area under the plasma concentration - time curve from time zero to 24 hours after dosing
BID	twice-a-day
BMI	body mass index
CL/F	apparent clearance
CLR	renal clearance
C _{max}	maximum plasma concentration
CRF	case report form
CRO	Contract Research Organization
CV(%)	coefficient of variation
DIO	diet induced obese
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBsAg	hepatitis B surface antigen
hCG	human Chorionic Gonadotropin
HDL-C	high-density lipoprotein cholesterol
HED	human equivalent dose
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
i.v.	Intravenous
IVRS	Interactive Voice Response System
kcal	Kilocalories
kg	Kilogram
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse effect level
µg	microgram(s)
µL	microliter(s)
OTC	over-the-counter
PK	pharmacokinetic(s)
PM	post meridiem
PO	per oral
QD	once-a-day
SAE	serious adverse event
SC	Study Coordinator
SD	standard deviation
SE	standard error
SOP	standard operating procedure
SSQ	Subjective Sensations Questionnaire
t _{1/2z}	half-life associated with terminal phase of the plasma concentration-time profile
T _{max}	time to reach maximum plasma concentration
VAS	visual analogue scale
VICF	volunteer informed consent form
WHO	World Health Organization

PROTOCOL SUMMARY

Protocol Number:	APD356-009
Title:	Behavioral modification and Lorcaserin for Overweight and Obesity Management (BLOOM) A 104-week, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Safety and Efficacy of Lorcaserin Hydrochloride in Obese Patients
Study Phase:	3
Name of Drug:	Lorcaserin hydrochloride (formerly known as APD356)
Dosage:	Lorcaserin 10 mg twice-a-day (BID)
Concurrent Control:	Matching placebo
Route and Formulation:	Oral, hard gelatin capsules
Objectives:	Primary: <ul style="list-style-type: none">• Year 1 primary endpoint: To assess the weight loss effect of lorcaserin at the end of the first year of treatment (Week 52)• Year 2 primary endpoint: To assess the ability of lorcaserin to maintain body weight at the end of the second year of treatment (Week 104) Secondary: <ul style="list-style-type: none">• To assess the ongoing safety of lorcaserin• To assess specifically any changes in heart valve regurgitation or pulmonary artery pressure associated with the use of lorcaserin• To assess potential further weight loss during the second year of treatment• To assess any changes in cardiovascular risk factors associated with obesity (i.e., dyslipidemia, insulin sensitivity, hypertension, central fat distribution, biomarkers of CV risk)• To assess any changes in mood• To assess any changes in Quality of Life measures (IWQOL-Lite)
Patient Population:	Overweight/Obese male and female patients between 18 and 65 years of age, inclusive All females, regardless of childbearing potential, must have a negative pregnancy test at Screening (serum hCG) and on Day 1 (urine dipstick). Females of childbearing potential must use adequate means of contraception. Body mass index (BMI) 30 to 45 kg/m ² with or without a comorbid condition (hypertension, dyslipidemia, CV disease, glucose intolerance, sleep apnea), or 27 to 29.9 kg/m ² with at least one comorbid condition.
Study Design:	Multicenter, double-blind, randomized, placebo-controlled, parallel-group. There will be no run-in period. Patients will be instructed to maintain a standardized diet and exercise program (Arena Healthy Lifestyle Program, see Appendix C).
Duration per Patient:	110 weeks total: 4 weeks for screening followed by 104 weeks on study medication plus a 2 week post-study telephone contact.
Study Site	Multicenter (~100 sites)

PROTOCOL SUMMARY (CONTINUED)

Patient Assignment:	<p>For the first year of treatment, patients will be randomly and evenly allocated to one of two treatment groups (placebo or lorcaserin 10 mg BID) for 52 weeks of double-blind treatment.</p> <p>After the first year of treatment, patients will be stratified into “responder” ($\geq 5\%$ body weight loss from Baseline to Week 52) and “non-responder” ($< 5\%$ body weight loss) groups.</p> <p>Within each of the two strata, patients receiving lorcaserin will be re-randomized (2:1) to either remain on lorcaserin 10 mg BID or be assigned to placebo for an additional 52-week treatment period. Patients receiving placebo during the first 52 weeks of the study will remain on placebo for the duration of the study.</p>
Sample Size:	~3,100 patients
Efficacy Assessments:	<p><u>Primary:</u></p> <ul style="list-style-type: none">• Year 1 primary efficacy assessment:<ul style="list-style-type: none">○ Proportion (%) of patients achieving $\geq 5\%$ weight reduction at the end of the first year of treatment (Week 52)○ Change in body weight (kg) from Baseline to the Week 52 visit○ Proportion (%) of patients achieving $\geq 10\%$ weight reduction at the end of the first year of treatment (Week 52)• Year 2 primary efficacy assessment: Maintenance of weight between the end of Year 1 and the end of Year 2 in the “responder” stratum, expressed as the proportion of patients maintaining a 5% or greater decrease in body weight from baseline <p><u>Secondary:</u></p> <ul style="list-style-type: none">• Change in body weight (kg) from the end of the first year (re-randomization baseline) to the end of Week 104• Change in body weight (kg) from baseline to the end of Year 2• Proportion of responder patients that maintain at least 75%, 50%, and 25% of the weight lost during Year 1 assessed at the end of Year 2• Change in waist and hip measurements and waist:hip ratio from Baseline to the Week 52 visit• Change in cardiovascular risk factors (systolic BP, diastolic BP, HDL cholesterol, triglycerides, CRP, fibrinogen, insulin sensitivity [HOMA-S]) from Baseline to Week 52• Change in use of medications for hypertension or dyslipidemia from Baseline to Week 52• Change in Quality of Life measures from Baseline to Week 52

PROTOCOL SUMMARY (CONTINUED)

Safety Assessments:	<ul style="list-style-type: none">• Clinical laboratory tests• Vital signs• Physical examination findings• 12-lead electrocardiograms (ECGs)• Echocardiograms: Primary assessment will be the proportion of patients who develop FDA-defined valvulopathy• Beck Depression Inventory - II• Adverse events
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1 INTRODUCTION

Serotonin (5-HT) and agonists that activate 5-HT_{2C} receptors are known to increase feelings of satiety and thus reduce food intake. Serotonin (5-HT) increases satiety via 5-HT_{2C} receptors located in the hypothalamus (i.e., PVN and DMH), a major center of the brain responsible for, among other functions, regulating hunger and food intake. 5-HT_{2C} receptors are also located in high density in the choroid plexus and to a lesser extent in limbic structures, extrapyramidal pathways, and the thalamus^{1,2}. 5-HT_{2C} receptors in these areas are not believed to play a role in regulating food intake. 5-HT_{2C} receptor expression is virtually absent in peripheral tissues. In addition, body weight and adipose tissue deposition are elevated in adult mice with 5-HT_{2C} receptor null mutation relative to their wild type littermates³. Drugs that non-selectively (fenfluramine, dexfenfluramine) and selectively (BVT.933) activate the 5-HT_{2C} receptor have been shown to induce weight loss in humans.

Lorcaserin is a potent and selective agonist for the 5-HT_{2C} receptor with no evidence of serotonin releasing properties that is in clinical development by Arena Pharmaceuticals, Inc. (San Diego, CA, USA) as a potential treatment for obesity. Functional assays indicate that lorcaserin selectivity for the 5-HT_{2C} receptor is approximately 15-fold and >100-fold relative to the 5-HT_{2A} and 5-HT_{2B} receptors, respectively. Although the pathophysiology of the cardiac valvulopathy and pulmonary hypertension associated with non-selective serotonergic agents such as fenfluramine is unknown, a substantial body of evidence implicates the 5-HT_{2B} receptor, expressed on valvular interstitial cells. Based on these characteristics, it is hypothesized that lorcaserin will be effective in the treatment of obesity and other conditions where weight loss is clinically indicated, while avoiding the cardiovascular effects associated with non-selective serotonergic agents.

Lorcaserin produces substantial reduction in body weight in diet-induced obese (DIO) Levin rats over a 28-day period. These effects are dose-proportional and reversible when the drug is removed from the animals. Although the effects on weight were persistent, the effects on food intake were more transient, suggesting that a mechanism(s) in addition to anorexia may be operant. Therefore, it is postulated that activation of the 5-HT_{2C} receptor with an agonist will increase satiety, and perhaps metabolic rate, in overweight and obese patients leading to overall weight loss.

In a phase 1 study, a test meal model was employed to assess the acute effects of lorcaserin on food intake in humans, and a pharmacological signal was observed at the 10 mg dose. At this dose, a non-significant, 6.5% reduction in meal size was observed, while a statistically significant (p=0.021) 10.7% reduction was evident when a single outlying subject, who demonstrated a strong period effect, was excluded from the analyses. This pharmacologic signal has been confirmed in 4-week and 12-week phase 2 studies in which significant, dose responsive, and progressive weight loss was observed at doses of 10 mg and 15 mg once daily, and 10 mg twice daily.

1.1 Background

Obesity has reached global epidemic proportions as the prevalence has nearly doubled from 20 years ago. Obesity is described as a condition in which an individual has a very high amount of body fat in relation to lean body mass, generally defined as a Body Mass Index

(BMI) of 30 kg/m² or higher. According to the World Health Organization, more than 1 billion adults worldwide are overweight, at least 300 million of whom are obese⁴. In the United States alone, approximately 30% of adults and 15% of children and adolescents are considered obese, and many more are overweight⁵. Obesity is a major risk factor for life-threatening diseases such as Type II diabetes, heart attack, stroke, and some forms of cancer, including breast and colon cancer with an estimated 300,000 obesity-related deaths annually in the United States alone.

Primary intervention for obesity includes lifestyle changes such as diet and exercise. However, as effective as these methods may be when adhered to, compliance with these regimens is often poor. This is partly due to unrealistic patient goals and the desire for rapid weight loss with little effort. Medical treatment of obesity is based on reduction of caloric intake, increase of caloric expenditure, increase of the feeling of satiety, depression of appetite, or combinations of these approaches. A classical approach to decrease the appetite is by giving medications that act by stimulating cerebral receptors for neurotransmitters, including 5-HT receptors.

Clinical support for this concept is provided by experiences with mCPP, a non-selective 5-HT_{2C} agonist, and fenfluramine, one of the key components of the highly effective and controversial Phen-Fen combination of the mid-1990s^{6,7}. Fenfluramine and dexfenfluramine were removed from the U.S. market in 1997 due to an increased incidence of valvular heart disease, observed in up to 18% of patients, and pulmonary hypertension^{8,9}. Recent evidence suggests that these findings may be associated with the drugs' activity at 5-HT_{2B} receptors, which are highly expressed in heart valves^{10,11,12,13}. In addition, fenfluramine and dexfenfluramine are known to cause a release of serotonin centrally and peripherally by activation of the 5-HT transporter^{14,15}. This activity may also play a role in the adverse effects observed with these drugs.

Lorcaserin is a highly selective agonist for the 5-HT_{2C} receptor. The selectivity of lorcaserin for 5-HT_{2C} receptors (>100-fold vs. 5-HT_{2B}; ~15-fold vs. 5-HT_{2A}) should minimize the potential for side effects. At target therapeutic concentrations, lorcaserin should have no activity at the 5-HT_{2B} receptor and limited activity at the 5-HT_{2A} receptor, thus mitigating the potential risk of side effects associated with these receptors. In addition, lorcaserin has no affinity for the 5-HT transporter.

1.2 Summary of Clinical Data

The safety, pharmacokinetics (PK), and pharmacodynamics of lorcaserin have been evaluated in four Phase 1 studies completed to date: a single dose study to assess the maximum tolerated single dose and PK (Protocol APD356-001, Part A), a single dose study to determine the effects of a high fat meal on lorcaserin PK parameters (Protocol APD356-001, Part B), a single dose study to assess the acute effects of lorcaserin on food intake in a test meal model (Protocol APD356-001, Part C), and a repeat dose study to assess the safety and PK during 14 days of administration (APD356-002).

In addition, the safety and efficacy of three doses (1, 5, and 15 mg) of lorcaserin administered before breakfast for 4 weeks were evaluated in a randomized, double-blind, placebo-controlled study in 352 obese patients. Patients were instructed to maintain their usual diet and exercise routines. Only the 15 mg dose was found to be effective. This study was followed up by a 12-week study in 469 obese patients in which doses of 10 mg and 15 mg once daily before breakfast, and 10 mg twice daily (before breakfast and dinner) were explored, again without changes in diet or activity levels. Significant, progressive, and dose responsive weight loss was observed with all 3 regimens.

[Table 1](#) summarizes the study design, population, number of subjects or patients, and doses tested for each of the above mentioned studies.

Safety: In phase 1, single and repeat doses of lorcaserin were well tolerated up to 20 mg in men and women, although women tended to report more adverse events than men in all studies. The most common side effects reported were related to the central nervous system (i.e., headache, lightheadedness, dizziness, blurred vision) and the gastrointestinal system (i.e., nausea, vomiting, indigestion). At the highest single dose tested (40 mg), 3 of 4 (75%) men experienced mild euphoria, while 1 of 2 (50%) women tested at this dose experienced euphoria, disorientation, dysphoric symptoms, and a hallucination. In the multiple dose phase 1 study, all doses (3, 10, and 20 mg qd x 14) were well tolerated. There were no serious adverse events (SAEs) reported, no withdrawals due to an adverse event (AE), and no reports of euphoria or dysphoria.

In the phase 2 studies, lorcaserin was well tolerated. The most common AEs were transient headaches, dizziness, and nausea (rarely with vomiting) that tended to occur as single events early in the studies. The frequency of these events in the two studies is displayed below [Table 2](#)). Please see the Investigators' Brochure for further details.

Discontinuations for adverse events in the phase 2 studies are displayed below ([Table 3](#)), and are described in detail in the Investigator's Brochure.

Adverse event profiles were similar for a bioequivalence study (APD356-005), a mass balance study (APD356-006), and a thorough QT/ECG study (APD356-007). No SAEs were reported during these 3 trials.

Table 1. Lorcaserin Clinical Study Summary

Protocol Number (Country)	Study Phase	Study Population	Study Design	Doses Tested (mg)	Duration of Treatment	Echocardiogram Schedule
APD356-001 - Part A (UK)	1	45 (25 males, 20 females) healthy volunteers, ages 18 to 60, BMI 23 to 32 kg/m ²	Single, ascending dose, randomized, double-blind, placebo-controlled safety and PK study to determine the maximum tolerated single dose	10, 20, and 40	Single dose	- Baseline - Within 1 week of the study exit visit on Day 6
APD356-001 - Part B (UK)	1	12 (6 males, 6 females) healthy volunteers, ages 18 to 60, BMI 23 to 32 kg/m ²	Single-dose, 2-period cross-over study to assess the effects of a high fat meal on lorcaserin PK	10	Single dose	- Baseline - Within 1 week after Period 2
APD356-001 - Part C (UK)	1	20 healthy male volunteers, ages 18 to 60, BMI 23 to 32 kg/m ²	Single-dose, 4-period cross-over study to assess the acute effects of lorcaserin on food intake in a test meal model	0.1, 1, and 10	Single dose	- Baseline - Within 1 week after Period 4
APD356-002 (US)	1b	27 (15 males, 12 females) healthy volunteers, ages 18 to 60, BMI ≥ 25 kg/m ²	Repeat, ascending dose, randomized, double-blind, placebo- controlled safety and PK study	3, 10, and 20 QD	14 days	- Baseline - 60 days after last dose - 90 days after last dose
APD356-003 (US)	2	352 obese male and female patient, ages 18 to 65, BMI 30 to 45 kg/m ²	Randomized, double-blind, placebo- controlled, parallel-group study to assess the safety and efficacy of lorcaserin compared to placebo	1, 5, and 15 QD	4 weeks	- Baseline - Day 29 (± 7 days) - Day 90 (± 7 days)
APD356-004 (US)	2	469 obese, otherwise healthy male and female patients, age 18-65; BMI 30-45 kg/m ²	Dose-ranging, double-blind, randomized, placebo-controlled, parallel-group study to assess the safety and efficacy of lorcaserin in obese patients	10 QD, 15 QD 10 BID	12 weeks	- Screening - Day 85 or Early term visit

UK: United Kingdom

US: United States

Table 2. Most Frequent Adverse Events in 4-Week Phase 2a Study APD356-003 and 12-Week Phase 2b Study APD356-004

Phase 2a APD356-003				
AE	PBO (N=86)	1 mg (N=90)	5 mg (N=89)	15 mg (N=87)
Headache	14.0%	15.6%	7.9%	20.7%
Nausea	3.5%	5.6%	5.6%	6.9%
Dizziness	3.5%	2.2%	1.1%	3.4%
Vomiting	2.3%	3.3%	2.3%	3.4%
Phase 2b APD356-004				
AE	PBO (N=118)	10 mg QD (N=117)	15 mg QD (N=118)	10 mg BID (N=116)
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%
Vomiting	0.8%	1.7%	1.7%	5.2%

Table 3. APD356-003 and -004: Patients Discontinued Due To an Adverse Event or Pregnancy

Treatment	Adverse Event	Outcome	Severity^a
Study APD356-003			
ADVERSE EVENTS			
1 mg	Influenza	R	Mod
1 mg	Abscessed tooth w/swelling	U	S
5 mg	Pneumonia	U	Mod
15 mg	Headache	R	S
15 mg	Stomatitis	U	M
15 mg	Influenza	U	S
PREGNANCY			
15 mg	Pregnancy	U	N/A
Study APD356-004			
ADVERSE EVENTS			
PBO	Pregnancy/Miscarriage	R	S
PBO	Fatigue	R	Mod
PBO	Upper respiratory infection	R	M
10 mg QD	Elevated blood pressure	R	Mod
15 mg QD	Headache	R	M
15 mg QD	Nervousness	R	Mod

Treatment	Adverse Event	Outcome	Severity ^a
15 mg QD	Dizziness	R	S
15 mg QD	Headache	R	Mod
15 mg QD	Blurred vision	R	Mod
15 mg QD	Left leg pain	O	Mod
15 mg QD	Fatigue	R	M
15 mg QD	Headache	R	Mod
15 mg QD	Insomnia	O	Mod
10 mg BID	Seizure ^b	R	S
10 mg BID	Elevated LFTs ^b	R	Mod
10 mg BID	Complete heart block ^b	O	M
10 mg BID	Vomiting, metrorrhagia	R	M-Mod
10 mg BID	Fatigue	R	Mod

Outcome: R = resolved; U = Unknown, O = Ongoing; Severity: S = severe; Mod = moderate; M = mild
 N/A=not applicable

^aAs assessed by the investigator

^bReason for study discontinuation listed as “Investigator Decision” or “Lost to Follow-up”; however, the discontinuation was temporally related to an AE and is therefore included in this table.

Serious Adverse Events: The only serious adverse events associated with lorcaserin treatment to date occurred in the 12-week study (APD356-004).

A 38-year old woman in the lorcaserin 10 mg QD group with a history significant for mood disorder (2001) developed major depression. Depressive symptoms were first reported on Study Day 71. The patient completed the dosing period of the study, but was diagnosed by the Investigator with major depression on Study Day 100, 2 weeks after the last dose of study drug. The patient subsequently received Lexapro, and reported improvement of symptoms in telephone follow-up. The AE was deemed unlikely related to study drug by the investigator.

A 35-year old woman in the lorcaserin 10 mg BID group with no significant medical history developed a new onset seizure. The patient presented to an emergency department on Study Day 71 with a generalized seizure. The last documented dose of study drug was at Study Day 61. A neurological workup revealed no discrete cause for the seizure and was consistent with idiopathic seizure disorder, including a typical spike slow-wave pattern on EEG. The AE resolved without treatment, and was deemed unlikely related to study drug.

Echocardiograms: In phase 2 studies, echocardiograms were obtained under a standard protocol and were read by a central reader or readers who were blinded to treatment but not to sequence. All 4 heart valves were evaluated, and pulmonary artery systolic pressure was estimated. Valvular insufficiency was rated as absent, trace, mild, moderate, or severe for all but the pulmonic valve. With regards to pulmonic valve regurgitation, the central reader assessed only if regurgitation was “Absent” or “Present” as is normal in clinical practice. Similar patterns of small increases and decreases in valvular insufficiency and pulmonary artery pressures were observed across treatments in both studies. There was no apparent effect of treatment on these assessments. See the Investigators’ Brochure for further details.

Thorough ECG Study: A 7-day study of lorcaserin at 15 mg QD and 40 mg QD showed no effect on heart rate, AV conduction, depolarization, or cardiac repolarization as measured by the PR, QRS or QTc interval durations. The validity of the trial was confirmed by use of a moxifloxacin positive control group, which showed the expected change in QTc duration, and a placebo group that showed no change in QTcI.

Pharmacokinetics: The time to maximum plasma concentration (T_{max}) following oral administration of lorcaserin was approximately 2 hours after dosing, and estimated plasma $t_{1/2}$ was 10 to 11 hours. Lorcaserin plasma levels achieved steady state by Day 5 of dosing. Exposure for the pharmacologically inactive, major circulating metabolite, N-sulfonate lorcaserin (M1), was 3-3.5-fold greater than for the parent, with a $t_{1/2}$ of ~40 hours.

Lorcaserin can be taken with or without food, as C_{max} and exposure were unchanged by a high-fat meal. However, the T_{max} in females was prolonged from 2 hours without food to about 6 hours with food.

Efficacy of Lorcaserin.

In the Phase 2a study (Protocol APD356-003), the primary efficacy endpoint was a reduction in body weight in patients completing the 28-day treatment period (Day 29). Compared to placebo, treatment with lorcaserin was associated with a highly statistically significant average weight loss of 1.3 kg in the 15 mg group versus 0.3 kg in the placebo group. No statistically significant weight loss was observed in the 1 mg or 5 mg groups. Similar results were observed in the intent-to-treat; last observation carried forward (LOCF) analysis. The table below summarizes the mean weight change for all patients completing the treatment period in each group (Table 4).

Table 4. APD356-003 Completers Analysis for Change from Baseline Weight during the Treatment Period

	Placebo (N=71)	1 mg (N=75)	5 mg (N=72)	15 mg (N=69)
Demographics (randomized patients; mean [sd])				
n	86	90	89	87
Age	40.1 (12.1)	41.1 (10.8)	40.2 (10.8)	38.3 (11.5)
Gender (% female)	77.9	82.2	82.0	78.2
Baseline weight (kg)	99.7 (17.0)	100.4 (16.9)	100.5 (17.4)	105.0 (20.7)
Baseline BMI (kg/m ²)	35.6 (4.6)	36.5 (5.1)	36.0 (4.5)	36.9 (5.7)
Change from Baseline – Week 4¹				
n	71	75	72	69
Mean (±SD)	-0.3 (1.45)	-0.3 (1.42)	-0.4 (1.63)	-1.3 (1.49)
Range	-4, 3	-4, 3	-5, 3	-5, 3
Parametric Analysis: Equal Slope ANCOVA Model²				
LS Mean (SEM)	-0.4 (0.19)	-0.3 (0.19)	-0.5 (0.20)	-1.3 (0.20)
Difference (Treatment – Placebo)		0.04	-0.13	-0.98
95% Confidence Interval		(-0.45, 0.53)	(-0.63, 0.36)	(-1.49, -0.48)
P-value		0.8733	0.5922	0.0002

¹ Baseline is the last available measurement before first dose of study drug (Day 1)

² Change from baseline weight is analyzed using an equal slope ANCOVA model with treatment, pooled site, and gender as fixed effects and baseline weight and age as covariates.

In the Phase 2b study (Protocol APD356-004), the primary efficacy endpoint was reduction in body weight in patients completing the 12-week treatment period. Compared to placebo, treatment with lorcaserin was associated with highly statistically significant weight losses of 1.8, 2.6, and 3.6 kg in the 10 mg QD, 15 mg QD, and 10 mg BID groups versus 0.3 kg in the placebo group (Table 5). Similar results were observed in the intent-to-treat, LOCF analysis.

Table 5. Summary of Primary Efficacy Data from Phase 2b Study APD356-004

	Completers Analysis			
	Placebo	10 mg QD	15 mg QD	10 mg BID
Demographics [Mean (SD)]				
n	88	86	82	77
Age	41.6 (10.9)	41.5 (12.2)	41.3 (11.3)	41.5 (11.3)
Gender (% female)	87.3	82.1	93.2	85.3
Baseline weight (kg)	100.2 (15.0)	100.6 (15.4)	100.3 (14.4)	98.8 (16.9)
Baseline BMI (kg/m ²)	36.4 (4.0)	36.2 (4.1)	36.9 (4.2)	36.2 (4.1)
Change in Weight from Baseline to Day 85^a				
Mean (SD) (kg)	-0.30 (2.36)	-1.82 (2.53)	-2.57 (2.58)	-3.59 (2.83)
Range	-7.6, 4.8	-9.1, 2.8	-10.3, 4.2	-11.7, 3.0
Parametric Analysis: Equal Slope ANCOVA Model^b				
LS Mean (SEM) (kg)	-0.57 (0.32)	-1.95 (0.31)	-2.91 (0.36)	-3.71 (0.33)
Difference (Treatment-Placebo)		-1.379	-2.333	-3.140
95% Confidence Interval		-2.133, -0.624	-3.098, -1.568	-3.915, -2.364
P-value		< 0.001	< 0.001	< 0.001

^a Baseline is the last available measurement before first dose of study drug (Day 1)

^b Change from baseline weight is analyzed using an equal slope ANCOVA model with treatment, pooled site, and gender as fixed effects and baseline weight and age as covariates.

1.3 Summary of Non-Clinical Data

Lorcaserin has been extensively evaluated *in vitro* and *in vivo* to determine its pharmacological, pharmacokinetic, and toxicological effects in animal models as summarized below. See the Investigators' Brochure for further details.

Pharmacology: Lorcaserin significantly reduced food intake and body weight gain in acute and chronic studies in rats. Blood glucose regulation and plasma lipids were also improved (i.e., insulin, amylin, total cholesterol, and triglycerides were all significantly decreased). Further, lorcaserin-induced weight loss was associated primarily with the loss of body fat, while lean body mass was conserved. Upon withdrawal of lorcaserin after 28 days, dietary intake and body weight returned to control animal levels within 10 days.

Pharmacokinetics: Lorcaserin was readily absorbed with good oral bioavailability across species (i.e., Sprague-Dawley rats [93%], beagle dogs [37%], and cynomolgus monkeys [51%]). Systemic exposure, measured by plasma concentrations after oral administration of 10 mg/kg, was relatively constant across most species tested (i.e., mouse, rat, dog and cynomolgus monkey). The plasma half-life of lorcaserin after intravenous (i.v.) administration was also relatively constant across most species (i.e., 3.4 to 4.7 hours in the rat, dog, and cynomolgus monkey). Oral exposure increased dose-proportionately up to doses of approximately 100 mg/kg in the rat and cynomolgus monkey. Target organ exposure to lorcaserin (i.e., the brain) occurred rapidly after oral administration in the rat;

lorcaserin brain concentrations were proportional to plasma concentrations, and exceeded plasma concentrations by approximately 13-fold. Lorcaserin was highly bound (~75%) to human plasma proteins. Lorcaserin metabolites produced *in vitro* include multiple monohydroxylated and dihydroxylated derivatives, such as the 7-hydroxy (M2) and N-hydroxy metabolites, as well as the N-sulfonate lorcaserin (M1). Lorcaserin metabolites produced by human liver microsomes were also produced by other species, including those used in toxicology studies (i.e., rats, rabbits and cynomolgus monkeys). Lorcaserin induced hepatic microsomal drug metabolism systems in the rat; this induction did not result in significantly lower lorcaserin plasma exposures and was reversible.

Toxicology: The toxicity of lorcaserin was assessed in safety pharmacology studies; single and repeat oral dose studies for up to 12 months in the monkey, 6 months in the rat, and 3 months in mice; developmental toxicity studies in pregnant rats and rabbits; and genotoxicity studies.

In rats, single doses of lorcaserin induced salivation at doses of 100 mg/kg or greater (human equivalent dose [HED] = 1.13 g/day); decreased activity and caused tremors at doses of 500 mg/kg or greater (HED = 5.65 g/day); and caused mortality at 1000 mg/kg (HED = 11.3 g/day). In mice, a single dose ≥ 100 mg/kg was associated with convulsions; doses ≥ 1000 mg/kg caused mortality.

In repeat-dose studies in rats and mice, the most notable findings included increased regeneration of red blood cells in the spleen, and reticulocytosis at doses ≥ 10 mg/kg/day (HED = 113 mg/day). Liver vacuolation and hypertrophy were observed at doses of 30 mg/kg/day or greater (HED = 338 mg/day) in rats, and 25 mg/kg/day in mice. Tremors, salivation, increased sensitivity to touch, and increased relative kidney weights were observed at 50 mg/kg/day (HED = 565 mg/day), and pulmonary histiocytosis was observed at doses of 100 mg/kg/day or greater (HED = 1.13 grams/day) in rats. Clonic convulsions, hunched posture, tremors, and eventually death were observed in all rats by Day 10 at 500 mg/kg/day. In mice, prostration and mortality were observed at 350 mg/kg/day. Clinical signs in rats included the pharmacological effects of decreased body weight gain and food consumption, and penile erection.

In monkeys, single doses of lorcaserin induced emesis at 300 mg/kg (HED = 6.8 g/day). In repeat-dose studies in monkeys, emesis was dose-limiting and the pharmacological effects of penile erection, decreased food consumption, and decreased body weight were observed. Mild, transient increases in AST and increased relative liver weights were observed at doses of 10 mg/kg/day or greater (HED = 226 mg/day). In the 12 month study, mild, multifocal renal tubular regeneration was observed at 2-125 mg/kg/day. The changes were not associated with changes in renal function, and were deemed clinically insignificant and not assessed as drug-related by two independent clinical renal pathology consultants. Mild, transient increases in ALT were observed at 100 mg/kg/day (HED = 2.3 grams/day). Convulsions were observed in one monkey on the first day of dosing at 100 mg/kg/day (HED = 2.26 g/d).

After 13 weeks of dosing, no histopathological changes were observed in the four heart valves or the pulmonary vasculature of the rat, mouse or cynomolgus monkey given

lorcaserin daily up to 200/100 mg/kg/day, 250 mg/kg/day (highest dose group reaching scheduled necropsy) and 125 mg/kg/day, respectively. In chronic studies, heart valve histopathology was normal after 12 months of lorcaserin administration at doses up to 125 mg/kg/day in the monkey, and after 6 months at doses up to 50 mg/kg/day in the rat.

The NOEL and NOAEL values in both the 13 week and 6 month studies in rats were 1 and 5 mg/kg/day, respectively. For monkey, 2 mg/kg/day constitutes a low effect level for the minimal histopathologic changes in kidney (1 of 8 animals with a single focus of minimal renal tubular regeneration).

Safety margins were derived for each species against empirically derived or modeled values of human exposure for the highest dose planned for phase 3, 10 mg BID. The predicted steady state for lorcaserin exposure for 10 mg BID is 0.932 hr- μ g/mL. Relative to estimated human exposure at the proposed dose for phase 3, the safety margins for male and female per species are 2.2 and 1.4 for rat based on the NOAEL of 5 mg/kg/day, 4.4 and 1.2 for mouse at the NOAEL of 50 mg/kg/day, and 1.2 and 0.5 for the monkey based on the low effect dose of 2 mg/kg/day.

Additional toxicology studies

No risks were identified in the safety pharmacology studies, genotoxicity studies and developmental studies in pregnant animals. Further details concerning the available pre-clinical data on lorcaserin may be found in the Investigator's Brochure.

1.4 Rationale for Proposed Clinical Study

This study has been designed to assess the safety and efficacy of lorcaserin after 104 weeks of administration. Eligible patients will be obese (BMI 30 to 45 kg/m²) with or without co-morbidities, or overweight (BMI 27 to 29.9 kg/m²) with at least one co-morbidity. The Year 1 primary endpoint will be the proportion of patients achieving \geq 5% weight reduction at the end of Year 1 (Week 52). The Year 2 primary endpoint, which is assessed in patients treated with lorcaserin in Year 1 who achieve 5% or greater weight loss from baseline to the end of Year 1, is the proportion of subjects maintaining at least a 5% weight loss at the end of Year 2 (Week 104).

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

- Year 1 primary endpoint: To assess the weight loss effect of lorcaserin at the end of Year 1 (Week 52)
- Year 2 primary endpoint: To assess the ability of lorcaserin to maintain body weight loss achieved during Year 1, as assessed at the end of Year 2 (Week 104)

2.2 Secondary Objective(s)

- To assess the ongoing safety of lorcaserin
- To assess specifically any changes in heart valve regurgitation or pulmonary artery pressure associated with the use of lorcaserin
- To assess potential further weight loss during the second year of treatment
- To assess any changes in cardiovascular risk factors associated with obesity (i.e., dyslipidemia, insulin sensitivity, hypertension, central fat distribution, biomarkers of CV risk)
- To assess any changes in mood
- To assess any changes in Quality of Life measures

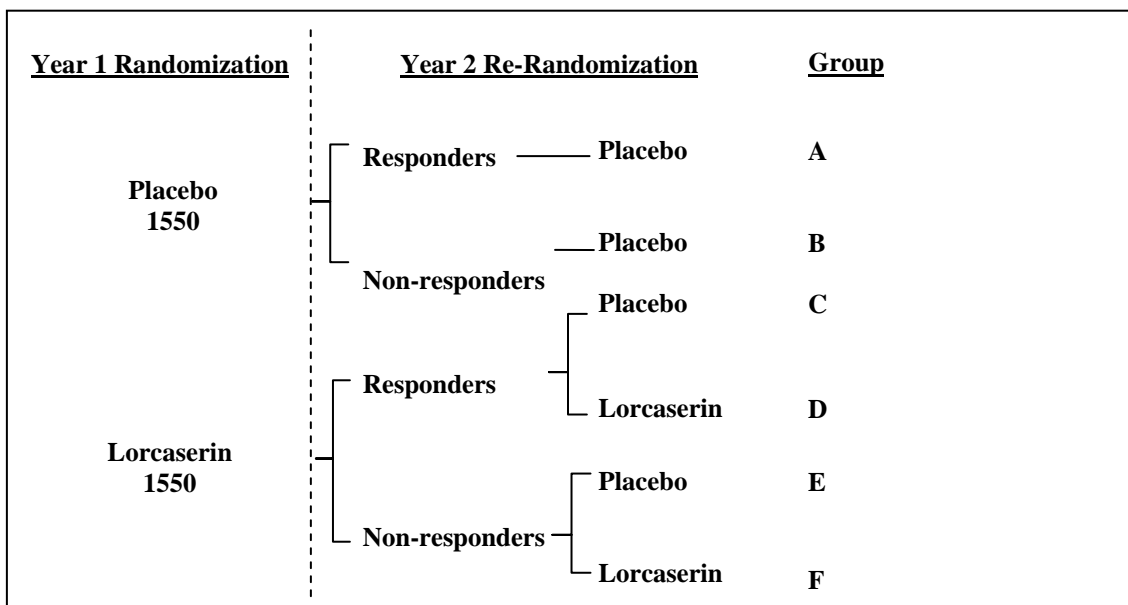
3 STUDY DESIGN

This study will be conducted as a randomized, double-blind, placebo-controlled, parallel group study to assess the effects of lorcaserin (lorcaserin hydrochloride) during 104 weeks of administration to obese male and female volunteers aged 18 to 65 years (inclusive). The primary efficacy objective for Year 1 of the study is to assess the proportion of patients achieving $\geq 5\%$ reduction in body weight after 52 weeks of treatment compared to baseline. The primary efficacy objective for Year 2 of the study is to assess the ability of lorcaserin to maintain patients' weight loss achieved by the end of Year 1 through the end of the second year.

In Year 1, approximately 3,100 patients will be randomized using a 1:1 schema assigning patients to 1 of 2 treatment groups: placebo or lorcaserin 10 mg twice-a-day (BID). To maintain the study blind, all patients will be instructed to take a dose of study medication (placebo or lorcaserin 10 mg) in the morning (approximately 60 minutes prior to breakfast) and a second dose of study medication in the evening (approximately 60 minutes prior to dinner).

Patients who complete the initial 52 weeks of treatment will be eligible to continue in the study. Patients will be stratified as "responders" ($\geq 5\%$ body weight loss from Baseline to Week 52) or "non-responders" ($< 5\%$ body weight loss). Patients receiving placebo during Year 1 will remain on placebo for Year 2. Patients receiving lorcaserin during Year 1 will be re-randomized within each of these two strata in a 2:1 ratio to either remain on lorcaserin 10 mg BID or switch to placebo, respectively, for Year 2. In order to maintain approximately balanced groups and the study blind, all patients will receive a new randomization number at the beginning of Year 2. It is anticipated that 60% of the patients initially randomized will complete the first year of treatment. Of those re-randomized at Week 52, it is anticipated that 60% of those patients will complete Year 2. A schematic diagram is shown in Figure 1.

Figure 1. Study Design Schematic



Based on these assumptions and a balanced completion across all treatment groups, Table 6 summarizes the anticipated number of patients for each sequence through Year 2.

Table 6. Treatment Sequences

Year 1 Treatment	No. of patients randomized	Projected number of patients (60%) completing Year 1	Year 2 Treatment	Est. No. of patients re-randomized¹	Projected number of patients (60%) completing Year 2
Placebo	1550	930	Placebo	930	558
Lorcaserin 10 mg BID	1550	930	Placebo	310	186
			Lorcaserin 10 mg BID	620	372

¹ The estimated number of patients re-randomized at Year 2 is based on the assumption of a 60% completion rate at the end of Year 1. The actual number of patients may vary from this estimation depending on the actual number of patients who complete Year 1 and are re-randomized.

Each patient will undergo screening procedures within 3 weeks, or sooner, prior to dosing on Day 1. Eligible patients will be randomized to receive study medication for an initial 52 weeks, with periodic follow-up visits to assess efficacy and safety parameters. See [Table 7](#) for detail of Year 1 procedures. Patients who complete the initial 52 weeks of treatment will be eligible to continue in the study for Year 2. See [Table 8](#) for detail of Year 2 procedures.

Table 7 (continued). APD356-009 Schedule of Procedures and Visits (Year 1) – footnotes

¹	All screening activities are to be completed within 28 days, or sooner, prior to dosing on Day 1.
²	At the completion of Year 1 or upon early termination from the study, all procedures should be performed as indicated. For patients who prematurely discontinue during Year 1, an exit visit will be performed upon exit from the study and a follow-up phone call will be performed approximately 2 weeks after the exit visit. Discontinued patients will be asked to return at the intended Week 52 visit, even if interim visits have been missed, for a follow-up body weight. Refer to Section 5.5.1 for guidance regarding the Exit echocardiogram for patients who discontinue the study during Year 1.
³	The screening echocardiogram should be performed for patients that have been deemed eligible for the study by meeting all other entry criteria.
⁴	PK sampling will be performed only at a subset of study sites at the Week 12 Visit (pre-dose and 2 hours (± 15 mins) after dose.
⁵	A plasma sample will be collected from each patient at Day 1 (baseline), Week 24, and Week 52 or upon Early Termination. Patients will have the ability during the informed consent process to opt out of having these samples collected. These plasma samples will not be used for genetic testing.
⁶	Serum hCG pregnancy test required at Screening and Week52/Exit for all female subjects. Urine dipstick pregnancy test will be done at other study visits as indicated for all female subjects.
⁷	Vital sign measurements (blood pressure, heart rate, respirations, and body temperature taken in supine position after 5-minute rest); Day 1 measurements will be taken before first dose
⁸	Sites will call the IVRS as indicated starting at the Screening Visit. The IVRS will be used to track screening and randomization and each patient's progress through the study to ensure that adequate drug supply is at the site. On Day 1 and at Week 52, the site will be requested to enter the patient's body weight, which will be used to stratify each patient for re-randomization at Year 2.
⁹	Randomized patients will be instructed to administer one dose in the morning (about 60 minutes prior to breakfast) and one dose in the evening (about 60 minutes prior to dinner).

Table 8 (continued). APD356-009 Schedule of Procedures and Visits (Year 2) – footnotes

- ¹ At the completion of Year 2 or upon early termination from the study, all exit procedures will be performed as indicated. In addition, there will be a phone follow-up 2-weeks after the final dose of study medication (~Week 106) for those who complete the dosing period or 2 weeks after the exit visit for those patients that discontinue the study early, during which any AEs will be collected and reported. For patients who prematurely discontinue during Year 2, consistent with Year 1 procedures, an exit visit will be performed upon exit from the study and a follow-up phone call will be performed approximately 2 weeks after last dose of study medication. Discontinued patients will be asked to return at the intended Week 104 visit, even if interim visits have been missed, for a follow-up body weight. Refer to Section 5.6.1 for guidance regarding the Exit echocardiogram for patients who discontinue during Year 2.
- ² A serum hCG pregnancy test will be done at the Week 104/Exit visit for all female subjects. A urine dipstick pregnancy test will be done at all other visits as indicated for all female subjects.

4 PATIENT ELIGIBILITY

The study population will consist of male and female patients ages 18 to 65 years (inclusive) who are considered obese based on a BMI 30 to 45 kg/m² with or without a co-morbid condition, or who are considered overweight based on a BMI 27 to 29.9 kg/m² and with at least one co-morbid condition (hypertension, dyslipidemia, CV disease, glucose intolerance, sleep apnea). Eligible patients must meet all the following entry criteria prior to being randomized to receive study medication. Any deviations from these criteria must be approved by Arena prior to the patient being randomized.

4.1 Inclusion Criteria

1. Males or females aged between 18 and 65 years (inclusive)
2. Able to give signed informed consent
3. Ambulatory and able to perform exercise program (Arena Healthy Lifestyle Program, see Appendix C)
4. a. Eligible female patients will be:
 - non-pregnant, evidenced by a negative serum hCG pregnancy test at Screening and a urine dipstick pregnancy test on Day 1 prior to dosing
 - non-lactating
 - surgically sterile or postmenopausal, or agree to continue to use an accepted method of birth control during and for at least 3 months after last study medication administration
 - Acceptable methods of birth control are: hormonal contraceptives; single barrier method; intrauterine device; surgical sterility for at least 3 months prior to screening for tubal ligation performed laparoscopically; surgical sterility for at least 6 months prior to screening for hysterectomy and/or bilateral oophorectomy; and/or postmenopausal status (defined as at least 2 years without menses). Abstinence is not considered an acceptable method of birth control for this study.
- b. Eligible male subjects will be:
 - surgically sterile (i.e., vasectomy) for at least 3 months prior to screening or agree to use a condom when sexually active.
5. Body Mass Index (BMI) is 30 to 45 kg/m² (obese) with or without co-morbid conditions or 27 to 29.9 kg/m² (overweight) with at least one treated or untreated co-morbid condition (hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea). For untreated co-morbid conditions the condition must be considered by the Investigator to be clinically stable.
6. Considered to be in stable health in the opinion of the Investigator, as determined by:
 - A pre-study physical examination
 - A medical history indicating either no clinically significant abnormalities or stable co-morbid condition(s)

- Vital signs within normal ranges or if outside of the normal range are not deemed clinically significant in the opinion of the Investigator
- Pre-study clinical laboratory findings within normal range, or if outside of the normal range, not deemed clinically significant in the opinion of the Investigator
- A 12-lead ECG showing no active ischemia

4.2 Exclusion Criteria

1. Prior participation in any study of lorcaserin. Patients who signed an informed consent for a prior lorcaserin study may be eligible provided they were not randomized in the prior study, and there were no clinically significant findings from the previous study echocardiogram that would exclude them from this study.
2. Clinically significant new illness in the 1 month before screening
3. Not suitable to participate in the study in the opinion of the Investigator including an existing physical or mental condition that prevents compliance with the protocol
4. Diabetes mellitus (type I, II or other). A remote history of gestational diabetes that has resolved is not exclusionary.
5. Recent history (within 2 years before entering the study) of major depression, anxiety, or other psychiatric disease requiring treatment with prescription medication (e.g., SSRI's, SNRI's [including bupropion], tricyclics, antipsychotics, lithium). Use of SSRI's and SNRI's (including bupropion) for reasons other than active psychiatric indications (e.g., migraine, weight loss, smoking cessation) must meet a 3-month washout.
6. Total score on the Beck Depression Inventory-II (BDI-II) ≥ 20 or a score > 0 specifically on question #9 (Suicidal Thoughts or Wishes)
7. History of a binge eating disorder as suggested by a score > 17 on the Binge Eating Scale
8. History of epilepsy or other seizure disorder
9. Surgical procedure for the treatment of obesity (i.e., gastric bypass, gastric banding)
10. Anticipation of surgery during the study period that may interfere with completion or compliance with the protocol
11. Uncontrolled hypertension, defined as systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 on 2 separate readings which should be done on 2 separate days. Patients who have uncontrolled hypertension at screening may be re-screened > 1 month following initiation or adjustment of antihypertensive therapy
12. History of valve replacement surgery or CABG or other invasive cardiovascular surgical procedure including PCI. A diagnostic cardiac catheterization does not exclude the patient if no stent placement, angioplasty, or plaque removal occurred during the procedure.
13. Myocardial infarction (diagnosed by cardiac enzyme[s] and/or diagnostic ECG), CVA, TIA or RIND within 6 months, cardiac arrhythmia requiring medical or surgical treatment within 6 months of screening

14. Major surgical procedure (intrathoracic, intracranial, intraperitoneal, liposuction) within 6 months of screening
15. Unstable angina
16. History of congestive heart failure caused by insufficiency or stenosis of any heart valve.
17. History of pulmonary artery hypertension
18. Symptomatic untreated congestive heart failure of any etiology (stably treated class I or II CHF of ischemic or hypertensive etiology is acceptable)
19. History of organ transplantation
20. Abnormal TSH lab value greater than 1.5x ULN. Patients with slightly higher TSH (~2x ULN) will be considered on an individual basis if T4 is in the mid-to high portion of the normal range or free T4 is normal. If initiation or adjustment of L-thyroxine is anticipated, patients should not be enrolled
21. Hyperthyroidism, including abnormal screening lab values with T4>ULN and TSH<LLN, and patients taking methimazole or PTU and/or beta-blockers for hyperthyroidism.
22. Fasting triglycerides > 499 mg/dL on 2 days (i.e., if elevated at Screening, but not on a subsequent re-check, patient will be eligible; if elevated on re-check, patient is not eligible). Patients with fasting triglycerides >499 and LDL-cholesterol <130 may be eligible for the study if they have no history of pancreatitis, CVA, TIA, RIND, or myocardial infarction, but must be approved through the ICON Medical Monitor prior to randomization. Patients with elevated triglycerides at screening may be re-screened >3 months after initiation or adjustment of lipid lowering treatment, if study enrollment has not been closed.
23. LDL-cholesterol \geq 190 mg/dL. Patients with elevated LDL-cholesterol at screening may be re-screened >3 months after initiation or adjustment of lipid lowering treatment, if study enrollment has not been closed.
24. HbA1c greater than ULN (i.e., > 6.5%)
25. Fasting glucose >126 mg/dL on 2 days (i.e., if elevated at Screening, but not on a subsequent re-check, patient will be eligible; if elevated on re-check, patient is not eligible).
26. Clinically significant abnormal hepatic (e.g., AST or ALT greater than 2.5x ULN, or total bilirubin greater than 1.5x ULN) or renal function lab tests (e.g., creatinine greater than 1.25x ULN) suggestive of hepatic or renal impairment
27. Positive result of HIV, hepatitis B or hepatitis C screens
28. Malignancy within 5 years of the screening visit (except basal cell or squamous cell carcinoma with clean surgical margins)
29. Initiation of a new prescription medication within 1 month prior to screening with the following exceptions:

- Patients being treated for dyslipidemia (e.g., statins) must be on a stable dose of prescription medication or OTC niacin for at least 3 months prior to screening
 - Patients being treated for hypothyroidism must be adequately replaced on a stable dose of medication (e.g., levothyroxine) for at least 3 months prior to screening
 - Patients receiving a short course (≤ 10 days) of prescription antibiotic, antifungal, or antiviral partially or entirely within the 1 month preceding the screening visit for the following conditions:
 - Dental work
 - Sinusitis
 - Pharyngitis
 - Bronchitis (acute)
 - Otitis media
 - Minor superficial skin infections (e.g., impetigo, carbuncle)
 - Uncomplicated urinary tract infection (cystitis, urethritis)
 - Vulvovaginal candidiasis
 - Occasional antiviral use for recurrent genital herpes simplex
30. Medication history that includes use of one or more of the following:
- Any use of fenfluramine or related derivatives (i.e., dexfenfluramine, norfenfluramine)
 - Use within 5 years of the Screening Visit agents that have documented correlation with increased incidence of valvulopathy and/or primary pulmonary hypertension (e.g., Cyproheptadine, Trazodone, Nefazodone, Amoxapine, tricyclic antidepressants, mirtazapine, pergolide, ergotamine, methysergide)
31. Recent treatment (i.e., within 1 month of the screening visit) with over-the-counter weight loss products or appetite suppressants (including herbal weight loss agents) or St. John's Wort, or within 3 months with a prescription anti-obesity drug (e.g., phentermine, sibutramine, orlistat) or lipid dissolving injections (e.g., Lipodissolve)
32. Recent treatment (i.e., within 3 months of the screening visit) with oral or parenteral corticosteroids, metformin, or topiramate
33. Recent history (within 2 years prior to the screening visit) of alcohol or drug/solvent abuse or a positive screen for drugs of abuse at screening. In some cases, patients with a positive drug screen may be eligible for the study with approval from the Medical Monitor if the patient has a documented medical history (e.g., osteoarthritis) requiring the need for chronic pain treatment and a documented concomitant medication resulting in a positive drug screen and provided the patient is considered by the Investigator to be reliable to participate in the study.
34. Significant change in smoking habits within 3 months prior to screening
35. Smoke more than $\frac{1}{2}$ pack of cigarettes per day, more than 2 cigars/day, or use 3 or more pinches of smokeless tobacco per day

36. Participated in any clinical study with an investigational drug, biologic, or device within 1 month prior to the first day of dosing
37. Significant change in diet or level of physical activity within 1 month prior to dosing.
38. Change in weight of >5 kg within 3 months
39. Use of very-low calorie (< 1,000/day) liquid weight loss diet within 6 months
40. Unwilling, or whose partner is unwilling, to use an adequate means of contraception during and for 3 months following completion/withdrawal of the study
41. Documented sensitivity to gelatin (lorcaserin will be contained in gelatin capsules).
42. Any of the following findings on screening echocardiography:
 - Aortic regurgitation mild or greater
 - Mitral regurgitation moderate or greater
 - Mitral or aortic valve stenosis greater than mild (i.e., AS: jet > 3.0 m/s, mean gradient > 25 mmHg, and AVA < 1.5 cm²; MS: mean gradient > 5 mmHg and MVA < 1.5 cm²)
 - Pulmonary artery pressure (PASP) >40 mm Hg (and/or tricuspid regurgitation jet velocity >2.9 m/s)
 - In cases where an actual PASP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a RVOTAT ≤ 100 msec will be excluded, suggesting an elevated mean pulmonary artery pressure; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.
 - Left ventricular ejection fraction <45%
 - Intracardiac mass, tumor or thrombus
 - Evidence of congenital heart disease
 - Clinically significant pericardial effusion (e.g., moderate or larger or with hemodynamic compromise)

5 STUDY METHODS

The schedule of events for Year 1 and Year 2 are presented in [Table 7](#) and [Table 8](#), respectively.

5.1 Screening and Enrollment

At the initial screening visit, potential patients will have a detailed oral presentation of the nature, purpose, risks, and requirements of the study in addition to receiving detailed written information. They will have adequate opportunity to ask the appropriate person of the clinical staff (i.e., Principal Investigator or designee) presenting the study about any aspect of the study. Once the patient is satisfied that he/she is willing to participate in the study, he/she will be asked to sign the study Volunteer Informed Consent Form (VICF). The clinical personnel obtaining written consent from the patient will also sign the form to confirm consent has been obtained. Once signed, the Investigator will retain the original for the patient's study records and provide the patient with a signed copy. The Investigator will verify that informed consent has been obtained from each patient prior to admission into the study and prior to the patient undergoing any study-related procedures. In some study centers, it is standard practice to conduct a few general procedures common to most all clinical protocols (i.e., medical history, drug abuse screen, and physical examinations) before a patient can be considered for a specific study. In these cases, this is allowed provided that the study center has a written SOP detailing the procedure and that each patient signs a general consent prior to undergoing the general procedures.

A unique patient screening number will be assigned upon completion of the VICF. The patient screening number will consist of six digits, ###-S###, where the first three digits are the assigned site number by Arena. The final three digits are the consecutive sequential screening number at the site. For example, site #19, the first patient screened will be 019-S001.

Within 28 days before administration of the study medication, or sooner, all screening activities subsequent to obtaining informed consent will be conducted and consist of:

- Complete medical history, including tobacco, alcohol, and caffeine use
- Physical and neurological examination, including height, weight, waist and hip circumference, waist/hip ratio, and vital signs (i.e., supine blood pressure, pulse rate, respiration rate and temperature after a 5 minute rest)
- Beck Depression Inventory and Binge Eating Scale
- 12-lead ECG
- Clinical laboratory tests (hematology, biochemistry, urinalysis and urine drug screen) thyroid function tests (TSH and T₄), hemoglobin A1c, and virology screen (HBsAg antigen, HIV antibodies, and Hepatitis C antibodies). Patients are required to fast for 10 hours prior to blood samples being taken for clinical laboratory tests.
- Screen for drugs of abuse
- Serum hCG pregnancy test (females only)
- Echocardiogram (this should be the last screening procedure after all other screening procedures have been completed and continued eligibility determined)

5.2 Screening Failures

A screening failure is defined as a patient who has signed the VICF, does not meet all the entry criteria as outlined in this protocol and has not been randomized or received study medication. A screening log will be maintained by the Investigator indicating the reason for the screening failure.

Deviations to the entry criteria may be allowed as approved by the Investigator and the Sponsor. Patients that are allowed to enroll in the study under a protocol deviation approval will not be considered screening failures. All protocol deviation approvals will be documented in writing and maintained in the Investigator and Sponsor files.

5.3 Randomization Procedures

5.3.1 Year 1 Randomization.

Approximately 100 study sites will randomize approximately 3100 patients (~30-32 patients/site) in this study. Enrollment will be competitive and no site is guaranteed a minimum number of patients for this study. The maximum number of patients enrolled at a single site is limited to 100 patients, unless permission is otherwise granted from Arena.

After signing the VICF and completing all screening procedures, eligible patients will be randomly assigned in a 1:1 ratio to receive 1 of 2 study treatments: placebo or lorcaserin 10 mg BID. Randomization and assignment of study treatment kits will be performed via the IVRS. The randomization numbers will be sequentially assigned 4-digit numbers (####, ranging from 0001 to 5000).

5.3.2 Year 2 Re-randomization

Patients who complete the initial 52 weeks of treatment will continue in the study. At the Week 52 visit, each patient's body weight will be entered into the IVRS system. The IVRS system will compare the Week 52 body weight with the body weight entered at the time of randomization (Day 1). Based on body weight, patients will be stratified as "responders" ($\geq 5\%$ body weight loss from Day 1 to Week 52) or "non-responders" ($< 5\%$ body weight loss). Patients receiving placebo during Year 1 will remain on placebo for Year 2.

Patients receiving lorcaserin during Year 1 will be re-randomized within each of these two strata in a 2:1 ratio to either remain on lorcaserin 10 mg BID or switch to placebo, respectively, for Year 2. At Week 52, each patient will receive a new 4-digit randomization number (####, beginning at 5001) for Year 2 and will begin to receive the treatment assigned during this re-randomization procedure.

5.4 Allowable Visit and Procedure Windows

The following are the allowable windows for specific study visits and procedures:

- Screening: within 28 days prior to dosing on Day 1
- Study Visit Days: ± 7 days (with the exception of Week 2 visit, which should be ± 3 days)
- Week 24, 52, 76, and 104 Echocardiograms: ± 14 days

5.5 Year 1 Dosing Period

Patients who meet all the entry criteria and are eligible for the study will report to the Investigator to be randomized and receive their study medication. The first dose of study medication will be given in the morning at the study site on Day 1. Patients will return to the study site during Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 for interim assessments and during Week 52 for re-randomization and interim assessment procedures.

The screening visit(s) can be scheduled as needed at any time of the day. However, it is required that the Day 1 visit occur in the morning. It is suggested that all other study visits also occur in the morning, but it is not a requirement. Prior to each visit that involves a blood draw; patients are to be instructed to fast for at least 10 hours to provide the most accurate assessment for clinical labs and body weight. Water intake is allowed as needed.

Between study visits, patients will be instructed to take their morning dose of study medication upon awakening and about 60 minutes prior to eating breakfast and their evening dose of study medication about 60 minutes prior to eating dinner. Patients should be encouraged to wait approximately 60 minutes after taking their study medication before they eat. Although evidence suggests that lorcaserin can be taken with or without food, it is important for patients to follow these instructions to standardize administration of study medication. Furthermore, peak drug levels at the time of meals may optimize presumptive drug effects on satiety.

In the event that a patient forgets to take a dose of study medication, the patient should be instructed in accordance with the following. If the morning dose is forgotten, then the patient may take the dose prior to noon of the same day. If the dose cannot be taken before noon of the same day, then the dose should be skipped and the evening dose taken as planned. If the evening dose is forgotten, then the patient may take the dose prior to midnight. If the dose cannot be taken before midnight, then the dose should be skipped and the next morning's dose taken as planned. Patients should not take more than the prescribed amount of 1 capsule in the morning and 1 capsule in the evening. If a dose is missed, this will be recorded in the CRF as part of the compliance assessment. Continued noncompliance may lead to a patient being removed from the study.

The following study procedures will be performed on every study visit day (see [Table 7](#) for schedule) unless otherwise specified:

- Beck Depression Inventory – II (Weeks 4, 12, 24, 36, and 52)
- Echocardiogram (Weeks 24 and 52)
- 12-lead ECG (Weeks 4, 24 and 52)
- Clinical laboratory assessment including hematology, serum chemistry, and urinalysis. Patients are required to fast for 10 hours prior to blood samples being taken for clinical laboratory tests (Day 1 [before first dose] and Weeks 4, 12, 24, 36, and 52). In addition, thyroid function and hemoglobin A1c will be tested during Weeks 24 and 52.
- CV risk markers (CRP, fibrinogen) (Day 1 [before first dose] and Weeks 24 and 52)

- Markers of glucose intolerance (fasting glucose and insulin) (Day 1 [before first dose] and Weeks 12, 24, 36, and 52)
- Collect pre-dose PK blood sample at subset of study sites (Week 12 visit only)
- Collect pre-dose plasma sample for banking (Day 1, Week 24, and Week 52 or upon Early Termination only). Patients will have the ability during the informed consent process to opt out of having these samples collected.
- Urine dipstick pregnancy test (females only); Day 1 test will be performed before first dose
- Vital sign measurements (blood pressure, heart rate, respirations, and body temperature taken in supine position after 5-minute rest); Day 1 measurements will be taken before first dose
- Body weight and waist/hip measurements; Day 1 measurements will be taken before first dose
- Quality of Life Assessment (Impact of Weight Questionnaire) (Day 1 [before first dose] and Weeks 12, 24, and 52)
- Diet and exercise counseling
- Collect study medication and conduct individual patient study medication accountability and reconciliation
- Concomitant medication assessment; Day 1 assessment will be completed before first dose
- Tobacco use assessment
- Adverse events assessments; Day 1 assessment will be completed before first dose

As the expected T_{max} of lorcaserin is approximately 2 hours, after the first dose of study medication (Day 1), the patients will remain in the clinic for approximately 2 hours after dosing. This will allow for close monitoring of each patient in the event that treatment emergent events are observed after the first dose. Each dose of study medication should be administered with plenty of water (approximately 8 oz or 240 mL).

The following study procedures will be performed after dosing on every study visit day (see [Table 7](#) for schedule) unless otherwise specified.

- Collect blood sample for PK analysis 2 hours (\pm 15 minutes) after dose (at a subset of sites only; Week 12 visit only)
- Record vital signs 2 hours (\pm 15 minutes) after the first dose (Day 1 only)
- Dispense new study drug pack (Day 1, and every 4 weeks thereafter); collect unused portion of previous pack (see Section 9.3 for package contents).
- Ensure that proper accountability information is recorded on the drug accountability log for each patient.
- Provide patient with instructions for administering study medication and reminder for next study visit.

- Remind patient of study exclusions and not to take any other medications without prior approval from the Investigator and to call if they experience any significant changes in their well-being.

5.5.1 Exit Procedures (Year 1 Study Completion/Early Termination/Re-randomization)

All procedures will be performed the day after the last dose of study medication at Week 52, with the exception of the Binge Eating Scale, medical history, virology screen, drugs of abuse screen and PK sampling (see [Table 7](#)). For patients who prematurely withdraw from the study during Year 1, reasonable efforts should be made to complete the exit procedures described above (weight, waist circumference, physical exam, BDI-II, clinical laboratory test, ECG, quality of life assessment, and AE monitoring [see [Table 7](#)]). Guidance for Year 1 Exit echocardiograms is provided below. Although all exit procedures are important and should be completed, if a patient is unwilling to undergo the procedures, at a minimum an exit weight should be obtained. Patients who withdraw from the study prematurely will also be followed up with a phone call 2 weeks after the last dose to assess any AEs reported following cessation of study medication.

When a patient misses a final or early termination visit, efforts to contact the patient for follow-up should include, at a minimum, two completed telephone calls and one certified letter. A record of the phone contacts and certified letter should be kept in the patient's source records at the study site. In particular reasonable efforts will be made to obtain a body weight measurement on *every* patient at the scheduled time of his or her Week 52 visit, even if interim visits have been missed.

If a patient discontinues during Year 1, the following guidance applies for the Exit echocardiogram:

- The patient discontinues from the study prior to Week 24 Visit, then an Exit echocardiogram will be performed at the time of exit **and** the patient will be scheduled for an additional post-study echocardiogram at the intended Week 52 visit.
- The patient discontinues from the study after the Week 24 echocardiogram, but prior to the Week 36 visit, then the Week 24 echocardiogram will serve as the Exit echocardiogram and the patient will be scheduled for an additional post-study echocardiogram to occur at least 3 months after the Week 24 echocardiogram (i.e., no sooner than the intended Week 36 Visit, but no later than the intended Week 52 Visit).
- The patient discontinues at or after the Week 36 Visit, but prior to the Week 52 echocardiogram, then an exit echocardiogram will be done at the time of exit and no additional echocardiogram will be performed.

Patients who complete the initial 52 weeks of treatment will be eligible to participate in the Year 2 dosing period. Patients will be re-randomized according to the process described in [Section 5.3.2](#).

5.6 Year 2 Dosing Period

Patients who are eligible for Year 2 of the study will report to the Investigator at Week 52 to be re-randomized and receive study medication. Patients will return to the study site during

Weeks 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, and 100 for interim assessments and during Week 104 for exit procedures.

The same general dosing instructions for Year 1 will also be used for Year 2. It is suggested that all Year 2 study visits occur in the morning, but it is not a requirement. Prior to each visit that involves a blood draw; patients are to be instructed to fast for at least 10 hours to provide the most accurate assessment for clinical labs and body weight. Water intake is allowed as needed.

Between study visits, patients will be instructed to take their morning dose of study medication upon awakening and about 60 minutes prior to eating breakfast and their evening dose of study medication about 60 minutes prior to eating dinner. Patients should be encouraged to wait approximately 60 minutes after taking their study medication before they eat.

If a patient forgets to take a dose of study medication, they should be advised in accordance with the guidance outlined in Section 5.5 (Year 1 Dosing) above. Patients should not take more than the prescribed amount of 1 capsule in the morning and 1 capsule in the evening. If a dose is missed, this will be recorded in the CRF as part of the compliance assessment. Continued noncompliance may lead to a patient being removed from the study.

The following study procedures will be performed on every study visit day (see [Table 8](#) for schedule) unless otherwise specified:

- Beck Depression Inventory - II (Weeks 64, 76, 88, and 104)
- Echocardiogram (Weeks 76 and 104, to be completed within 14 days after the last dose of study medication)
- 12-lead ECG (Weeks 76 and 104)
- Clinical laboratory assessment including hematology, serum chemistry, and urinalysis. Patients are required to fast for 10 hours prior to blood sample being taken for clinical laboratory tests (Weeks 64, 76, 88, and 104). In addition, hemoglobin A1c (HbA1c) will be tested during Weeks 76 and 104.
- Thyroid function tests will be done at the Week 104 visit only.
- CV risk markers (CRP, fibrinogen) and markers of glucose intolerance (fasting glucose and insulin) (both on Weeks 76 and 104)
- Urine dipstick pregnancy test (females only). Serum hCG pregnancy test required at Week 104/Exit.
- Vital sign measurements (blood pressure, heart rate, respirations, and body temperature taken in supine position after 5-minute rest)
- Body weight and waist/hip measurements
- Quality of Life Assessment (Impact of Weight Questionnaire - Lite) (Weeks 76 and 104)
- Diet and exercise counseling
- Collect study medication and conduct individual patient study medication accountability and reconciliation

- Concomitant medication assessment
- Adverse events assessments
- Dispense new study drug pack (Week 52 and every 4 weeks, thereafter); collect unused portion of previous pack (see Section 9.3 for package contents)
- Ensure that proper accountability information is recorded on the drug accountability log for each patient
- Provide patient with instructions for administering study medication and reminder for next study visit
- Remind patient of study exclusions and not to take any other medications without prior approval from the Investigator and to call if they experience any significant changes in their well-being

The same general dosing instructions for Year 1 will also be used for Year 2.

5.6.1 Exit Procedures (Study Completion/Early Termination)

All procedures will be performed the day after the last dose of study medication at Week 104 (see Table 8). There will be a telephone follow-up 2-weeks after the final dose of study medication (~Week 106) for those who complete 104 weeks of treatment, during which any AEs will be collected and reported. For patients who prematurely withdraw from the study during Year 2, reasonable efforts should be made to complete the exit procedures described above; these patients will also be followed up with a phone call 2 weeks after the last dose to assess any AEs reported following cessation of study medication. Although all exit procedures are important and should be completed, if a patient is unwilling to undergo the procedures, at a minimum an exit weight should be obtained.

When a patient misses a final or early termination visit, efforts to contact the patient for follow-up should include, at a minimum, two completed telephone calls and one certified letter. In particular reasonable efforts will be made to obtain a body weight measurement on every patient at the scheduled time of his or her Week 104 visit, even if interim visits have been missed or if a patient discontinues during Year 2.

If a patient discontinues during Year 2, the following guidance applies for the Exit echocardiogram:

- The patient discontinues from the study prior to Week 76 echocardiogram, an Exit echocardiogram will be performed at the time of exit and no additional echocardiograms will be performed, except as follows:
 - If a patient has **FDA-defined valvulopathy** on the echocardiogram obtained at Week 52, **AND** the patient discontinues from the study between Week 52 and Week 76, the following additional paradigm will be followed to assure that an appropriate subsequent echocardiogram is obtained:
 - If the Exit echocardiogram is obtained *prior to Week 64*, the patient will be asked to return for another echocardiogram at the time (± 4 weeks) of the intended Week 76 echocardiogram. This echo will be analyzed as the Week 76 echo.

- If the Exit echocardiogram is obtained *after Week 64*, the Exit echo will be analyzed as the Week 76 echo.
- Sites will be notified by ICON or the Sponsor to inform them when a patient meets these criteria. Most sites will have no patients who meet these criteria.
- The patient discontinues from the study after the Week 76 echocardiogram, but prior to the Week 88 Visit, then the Week 76 echocardiogram will serve as the exit echocardiogram and no additional echocardiogram will be performed.

The patient discontinues from the study after the Week 88 Visit, but prior to the Week 104 echocardiogram, an exit echocardiogram will be performed at the time of exit and no additional echocardiograms will be performed. For patients who discontinue from the trial prior to Week 52, but who return for the intended Week 52 echo, AND have FDA-defined valvulopathy on the intended Week 52 echocardiogram, the following additional paradigm will be followed to assure that a follow-up echocardiogram is obtained:

- The patient will be asked to return for an additional echocardiogram at the time of the intended Week 76 echocardiogram.
- Sites will be notified by ICON or the Sponsor to inform them when a patient meets these criteria. Most sites will have no patients who meet these criteria.

6 CONCOMITANT MEDICATIONS AND OTHER RESTRICTIONS

6.1 Concomitant Medication

All concomitant medications (OTC and prescribed) taken by patients during the screening period and during the study will be recorded in the CRF with start date/time and stop date/time, if known.

In general, Investigators should avoid co-administering CNS active drugs, and particularly serotonergic drugs, with lorcaserin until further safety data are obtained. See below for specific restrictions.

The following concomitant medication restrictions will apply:

- No new prescriptions within **1 month** prior to the Screening Visit except patients receiving a short course (≤ 10 days) of prescription antibiotic, antifungal, or antiviral partially or entirely within the 1 month preceding the screening visit for the following conditions:
 - Dental work
 - Sinusitis
 - Pharyngitis
 - Bronchitis (acute)
 - Otitis media
 - Minor superficial skin infections (e.g., impetigo, carbuncle)
 - Uncomplicated urinary tract infection (cystitis, urethritis)
 - Vulvovaginal candidiasis
 - Occasional antiviral use for recurrent genital herpes simplex
- Patients receiving treatment for dyslipidemia must be on a stable dose of prescription medication or OTC niacin for at least **3 months** prior to the screening visit.
- Patients receiving treatment for hypothyroidism must be adequately replaced on a stable dose of prescription medication for at least **3 months** prior to the screening visit.
- Patients must not have used prescription weight loss drugs (e.g., phentermine, sibutramine, orlistat) within **3 months** or OTC medication (including herbal supplements) for the treatment of obesity within **1 month prior** to the screening visit and for the duration of the study.
- Patients must not have received metformin or topiramate within **3 months** of the screening visit. Topiramate is also excluded for the duration of the study.
- Patients must not have received oral or parenteral corticosteroids within **3 months** of the screening visit. Limited use of oral and parenteral corticosteroids will be allowed if needed during the study at the discretion of the Investigator.
- Patients must not have received prescribed medication for the treatment of depression, anxiety, or other psychiatric disease within **2 years** of the screening visit. In addition, prescribed medication for the treatment of depression (e.g., SSRI's, SNRI's, tricyclics, MAOI's) will not be allowed during the study. Other prescribed

medication for the treatment of new onset or recurrent psychiatric disease, other than depression, during the study must be pre-approved by the ICON Medical Monitor.

- Patients must not have taken St. John's Wort within **1 month** prior to the screening visit and for the duration of the study. St. John's Wort has been associated with serotonin syndrome when used with another serotonergic drug.
- Prescribed antidepressants such as SSRI's and SNRI's for reasons other than active psychiatric indications (i.e., migraine, weight loss) must meet a **3-month** washout prior to the screening visit and will not be allowed after randomization.
- Patients must have no history of fenfluramine or dexfenfluramine use.
- Patients must not have received agents that have documented correlation with increased incidence of valvulopathy and/or pulmonary hypertension (e.g., Cyproheptadine, Trazodone, Nefazodone, Amoxapine, tricyclic antidepressants, mirtazapine, pergolide, ergotamine, methysergide) within **5 years** of the screening visit and for the duration of the study.
- Patient's who develop new onset Type II diabetes during the study may be treated with oral medications. If a patient requires insulin in any form (i.e., injected or inhaled), exenatide (i.e., Byetta), or pramlintide (i.e., Symlin), they will be withdrawn from the study.

6.1.1 Diet

As poppy seeds can sometimes cause a positive result on the drugs of abuse test, patients will be advised to avoid eating poppy seeds or foods containing poppy seeds for at least 24 hours before attending any visit requiring urine sampling for drugs of abuse.

Patients will be required to fast for 10 hours prior to each study visit requiring a blood sample for clinical laboratory tests.

Patients will be required to follow the diet program (Arena Healthy Lifestyle Program, see Appendix C) as prescribed by their study dietician/counselor. The prescribed diet will be approximately 600 calories less per day than the patient's calculated Estimated Energy Requirement (calculated using WHO criteria with an activity factor of 1.3; for patients who engage in ≥ 1 hour /day aerobic exercise, an activity factor of 1.4 will be used).

Patients with a history of eating disorders as determined by a score > 17 on the Binge Eating Scale will be excluded.

6.1.2 Physical Activity and Exercise

Patients will participate in the Arena Healthy Lifestyle Program (Appendix C) diet and exercise program as designed specifically for this study.

6.1.3 Smoking

Patients who smoke less than half-a-pack of cigarettes per day or equivalent other forms of tobacco (i.e., ~ 2 cigars/day; ~ 3 pinches of smokeless tobacco) will be allowed in this study

provided there are no significant changes in tobacco use habits within 3 months of study start. Patients enrolled in the study who quit smoking and/or cease use of tobacco products will be allowed to continue in the study, but will be excluded from the per protocol analyses, since smoking cessation is associated with weight gain.

6.1.4 Withdrawal Criteria

6.1.5 Reasons for Withdrawal

The study will be terminated early if, in the opinion of the Sponsor, Investigator, or Institutional Review Board (IRB), an unacceptable risk to the safety and welfare of patients is posed by the continuation of the study in light of review of the key safety data.

Patients will be informed that they are free to withdraw from the study at any time should they so wish. The clinical investigator may remove a patient if, in his/her opinion, it is in the best interest of the patient. A patient may be withdrawn from the study for any of the following reasons:

- Withdrawal of consent - any patient may withdraw his/her consent from the study at any time. The Investigator should make a reasonable attempt to document the specific reason why consent is withdrawn.
- Deviation/noncompliance with the protocol
- An adverse event
- Lost to follow up

6.1.6 Handling of Withdrawals

Although a patient is not obliged to give his/her reason for withdrawing prematurely, the Investigator will make a reasonable effort to obtain the reason while fully respecting the patient's rights. If there is a medical reason for withdrawal, the patient will remain under the supervision of the study physician until in satisfactory health. Reasonable efforts will be made to contact a patient who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health.

If a patient is prematurely discontinued from this study, the procedures described in Section 5.5.4 must be followed.

6.2 Maintenance of Randomization Codes and Code-break Procedures

The randomization code will be generated by a Contract Research Organization (CRO) statistician not directly involved with the study. The randomization code will be used by a third party contract manufacturer to build the appropriate patient kits according to the code, and to perform re-randomization at Week 52. All other personnel directly related to this study (i.e., Investigators, site personnel, pharmacy personnel, monitors, CRO personnel, Arena personnel) will remain blinded until the Week 104 database lock at which time the randomization code will be broken in order to complete the data analysis. The CRO will obtain written consent from Arena prior to breaking the code.

An Echocardiographic Data Safety Monitoring Board (DSMB) will review echocardiographic safety data and patient demographics following Week 24 and Week 52 assessments. Echocardiographic data *only* will be analyzed and unblinded by a pre-specified statistician at the CRO who is not otherwise involved with the conduct or analysis of the APD356-009 study, and provided to the DSMB. The DSMB will recommend continuation or termination of the study at each of the two meetings, but will not reveal the unblinded data to any personnel directly related to this study.

Breaking of the randomization code prior to database lock at Week 104 and without Arena permission is expressly forbidden except in the event of a medical emergency where the identity of the study medication must be known in order to properly treat the patient. In the event of a medical emergency, it is requested that the investigator make every effort to contact the study monitor or designee prior to breaking the code. If the blind is broken, the individual responsible should document the date, time, and reason for breaking the blind. A written report should be sent to Arena within 1 working day.

6.2.1 Replacements

Patients who have been randomized and received study medication who withdraw from the study, for whatever reason, will not be replaced.

6.3 Ethics and Regulatory Considerations

The study will be conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki on biomedical research involving human volunteers (1996 Version), the ICH Guidelines for GCP, Title 21 of the US Code of Federal Regulations (CFR) Part 50 (21CFR §50 (Protection of Human Subjects), 21 CFR §56 (Institutional Review Boards), and 21 CFR §312 (IND), the study protocol and ICON SOPs, and where applicable sponsor SOPs. The protocol and informed consent will be submitted for consideration by the appropriate IRB and written approval from the Chair or designated deputy of the IRB is required before clinical activities of the study can commence.

The IRB must be notified promptly by the investigator of the following:

- Deviations from, or changes in, the protocol to eliminate immediate hazards to the trial volunteers
- Changes increasing the risk to volunteers and/or affecting significantly the conduct of the trial
- All AEs that meet the definition of a SAE
- New information that may affect adversely the safety of the volunteers or the conduct of the trial

Any changes to the protocol will be made by means of a formal written protocol amendment. All amendments will require IRB approval before implementation except when changes to the protocol are required immediately to eliminate hazards to the volunteer or when the changes involve only logistical or administrative aspects of the trial.

7 CLINICAL MEASUREMENTS AND PROCEDURES

7.1 Efficacy Parameters

7.1.1 Body Weight

Each patient will be weighed throughout the study at the designated time periods to assess for changes. All efforts should be made to schedule study visits prior to 10:00 a.m. to capture the fasted body weight and to reduce the variability in body weight normally observed throughout the day. All weights will be measured in kilograms (kg).

Patients will be weighed at each study visit using the digital scale provided by Arena or similar scale already at the site as approved by Arena. The scale meets NTEP standards, has a precision to the nearest 100 g, and is approved for providing certifiable weights. The scale provided by Arena will remain the property of Arena and use will be reserved only for the Arena clinical trial. The provided scale will be returned to Arena at the conclusion of the study unless the Investigator is otherwise instructed.

A calibration log will be maintained for each scale used in the study. Calibration records should indicate that the scale was calibrated at a minimum frequency of once per week.

Prior to being weighed, it is suggested that each patient remove their outer clothing and shoes and be provided with a medical gown or asked to wear light clothing (i.e., T-shirt and shorts) for the weighing process. Patients may keep on their undergarments and socks during the weighing process. Patients should be encouraged to void prior to weighing at each visit.

7.1.2 Waist and Hip Measurements

Excess abdominal fat carries particularly elevated health risks. Waist circumference is the most practical marker of abdominal fat. A waist circumference greater than 102 cm (40 in) in men and greater than 88 cm (>35 in) in women is correlated with increased cardiovascular disease risk.

Waist/hip ratio assesses the differences in the circumference of the patient's waist and hip and is used to determine health risk. Waist/hip ratio is a good indicator of visceral adiposity. Normal waist/hip ratio for males and females is typically less than 1.0 and less than 0.8, respectively.

The waist and hip circumferences will be measured at each study visit to the nearest integer. For a given patient, the same site personnel should measure the waist and hips throughout the study to avoid variability in the method of measurement. All measurements will be reported in centimeters (cm).

In order to standardize the method used, measurements should be obtained as follows:

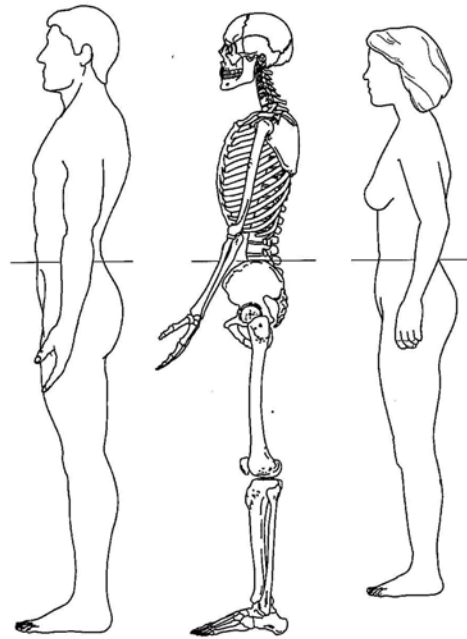


Figure 2: Measuring tape position for waist circumference

Waist measurement: waist measurement will be done according to the NHLBI Guideline in the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (September 1998). To define the level at which the waist circumference is measured, a bony landmark is first located and marked. The patient stands and the examiner, positioned at the right of the patient, palpates the upper hip bone to locate the right iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn, and then crossed with a vertical mark on the midaxillary line. The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor and the tape is snug, but does not compress the skin. The measurement is made at a normal minimal respiration. See [Figure 2](#).

Hip Measurement: With a tape measure, comfortably measure the distance around the largest extension of the buttocks.

7.2 Safety Parameters

7.2.1 Clinical Laboratory Assessments

All details regarding clinical laboratory sample collection, preparation, and shipment are included in the laboratory manual provided by the central laboratory.

In the event of abnormal clinical laboratory values, the physician will make a judgment whether or not the abnormality is clinically significant. Hematology and Serum Chemistry

Blood samples for hematology, serum chemistry, HIV and hepatitis screens, and drugs of abuse screens will be collected according to the laboratory manual provided by the central laboratory and according to the schedule of events ([Table 7](#) and [Table 8](#)).

The clinical laboratory tests that are included in this study are as follows:

Biochemistry

Sodium
Potassium
Chloride
Bicarbonate
BUN
Creatinine
Calcium
Phosphate
Glucose
Total bilirubin
Total proteins
Albumin
Globulin
Alkaline phosphatase
AST
ALT
Total Cholesterol (LDL, HDL-C)
Triglycerides
Uric acid

Additional tests

Thyroid function tests: TSH, T₄
Hemoglobin A1c
CRP
Fibrinogen
Fasting insulin

Hematology

Hemoglobin
Hematocrit
Red cell count
Platelets
White cell count
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils

HIV, HBsAg, and hepatitis C tests will be performed at screening only, along with a screen for drugs of abuse.

7.2.1.1 Drugs of Abuse Screen

Urine samples for the drugs of abuse screen will be collected according to the laboratory manual provided by the central laboratory and according to the schedule of events ([Table 7](#)).

The drugs of abuse screen will include amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, and cannabinoids.

7.2.1.2 Urinalysis

Urinalysis parameters for clinical laboratory tests include the following:

- pH
- glucose
- ketones
- protein
- leukocyte esterase
- blood

If there are any abnormalities in the urinalysis that would suggest the need for urine microscopy, then this will be performed and reported as a comment.

7.2.2 Vital Sign Measurements

Supine blood pressure, heart rate and respiratory rate will be measured after the patient has been resting for 5 minutes. Oral temperature will be measured.

7.2.3 12-lead ECG

In this study, measurements will be made in the median mode of Lead II.

The median mode uses the 12SL methodology of earliest onset and latest offset of all 10 seconds of data, for all 12 leads. All interval measurements will be made from a single lead (lead II). If lead II is unsuitable for measurement, the following lead progression will be used: I, V4, V5, V3, any suitable lead.

7.2.3.1 ECG Equipment

All sites will be provided with a GE Medical MAC 1200 consisting of at least 1 ECG machine with modem, 1 patient cable consisting of 10 patient lead wires and 1 interconnecting cable and 1 power cord. This equipment will be provided by Biomedical Systems (BMS), St. Louis, MO.

The machines will be set at 25-mm/sec paper speed at a sensitivity of 10 mm/mVolt.

The Mac 1200 performs a self-test calibration when the unit is powered up. Once the self-test calibration is complete, a standard 12-lead ECG is recorded and stored electronically. If any errors are displayed, Biomedical Technical Support has to be contacted immediately.

A lead II rhythm strip will be printed at the bottom of the recording. An electronically transmitted ECG will be used for the analysis and interval assessment.

7.2.3.2 ECG Acquisition

In this study, 12-lead ECGs will be acquired utilizing ECG equipment provided by BMS. ECGs are acquired at the following timepoints:

<u>Time point</u>	<u>Visit Code Entered in BMS Database</u>
Screening	SCR
Week 4	W4
Week 24	W24
Week 52	W52
Week 76	W76
Week 104	W104
Unscheduled	UNSCH
Early Termination	ET

The 12-lead ECG equipment provided will be set to 25-mm/sec and 10 mm/mV. The operator will enter certain patient demographic information prior to obtaining the ECG. The following patient information will be entered into the machine:

- Patient initials (example: XYZ or X-Z)
- Patient number (for the screening ECG, enter the patient screening number (###-S###), at all other visits, enter the 4 digit randomization number [####])
- Patient gender
- Patient race
- Patient date of birth (mm/dd/yyyy)
- Visit number

ECGs will be recorded with patients in the recumbent position and resting. In case of baseline tremor, measures will be taken to eliminate this as it may interfere significantly with the quality of the interpretation. Prior to electrode placement, the 10 anatomical sites will be prepared to allow for proper skin/electrode interface. Patients with excessive hair will be dry shaven, as needed.

Intervals to be provided on the confirmed read for each ECG are: RR, PR, QRS, QT, QTcB, QTcF, QRS axis. All interval measurements will be made from a single lead (lead II). If lead II is unsuitable for measurement, the following lead progression will be used: I, V4, V5, V3, any suitable lead. A complete interpretation will be performed by the central reader.

Interval measurements will be performed in a digital environment using electronic calipers. Each interval will be measured as a single measurement of an averaged complex from the chosen lead, utilizing a validated median template methodology, with a sample of at least 3 to 5 original complexes.

The QT interval will be measured using the QT tangent method. The tangent method measures from the onset of the Q wave to the intersection between the tangent line of the steepest part of the terminal portion of the T wave and the isoelectric line, in the presence of a U wave and/or nadir measure end of T wave. If a secondary inflection wave is inscribed on the terminal T wave and is greater than 25% of the maximum positive T wave voltage,

determine the offset of the T wave by measuring the end of the secondary inflection (T^2) using a tangent line from the steepest part of the terminal slope of the T wave to the isoelectric line.

Post-screening ECGs will be compared with the Day 1 ECG (baseline ECG).

A final evaluation will indicate if the ECG is normal, abnormal clinically insignificant or abnormal clinically significant. However, the Principal Investigator will provide the final overall assessment of clinical significance for any abnormal values. The BMS cardiologist will confirm the ECG.

7.2.4 Echocardiography Procedures

In this study, echocardiographic images are acquired to establish the cardiac safety of lorcaseerin. Stringent criteria for image quality and reproducibility are essential. See Appendix B for a detailed description of the echocardiography procedures.

Biomedical Systems (BMS), Inc (St. Louis, Mo) will provide standardized training for all echocardiographers, and will implement centralized procedures for collecting, analyzing, and reporting echocardiographic data. All echocardiograms will be over-read by 2 blinded central readers (primary and secondary) with the following exception: if the primary reader notes upon initial read of the echocardiogram that the patient obviously will not qualify for the study on the basis of an observation of mitral or aortic valve stenosis, left ventricular ejection fraction < 45%, intracardiac mass, tumor or thrombus, evidence of congenital heart disease, or pericardial effusion.

A panel of up to 20 cardiologists trained on the protocol by BMS will serve as blinded central readers for this study. The panel will be under the supervision of [redacted] Biomedical Systems Medical Director of Echocardiography.

Whenever possible, all echocardiograms for a single patient will be read by the same primary reader throughout the study to minimize variability in the over-read process. The secondary reader will be assigned randomly for each patient throughout the study. Any discrepant readings between the primary and secondary readers will be adjudicated by a third reader at BMS. When the two readings “match” according to the following criteria, the results from the primary reader will be entered into the database; in the event of discrepant reads, the third reader will determine which read is entered into the database.

“Match” criteria for primary and secondary echocardiogram reads:

- Aortic and mitral valve regurgitation scores are identical
- LVEF: absolute value from secondary reader is within $\pm 10\%$ of primary reader (example: primary read = 50%; secondary read must be 40-60 to “match”)
- Pulmonary artery systolic pressure: value from secondary reader is within 10 mm Hg of primary reader (example: primary read = 20 mm Hg; secondary read must be 10-30 mm Hg to “match”)

Valvular regurgitation will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography.¹⁶

Pulmonary artery pressure will be estimated from the tricuspid regurgitant (TR) jet velocity. In some cases, pulmonary artery pressure will not be measurable due to inadequate or immeasurable TR jet velocity. In patients with no or limited tricuspid valve regurgitation, an accurate TR jet cannot be measured. In these cases, a patient will qualify on the basis that the pulmonary valve flow acceleration time will be ≥ 120 msec, indicating the pulmonary artery pressure is not elevated.

For readings (Week 24, 52, 76, and 104) meeting certain pre-defined criteria, an alert will be sent to the study site by BMS. For patients with these alerts, Arena recommends either follow-up of the patient by a cardiologist, or in some cases withdrawal of study medication. In addition, a corresponding AE should be recorded.

For example:

Recommend referral to a cardiologist (alert sent from BMS to study site by FAX):

- Mitral regurgitation increased at least 2 categories from baseline *and* rated moderate or greater
- Aortic regurgitation rated \geq moderate
- Pulmonary artery pressure >50 mm Hg with at least 10 mm Hg increase from baseline
- LVEF ≤ 35

Withdrawal of study medication and referral to a cardiologist (alert sent from BMS to study site by FAX and follow-up phone call):

- Severe mitral regurgitation
- Severe aortic regurgitation
- Pulmonary artery pressure ≥ 60 mm Hg

7.3 Other Parameters

7.3.1 Pharmacokinetic Analyses

Pharmacokinetic samples will be collected at only 10% of study centers. Blood samples will be collected during the Week 12 visit prior to dosing, and at 2 hours after dosing according to the schedule of events (Table 7). For this visit, which should be scheduled for the morning, the patient will be instructed not to take the morning dose of study medication, but to bring the study medication to the visit. The dose will be administered after the pre-dose blood collection. The exact times of each blood draw, study medication dosing during the visit, and the previous day's dosing will be recorded.

At each collection, 7 mL of blood will be collected into a Vacutainer tube containing sodium heparin (green top) and refrigerated immediately (cryoblock). Within 30 minutes of collection, the plasma fraction will be separated by centrifugation at 2,000 rpm for 15 minutes at 4°C. The plasma fraction will be separated and transferred into two labeled 5-mL polypropylene tubes and frozen at approximately -20°C.

Shipping instructions are included in the pharmacokinetic sample manual provided by the central laboratory. Samples will be batch-shipped to the central laboratory who will then forward the sample to the bioanalytical lab for analysis.

7.3.2 Insulin resistance (HOMA-IR)

Insulin resistance will be calculated according to the homeostatic model assessment of insulin resistance, using HOMA2 Calculator software, under license from the Chancellor, Masters and Scholars of the University of Oxford.¹⁷

7.3.3 Depression Symptom Assessment

Although only one case of clinical depression that was deemed of unlikely relationship to lorcaserin has been observed in clinical trials to date, and assessments of mood in phases 1 and 2 do not indicate a depressive effect, lorcaserin is a centrally acting drug. Therefore, symptoms of depression will be assessed at screening and at Weeks 4, 12, 24, 36, 52, 64, 76, 88, and 104 (or early termination) by the Beck Depression Inventory Second Edition (BDI-II)^{18,19}. BDI-II is a 21-item self-report instrument intended to assess the presence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV)²⁰. The patient is asked to consider each statement as it relates to the way he/she has felt for the past two weeks, to more accurately correspond to the DSM-IV criteria. Each of the 21 items corresponding to a symptom of depression is summed to give a single score for the BDI-II. There is a four-point scale for each item ranging from 0 to 3. On two items (16 and 18) there are seven options to indicate an increase or decrease of appetite and sleep. A total score of 0-13 is considered minimal depression range, 14-19 is mild, 20-28 is moderate, and 29-63 is severe.

To assure the safety and adequate care of individual patients, the following schedule of events should be employed by each study site in response to BDI-II scores:

- Score <20: no action
- Score 20-28: consider referring patient to his/her primary care physician for evaluation of possible clinical depression
- Score >28: refer patient to mental health practitioner or to primary care physician for evaluation of clinical depression

In addition, any patient scoring > 0 specifically on question #9 (Suicidal Thoughts and Wishes) will be referred to a mental health practitioner or to primary care physician for evaluation.

7.3.4 Binge Eating Scale (Screening Only)

The Binge Eating Scale (BES) consists of 16 items, 8 describing the behavioral manifestations of binge eating and 8 describing feelings and cognitions associated with binge eating (Appendix D). Each item consists of four statements that reflect a range of severity (0 indicates no binge eating problem and 3 indicates a severe binge eating problem). Subjects

choose the statement that best describes their perceptions and feelings about their eating behavior. The BES is scored by adding the individual values for the 16 items with the possible range of scores from 0 to 46.²¹

7.3.5 Quality of Life Assessment

The Impact of Weight on Quality of Life-Lite© (IWQOL-Lite) is a validated, 31-item self-report measure of obesity-specific quality of life.^{22,23} The IWQOL-Lite provides an overall total score as well as scores on five domains: 1) physical function, 2) self-esteem, 3) sexual life, 4) public distress, and 5) work (Appendix F).

7.3.6 Research Plasma Samples

Extra plasma samples will be collected and banked for each patient at Day 1 (baseline), Week 24, and Week 52 or upon Early Termination from the study. Patients will be provided the opportunity during the informed consent process to decline having these samples collected and banked. The samples will be retained and stored for 2 years after marketing application approval, or, if the application is not approved or never submitted, for 2 years after the termination of the study. The sample may be used in the future for blood chemistry analysis. No genetic testing will be conducted on these samples.

At each collection, 7 mL of blood will be collected into a Vacutainer tube containing EDTA (purple top) and refrigerated immediately (cryoblock). Within 30 minutes of collection, the plasma fraction will be separated by centrifugation at 2,000 rpm for 15 minutes at 4°C. The plasma fraction will be separated and transferred into two labeled 3-mL polypropylene tubes and frozen at approximately -20°C.

Shipping instructions are included in the manual provided by the ICON central laboratory. Samples will be batch-shipped to the ICON central laboratory who will then forward the sample to Steelgate, Inc. for permanent storage.

8 REPORTING ADVERSE EVENTS

Adverse events will be recorded and reported in accordance with ICH GCP and 21 CFR§312.32. The definitions of AEs and SAEs will be as given in the ICH Topic E2A, ICH Guideline “Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.” The outcome of an AE will be defined according to ICH Topic E2B, ICH Guideline “Note for Guidance on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports.” The relationship to investigational product will be classified using the WHO criteria (Edwards and Biriell, World Health Organization Collaborating Centre for International Drug Monitoring 1994).

8.1 Adverse Event Reporting

Patients will be instructed that they may report AEs spontaneously at anytime. All events reported before administration of first dose of study medication will be recorded as concurrent medical conditions and all events reported following first dose of study medication will be recorded as AEs.

Monitoring of adverse events will be continued up to 30 days after the last dose of study medication. In the event that an adverse event is not resolved by this time, Arena, the ICON Medical Monitor, and the Investigator will discuss and decide whether to continue to monitor the AE or close-out the event in the database if no further follow-up is necessary.

An AE is defined as: “Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.” An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. AEs can be any of the following:

- Unfavorable changes in general condition
- Subjective or objective signs/symptoms
- Concomitant disease or accidents
- Clinically relevant adverse changes in laboratory parameters observed in a patient in the course of a clinical study
- Pre-existing conditions which worsen in severity or frequency or which have new signs/symptoms associated with them

Adverse events will be elicited at the time indicated in the schedule by asking the question: “Since you were last asked, have you felt unwell or different from usual in any way?” Any adverse or unexpected events, signs and symptoms, will be fully recorded on the Adverse Event Form including details of intensity, onset, duration, outcome and relationship to the drug. Whenever possible, a constellation of signs and symptoms should be recorded as a unifying diagnosis (e.g., self limited fever, runny nose, cough, scratchy throat should be captured as an upper respiratory infection rather than by the individual signs and symptoms). Adverse events may also be reported spontaneously at any time. The type and duration of follow-up of patients after AEs will also be documented.

8.2 Serious Adverse Events and Expedited Reporting of Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

SAEs will be captured from the time of randomization to 30 days after the last dose of study drug.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such a medical event includes allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Elective hospitalization and/or surgery for clearly pre-existing conditions (for example a surgery that has been scheduled prior to the patient's entry into the study) will not be reported as a SAE. All other hospitalizations, including elective hospitalizations for any condition that was not pre-existing, will be reported as a SAE.

All SAEs, whether or not considered related to study treatment, must be reported to ICON within 24 hours of becoming aware of the event by phone or fax. In addition, a completed written report using ICON's SAE form must be submitted by fax within 24 hours of notification to:

ICON
[SPECIFIC CNOOTACT INFORMATION REDACTED]

In other situations as defined in ICH Topic E2A, ICH Guideline and 21 CFR§ 312.32, expedited reporting of AEs may also be appropriate. In these situations the process will be as detailed for SAEs above:

- Unexpected, non serious adverse events, that are suspected to be related to the study product
- Adverse events of special interest that could materially influence the benefit-risk assessment of a medicinal product, such as: an expected, adverse event that proves an increase in the rate of occurrence, judged to be clinically important.

Patients who become pregnant during the study will be discontinued immediately. Although not considered a SAE or AE, pregnancies occurring during the period of study drug administration (Day 1 to Week 104/Exit) until 30 days after the last dose of study drug should be reported to the ICON Medical Monitor and IRB in the same manner as a SAE.

Pregnancies will be followed every trimester through the first well baby visit. For female partners whom become pregnant by male study patients during the course of the study, reasonable efforts will be made to collect information on the partner's pregnancy through the first well baby visit as provided by the male study patient.

Please contact ICON Medical Safety Group at 1-888-723-9952 for guidance should an adverse event meet one of these criteria.

8.3 Assessment of Adverse Event Severity

The severity of each AE will be assessed at onset by a nurse and/or physician. When recording the outcome of the AE the maximum severity of the AE experienced will also be recorded.

The following guidelines will be used to assess severity:

Mild: Awareness of sign or symptom but easily tolerated.

Moderate: discomfort enough to cause interference with usual activity.

Severe: incapacitating with inability to work or do usual activity.

8.4 Assessment of Adverse Event Relationship to Study Medication

The relationship of an AE to investigational product(s) will be classified using modified WHO criteria (Edwards and Biriell, World Health Organization Collaborating Centre for International Drug Monitoring 1994) as follows.

Probable: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possible: a clinical event, including laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Not related: a clinical event, including laboratory test abnormality, with sufficient evidence to accept that there is no causal relationship to drug administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; proof of other cause; etc.).

8.5 Assessment of Adverse Event Outcome

Outcome of AEs will be defined according to ICH Topic E2B, ICH Guideline.

- Resolved
- Resolving
- Not resolved
- Resolved with sequelae
- Fatal
- Unknown

8.6 Action Taken for Adverse Event

Any action taken will be recorded on the CRF according to the following:-

- None
- Concomitant medication required
- Trial drug discontinued
- Withdrawal from study
- Other
- If 'Other' is selected, it must be specified on the CRF and in the source documents.

8.7 Collection of Extra Laboratory Samples/Investigations

In the event of a clinically important AE, a suitable sample may be collected for drug assay or for additional laboratory tests. The investigator must ensure that the sample is properly labelled and stored. The investigator and others responsible for care of the patients should institute any supplementary investigations of significant AEs based on the clinical judgment of the likely causative factor. This may include seeking a further opinion from a specialist in the field of the AE. The company may suggest special tests based on expert advice.

8.8 Follow-up of Adverse Events Present at Last Scheduled Study Visit

Adverse events present at the last scheduled study visit that require follow-up or a repeat laboratory test will be followed-up initially for 30 days. Adverse events requiring further follow-up or ongoing at 30 days after the last patient's last visit, will be reviewed with the Sponsor on an individual basis to determine whether the database will be locked and subsequently updated once the events of ongoing AEs are resolved or whether database lock will be held.

9 MATERIALS

9.1 Test Article

Lorcaserin, a monohydrochloride salt of a single enantiomer (ee > 98%), is a white to off-white colored powder. Lorcaserin is freely water-soluble (>400 mg/mL) and aqueous solubility is unaffected by pH in the range of 1 through 8.

9.2 Test Article Composition

The formulation to be used in this clinical study comprise of white, opaque, size 4 hard gelatin capsules containing lorcaserin (active) and microcrystalline cellulose, NF (Emcocel® 50M) as the diluent. Microcrystalline cellulose is an excipient and does not have any pharmacological activity. The placebo comprises of white, opaque, size 4 hard gelatin capsules containing microcrystalline cellulose, NF (Emcocel® 50M). Lorcaserin capsules will be provided as 10 mg strength.

Arena will supply the lorcaserin and placebo capsules. Lorcaserin used for the capsules was manufactured under cGMP compliance at Cilag AG, Switzerland. The lorcaserin and placebo capsules will be manufactured under cGMP compliance by Aptuit, Inc., Kansas City, MO and shipped to the clinical study site prior to the study start.

9.3 Drug Packaging and Storage

Blinded study medication will be packaged in the individually labeled kits according to the randomization code. The kits comprise 5 blister cards; each contains 7 capsules labelled for morning (AM) dosing and 7 capsules labelled for evening (PM) dosing. These blister cards will be stored at room temperature (between 15 and 30°C) in temperature controlled area with limited access.

9.4 Dosage and Administration

All enrolled patients will receive two oral doses per day (one dose in the morning prior to breakfast and one dose in the evening prior to dinner) of study medication (lorcaserin or placebo) for 104 weeks. Dosing will be done in a double-blind manner so that neither the patient nor the Investigator will know which treatment has been assigned. Patients should take the study medication each morning and evening approximately 60 minutes before breakfast and dinner and be encouraged to take the study medication with an adequate amount of water (8 oz or 240 mL). Patients should not crush, break, chew, or dissolve the capsules.

9.5 Test Article Accountability

The Investigator will maintain accurate records of the receipt of all study medication. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each patient in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. Throughout the duration of the study, study medication will be reconciled on a periodic basis by the Arena monitor or contracted designee. The Investigator agrees to provide sufficient access to study medication as required for the reconciliation process to be completed in a timely fashion.

At completion of the study, all study medication will be reconciled by the Arena monitor or contracted designee and then returned at the direction of Arena to either Arena or a third party contractor to be retained or destroyed according to applicable U.S. regulations. Prior to any action being taken with study medication after the study is completed, the Investigator will contact Arena (or contracted CRO) for approval of such action.

10 DATA MANAGEMENT

10.1 Data Collection

Data for ECGs and echocardiograms will be collected digitally and managed, interpreted, analyzed, and reported by BMS, St. Louis, MO, in accordance with BMS SOPs.

All clinical laboratory data will be managed by the central laboratory according to their SOPs.

All other study-related data not mentioned above will be collected utilizing the RAVE electronic data capture system as developed by MediData.

Clinical laboratory data, ECG data, and echocardiogram data will be transferred to Arena Pharmaceuticals, Inc. data management.

Once all queries are resolved and upon database lock, ICON will provide SAS transfer datasets to Arena and to the ICON biostatistician for analysis.

10.2 Data Coding

10.2.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA, version 6.1 or later) and tabulated, including categorical information of interest such as onset and resolution times, time of onset relative to dose, severity at onset, maximum severity, causal relationship to study medication, and action taken. Whenever possible, a constellation of signs and symptoms should be recorded as a unifying diagnosis (e.g., self limited fever, runny nose, cough, scratchy throat should be captured as an upper respiratory infection rather than by the individual signs and symptoms). Adverse events will be regarded as 'pre-treatment' if they occur between Screening and the time of administration of the first dose of lorcaserin. Any 'pre-treatment' AEs will be added to the patient's medical history and their eligibility for the study should be reassessed.

All other AEs that occur after the first dose of study medication will be considered to be 'treatment-emergent'. Adverse events will be listed by patients and by treatment. They will be summarized per treatment and expressed in terms of maximum severity and relationship to study medication. Data from placebo patients will be pooled if appropriate.

10.2.2 Concomitant Medications

Due to the variability in how medications are recorded, a standard naming convention is required in order to tabulate this data effectively. A common method of standardization is to categorize medications by their Preferred Term. In order to do this, medications will be coded using the World Health Organization Drug Dictionary (WHODRUG).

11 STATISTICAL METHODS AND DATA ANALYSIS

11.1 Tests of Hypotheses and Significance Levels

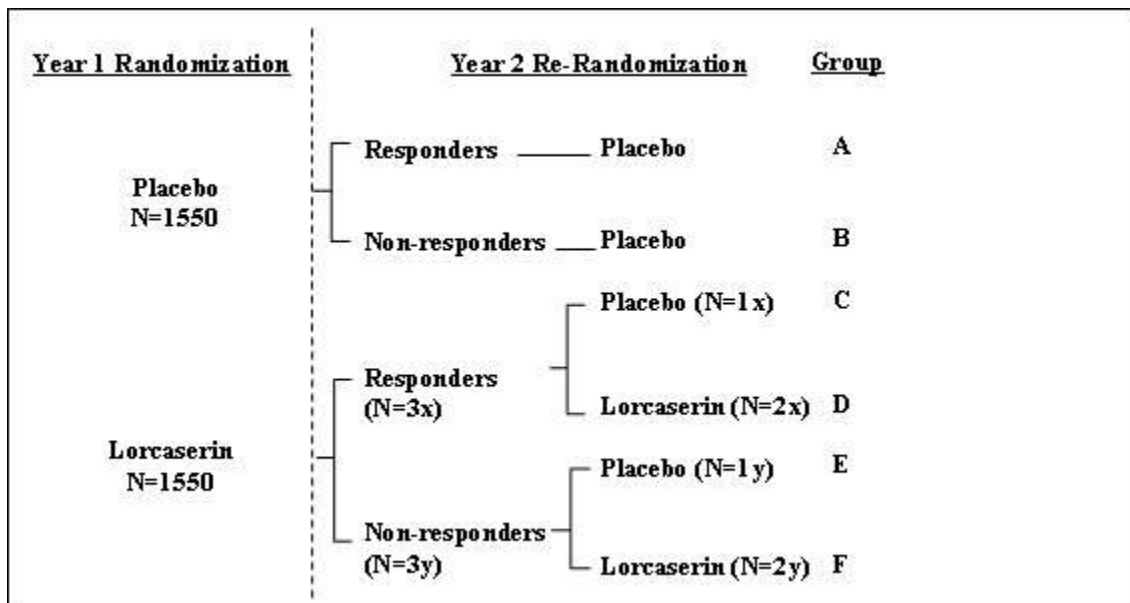
Unless otherwise specified, all statistical analyses will be conducted using two-sided tests at the 5% level of significance.

11.2 Sample Size Considerations

Based on the results of other trials²⁴, it is anticipated that 20% of subjects in the placebo group (Group A) will achieve a 5% or greater weight loss in Year 1. The Year 1 primary analysis comparison (lorcaserin 10 mg BID versus placebo), will be tested at the 0.05 level of significance (two-sided). Based on sample size estimation methods for the comparison of two proportions, the sample size of 1550 placebo patients and 1550 lorcaserin-treated patients will provide greater than 95% power to detect a difference of 5.5 percentage points (i.e., from 20% to 25.5%).

The echocardiographic safety endpoint was the primary determinant of sample size. The primary analysis of echocardiographic safety data will consider the proportion of patients who develop “FDA-defined valvulopathy”, which is mild or greater aortic regurgitation or moderate or greater mitral regurgitation at Week 52. A noninferiority analysis to establish that the rate of FDA-defined valvulopathy in patients treated with lorcaserin is no worse than the rate in the placebo group will be used. Based on the results of the previous 12-week trial, we estimate that the proportion of patients who will develop FDA-defined valvulopathy in the placebo group is approximately 5% per year. Using a noninferiority margin of -0.025 (equivalent to a relative risk of 1.5, and corresponding to an FDA-defined valvulopathy rate of 0.075 in the lorcaserin-treated group), and based on a one-sided test at the 5% level of significance, the total sample size required to provide 80% power is 1879 patients. Under the assumption that the dropout rate could be as high as 40%, a total of approximately 3100 patients will be randomized (approximately 1550 patients per treatment group).

Figure 3. Study Design Schematic



11.3 Randomization

Patients will be initially randomized to placebo or lorcaserin 10 mg BID in a 1:1 ratio. Patients who continue in the second phase of the trial (Year 2) will be re-randomized as follows. Patients will be stratified as “responders” ($\geq 5\%$ body weight loss from Baseline to Week 52) or “non-responders” ($< 5\%$ body weight loss). Patients receiving placebo during Year 1 will remain on placebo for Year 2. Patients receiving lorcaserin during Year 1 will be re-randomized within each of these two strata in a 2:1 ratio to either remain on lorcaserin 10 mg BID or switch to placebo, respectively, for Year 2. In order to maintain approximately balanced groups and the study blind, all patients will receive a new randomization number at the beginning of Year 2.

11.4 Study Populations

The analyses of all efficacy variables will use the Modified Intent to Treat (MITT) population as primary. Under this approach, patients are counted in the treatment group to which they were initially randomized for the Year 1 analyses and regardless of the treatment received during the course of the trial. A Week 52 population and per-protocol population will be used as secondary analysis populations for the Year 1 primary endpoints as described below.

Modified Intent-to-treat (MITT1) Population for Year 1:

This population consists of all patients randomized who received at least one study dose, have a baseline weight measurement, and have a post randomization weight measurement. To avoid the confounding influence of additional therapy after discontinuation from the study on efficacy comparisons, the efficacy analyses will treat data as missing after the discontinuation from the study. The last observation on or prior to discontinuation will be carried forward and used in the analysis. This population will be used for Primary Efficacy Analysis of Year 1.

Week 52 (W52) Population:

All randomized patients who have a post-baseline body weight recorded within 2 weeks (Days 357-371) of the scheduled 52-Week Visit (this includes patient who withdraw from the study prior to Week 52, and return for a body weight measurement within 2 weeks (Days 357-371) of their scheduled Week 52 visit). Only the Year 1 primary endpoint and change in body weight from Baseline to Week 52 will be analyzed using this population.

Per-Protocol (PP1) Population for Year 1:

The per-protocol (PP) population excludes patients and/or data points with clinically important protocol deviations based on a set of prespecified criteria (Details in the SAP). This is not just a repetition of the exclusion and inclusion criteria in the protocol, but a clinical assessment of deviations from the protocol-specified criteria that will either affect or confound the measures of efficacy. The PP population is considered a secondary approach to

analysis. Any substantial differences between conclusions based on the MITT compared to the PP approach will be investigated. The analysis of the per-protocol population does not estimate missing data.

Modified Intent-to-treat (MITT2) Population for Year 2:

This population consist of all randomized patients who complete Year 1, are re-randomized at Week 52 and take at least one dose of study medication after re-randomization, have at least one weight measurement post re- randomization. To avoid the confounding influence of additional therapy after discontinuation from the study on efficacy comparisons, the efficacy analyses will treat data as missing after the discontinuation from the study. The last post re-randomization observation on or prior to discontinuation will be carried forward and used in the analysis. This population will be used for the Primary Efficacy Analysis of Year 2. Some additional efficacy parameters will also be analyzed using this population.

Per-protocol (PP2) Population for Year 2:

The per-protocol (PP) population excludes patients and/or data points with clinically important protocol deviations based on a set of prespecified criteria (Details in the SAP). This is not just a repetition of the exclusion and inclusion criteria in the protocol, but a clinical assessment of deviations from the protocol-specified criteria that will either affect or confound the measures of efficacy. The PP population is considered a secondary approach to analysis. Any substantial differences between conclusions based on the MITT compared to the PP approach will be investigated. The analysis of the per-protocol population does not estimate missing data.

The last-observation-carried-forward (LOCF) imputation method for missing weights will be used in the primary and some secondary efficacy analyses related to body weight in the MITT1 and MITT2 populations. To avoid the confounding influence of additional therapy after discontinuation from the study on efficacy comparisons, the efficacy analyses will treat data as missing after the discontinuation from the study for the MITT1 and MITT2 populations (i.e. weight assessments collected after discontinuation will not be used instead LOCF imputation will be used for the MITT1 and MITT2). For Year 1, if the Week 52 weight is missing, then the patient's last available post-baseline weight will be carried forward. For Year 2, if the patient's weight at Week 104 is missing, then the patient's last available post re-randomization weight will be carried forward.

The primary efficacy endpoints for Year 1 and 2 will be analyzed by using the MITT1 and MITT2 populations with LOCF method. Sensitivity analyses of the primary endpoints will be performed using the PP1 and W52 populations for Year 1, and the PP2 population for Year 2.

Safety Analyses Population:

Safety population will include all patients who are randomized and receive at least one dose of study drug. Safety endpoints will be analyzed using the Safety population. Missing or invalid data will not be imputed.

11.5 Efficacy Parameters

11.5.1 Primary Efficacy Analysis (Year 1)

The primary efficacy endpoints for the first phase of the study (Year 1) will be the proportion of patients achieving $\geq 5\%$ reduction in body weight at the end of year 1, change from baseline in body weight at year 1 and the proportion of patients achieving $\geq 10\%$ reduction in body weight at the end of year 1, using a modified intent-to treat population, including all patients who take at least one dose of study medication and have at least one post-baseline weight. These endpoints will be computed using each patient's baseline weight and their weight at the Week 52 visit. If the Week 52 weight is missing, then the patient's last available post-baseline weight will be carried forward (LOCF). The 5% responders and the 10% responders will be analyzed using a logistic regression model with effects for treatment, gender, baseline weight (kg), and age (years). Change in weight will be analyzed using ANCOVA models with treatment and gender as the factors, and baseline body weight as covariate. Details on the procedures used the testing procedure for the primary endpoints are presented in the Multiplicity Section.

11.5.2 Primary Efficacy Analysis (Year 2)

The primary efficacy endpoint for the second phase of the study (Year 2) will be the percent of lorcaserin Year 1 "responders" (those patients who lose $\geq 5\%$ of body weight during Year 1) who maintain at least 5% weight loss (based on Baseline weight) at the end of Year 2. This endpoint will be analyzed using a modified intent-to treat population that will include all Year 1 lorcaserin responders who were re-randomized, received at least one dose of study drug in Year 2, and provided at least one weight measurement in the second year of the study. If the patient's weight at the end of Year 2 is missing, the patient's last available post re-randomization weight will be carried forward (LOCF). The primary comparison at Week 104 will be the proportion of patients stratified to the $\geq 5\%$ weight loss group ("responders") who maintain at least 5% weight loss (based on Baseline weight) at Week 104 in Group D versus Group C. Secondary comparisons will include (1) the change in weight from Week 52 to Week 104 in all patients on lorcaserin (Groups D and F) versus all patients receiving placebo during Year 2 who received lorcaserin during Year 1 (Groups C and E); (2) change in weight from Baseline to Week 104 in each group; (3) proportion of responders who maintain at Week 104 at least 75%, 50%, and 25% of the weight loss achieved at Week 52 in Group D versus C.

A secondary efficacy endpoint for the second phase of the study (Year 2) will be the change in weight from the end of Year 1 (Week 52; re-randomization baseline) to the end of Year 2 in all patients. This endpoint will be analyzed using a modified intent-to treat population and an analysis of covariance (ANCOVA) model with effects for treatment, gender, body weight at Week 52, and age. If the patient's weight at the end of Year 2 is missing, the patient's last available post re-randomization weight will be carried forward (LOCF). The key comparisons will be as follow: Patients on lorcaserin during Year 1 and during Year 2 (Groups D and F) versus patients on lorcaserin during Year 1 and on placebo during Year 2 (Groups C and E).

11.5.3 Additional Efficacy Analyses of the Year 1 and Year 2 Primary Endpoints

In order to assess the potential effects of missing observations, sensitivity analyses will be completed, as follows.

- The Year 1 primary efficacy analysis will be repeated using the subset of patients who provide a weight value at Week 52 (observed cases). This analysis will additionally be repeated by classifying all patients who do not provide a weight at Week 52 as nonresponders (i.e., as not having achieved a 5% or greater weight reduction from baseline).
- The Year 2 primary efficacy analysis will be repeated using the subset of patients who provide a weight value at Week 104 (observed cases).

[SOME ADDITIONAL ANALYSES REDACTED]

The statistical methodology for these analyses will be described in the Statistical Analysis Plan.

11.6 Analysis of Demographics and Safety Data

All patients who receive study medication will be evaluated for safety. All baseline patient characteristics of demographic data (age, height, weight, race), social history (smoking status, caffeine intake, alcohol intake), medical history (abnormalities only), physical examination (abnormalities only), and concomitant medications at study entry will be listed for all patients.

11.6.1 Demographics

Demographic data will be summarized and tabulated. Continuous variables will be summarized using number of values (n), mean, standard deviation (SD), coefficient of variation (CV[%]), median, minimum, and maximum. Frequencies and percentages will be reported for all categorical data.

11.6.2 Adverse Events

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA, version 6.1 or later) and tabulated, including categorical information of interest such as onset and resolution times, time of onset relative to dose, severity at onset, maximum severity, causal relationship to study medication, and action taken. Adverse events will be regarded as 'pre-treatment' if they occur between Screening and the time of administration of the first dose of lorcaserin. Any 'pre-treatment' AEs will be added to the patient's medical history and their eligibility for the study should be reassessed.

All other AEs that occur after the first dose of study medication will be considered to be 'treatment-emergent'. Adverse events will be listed by patients and by treatment. They will be summarized per treatment and expressed in terms of maximum severity and relationship to study medication. Data from placebo patients will be pooled if appropriate.

11.6.3 Physical Examinations

Physical examination results (abnormalities only) from other time points in the study and at the post-study examination will also be listed.

11.6.4 Concomitant Medication

Pre-treatment and concomitant medication administered during the study will be listed. Concomitant medications will be coded using the WHODRUG Dictionary.

11.6.5 Vital Signs

Individual vital sign measurements will be listed by treatment and measurement time, and summarized using descriptive statistics. Individual change from baseline in vital sign measurements will be calculated and summarized descriptively. A clinically significant change from baseline will be recorded as an adverse event.

11.6.6 Clinical Laboratory Values

Individual lab values will be listed by treatment and visit, and summarized using descriptive statistics. Individual change from baseline in lab values will be calculated and summarized descriptively. Shift tables from baseline to last double-blind visit will also be produced for the laboratory assessments based on the categories of Low, Normal, and High. A clinically significant change from baseline will be recorded as an adverse event.

11.6.7 Beck-Depression Inventory - II

The Beck Depression Inventory-II (BDI-II) is a 21-item test presented in multiple choice format to measure presence and degree of depression in adolescents and adults. The BDI-II was revised in 1996 for consistency with the DSM-IV criteria.

Each of the inventory items corresponds to a specific category of depressive symptom and/or attitude. Each category describes a specific behavioral manifestation of depression and consists of a graded series of four self-evaluative statements. The statements are rank ordered and weighted to reflect the range of severity of the symptom from neutral to maximum severity. Numerical Values of zero, one, two, or three are assigned to each statement to indicate degree of severity.

The score for each category will be listed by treatment and visit, and summarized using descriptive statistics. Additional analyses may be conducted on these data as deemed necessary.

11.6.8 12-Lead ECGs

Individual ECG values will be listed by treatment and visit, and summarized using descriptive statistics. Intervals to be provided for each ECG are: RR, PR, QRS, QT, QTc, QRS axis. Post-screening ECGs will be compared with the baseline ECG. Any clinically significant change from baseline will be recorded as an Adverse Event.

11.6.9 Echocardiograms

The primary analysis of echocardiographic safety data will consider the proportion of patients who develop “FDA-defined valvulopathy”, which is mild or greater aortic regurgitation or moderate or greater mitral regurgitation. A noninferiority analysis to establish that the rate of FDA-defined valvulopathy in patients treated with lorcaserin is no worse than the rate in the placebo group will be used. Based on the results of the previous 12-week trial, we estimate that the proportion of patients who will develop FDA-defined valvulopathy in the placebo group is approximately 5% per year. Using a noninferiority margin of -0.025 (equivalent to a relative risk of 1.5, and corresponding to an FDA-defined valvulopathy rate of 0.075 in the lorcaserin-treated group), and based on a one-sided test at the 5% level of significance, the total sample size required to provide 80% power is 1879 patients. Under the assumption that the dropout rate could be as high as 40%, a total of approximately 3100 patients will be randomized (approximately 1550 patients per treatment group).

Secondarily, the proportion of patients who experience any increase in mitral or aortic valve regurgitation will be analyzed. At each of Weeks 24, 52, 76, and 104 the echocardiographic endpoint (proportion of patients who experience an increase in mitral or aortic valve regurgitation) will be analyzed by comparing the proportion of patients in the lorcaserin group with the proportion of patients in the placebo group. Each comparison will be made using Pearson’s chi-square test. In addition, 95% confidence intervals for the difference in proportions between each active group and placebo group will be reported.

The mean pulmonary artery pressures in lorcaserin-treated patients and placebo treated patients will be compared.

The following additional parameters will be collected, reported in the database and summarized using descriptive statistics:

- LA volume (end-systolic); pulmonary flow acceleration time, LVEF; LV internal diameter (diastole); LV internal diameter (systole); interventricular septal thickness (diastole); posterior wall thickness (diastole)

The following parameters will be imaged and/or derived, but will not be evaluated using pre-specified analyses:

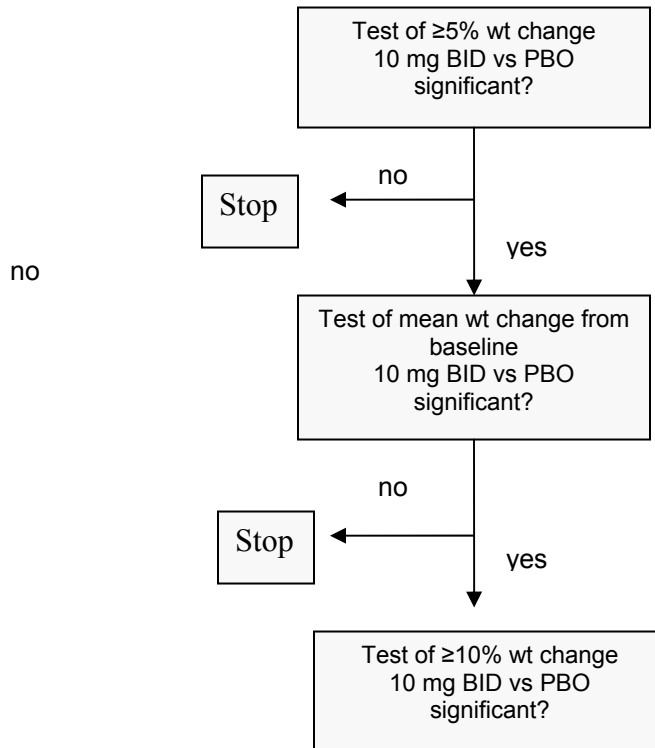
- Mitral deceleration time, mitral E/A ratio, tissue Doppler imaging, observation of the inferior vena cava

11.7 Multiplicity

The principal evaluation of the efficacy of lorcaserin will be assessed using a closed testing procedure. First, the statistical significance of the lorcaserin 10 mg BID versus placebo will be determined for the proportion of patients who lose at least 5% of their baseline body weight. If the result is significant ($p < 0.05$ two-sided), the primary hypothesis will be considered satisfied and this study will be declared positive. Then, the change from baseline in body weight comparison will only be tested if the proportion of 5% responder comparison is significant and the proportion of patients who lose at least 10% of their baseline body

weight comparison will only be tested if the change from baseline comparison is significant. This closed testing procedure preserves the overall Type I error rate for testing primary efficacy hypothesis. Figure 4 below describes the testing procedure for the primary hypothesis.

Figure 4. Flowchart for the Primary Hypothesis Testing Procedure



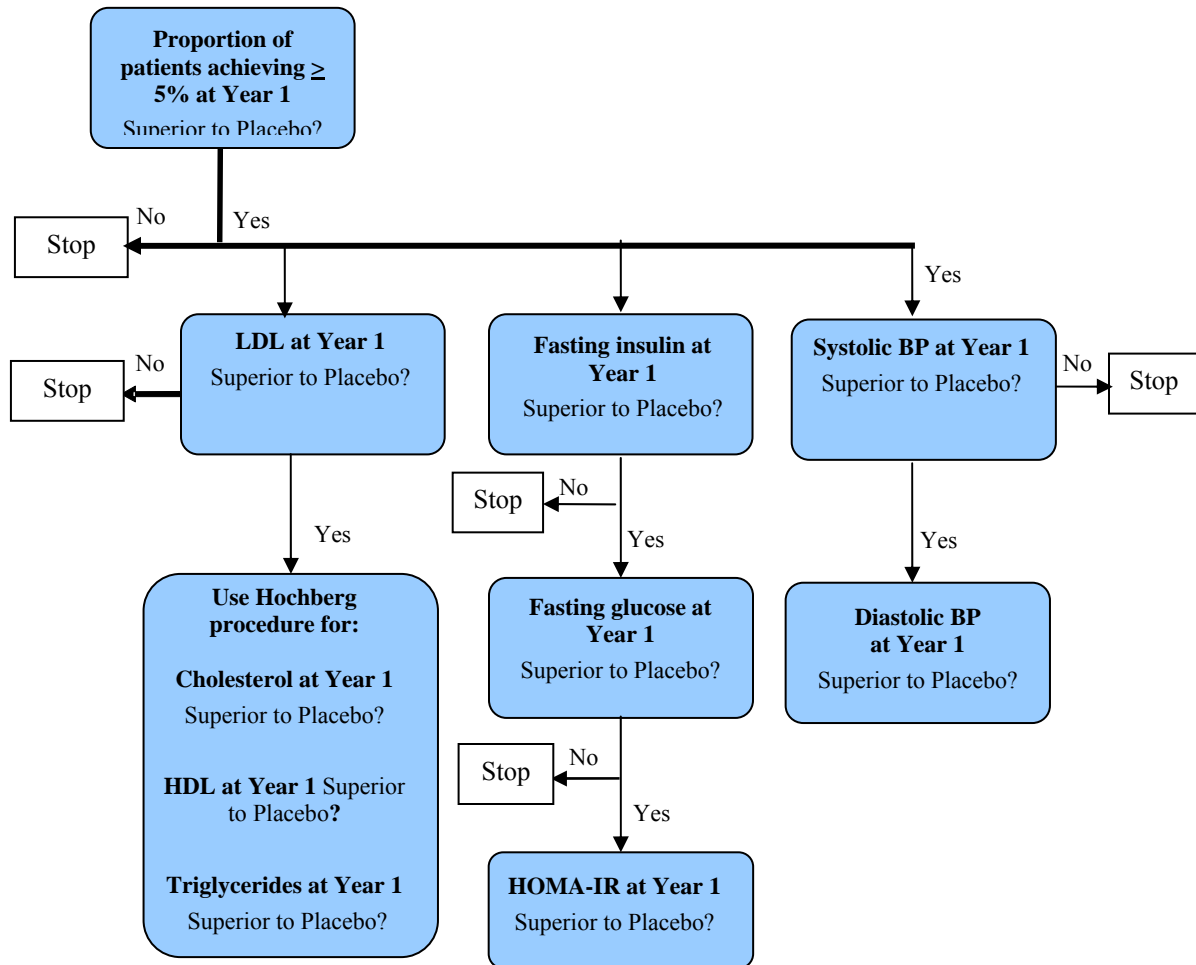
The endpoints in the secondary hypotheses are grouped into 3 families: lipid family, glucose family and BP family. Once the test of the primary hypothesis on the 5% responders is significant, the secondary hypotheses on lipid, glucose, and CV families will be tested simultaneously at 0.05 level in a conditional manner prioritized in the following order: for the Lipid family (LDL, and using Hochberg procedure for cholesterol, HDL, triglycerides); for the Glucose family (fasting insulin, fasting glucose, HOMA-IR) and for the BP family (systolic blood pressure, diastolic blood pressure).

Figure 5, below, describes the general testing procedure for the efficacy endpoints of the secondary hypotheses and their relationship to testing of the primary hypothesis. The three families of endpoints will be tested simultaneously only if the primary efficacy hypothesis is satisfied. For each family except the lipid family, the endpoints will be tested in order. The first endpoint within a family will be assessed. The second endpoint within a family will be assessed only if the first endpoint is significant. The third endpoint will be assessed only if the second endpoint is significant. For the lipid family, the first endpoint (LDL) will be assessed. If LDL is significant, the last three endpoints (Cholesterol, HDL and TG) will be assessed using the Hochberg procedure. The Hochberg procedure for 3 endpoints:

- test each endpoint in order from highest to lowest p-value
- if all three endpoints are significant at $\alpha=0.05$, then stop and declare all three significant
- if highest p-value >0.05 , then next highest needs to be significant at $\alpha/2=0.025$. If so, then declare 2 smallest to be statistically significant
- if 2nd highest p-value > 0.025 then test smallest of the 3 p-values against $\alpha/3=0.0167$. If so, then declare the smallest to be statistically significant

All comparisons will be tested at $\alpha=0.05$ level (two-sided).

Figure 5. Testing Procedure for the Efficacy Hypotheses



The testing procedure for secondary hypotheses, as described above preserves the overall α -level at 0.05 level for each family (lipid, glucose and BP) at Year 1, but it does not preserve the Type I error in the strong sense (independent of which hypotheses are true or false) for all tests combined. Comparisons involving other efficacy endpoints and time points are considered supportive or exploratory and will be made at $\alpha=0.050$ level (two-sided). No multiplicity adjustment will be made for these other comparisons.

From a safety standpoint, application of a multiplicity adjustment could potentially mask a safety concern. Thus, no experiment-wise control of type I error will be applied to the safety analyses, with the realization that spurious statistical significance may be observed.

12 REGULATORY REQUIREMENTS

12.1 Pre-study Documentation

Arena must receive the following documentation prior to initiation of the trial:

- Signed protocol signature page
- FDA form 1572 signed by the Principal Investigator (PI)
- Curriculum vitae of the PI and Sub-investigators, updated within 2 years
- Current medical licenses for the PI and all Sub-investigators
- Financial disclosure form signed by the PI and all Sub-investigators listed on the FDA Form 1572
- Copy of the IRB approval letter for the study and approved VICF
- IRB Membership List.

Documents should be faxed or mailed to:

ICON Clinical Research
[SPECIFIC CONTACT INFORMATION REDACTED]

12.2 Investigator Obligations

As indicated on FDA Form 1572, the Principal Investigator (PI) is responsible for ensuring that all study site personnel, including Sub-investigators and other study staff members, adhere to all FDA regulations and guidelines regarding clinical trials, including guidelines for GCP (including the archiving of essential documents), both during and after study completion. The PI will be responsible for the patient's compliance to the study protocol. The PI is responsible for providing Arena an adequate final report shortly after the he/she completes participation in the study, in accordance with 21 CFR §312.64.

12.3 Patient confidentiality

All information obtained during the conduct of the study with respect to the patients' state of health will be regarded as confidential. This is detailed in the written information provided to the patient. An agreement for disclosure of any such information will be obtained in writing and is included in both copies of the VICF signed by the patient. The study data shall not be disclosed to a third party without the written consent of the sponsor.

12.4 Informed consent

According to the ICH guideline for GCP (E6), the investigator will obtain and document informed consent for each patient screened for this study. All patients will be informed in writing of the nature of the protocol and investigational therapy, its possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate prior to the initiation of study procedures. The patient's medical record should contain written documentation indicating that informed consent was obtained. The VICF must be reviewed and approved by the Investigator's designated IRB and by Arena clinical staff. The

VICF should include all the elements as outlined in Section 4.8.10 of the ICH guideline for GCP (E6).

12.5 Institutional Review Board

This protocol and relevant supporting data are to be submitted to the appropriate IRB for review and approval before the study can be initiated. Amendments to the protocol will also be submitted to the IRB prior to implementation of the change. Arena must receive a letter documenting the IRB approval prior to initiation of the study. The PI is also responsible for informing the IRB of the progress of the study and for obtaining annual IRB renewal. The IRB must be informed at the time of completion of the study and should be provided with a summary of the results of the study by the PI. The PI must notify the IRB in writing of any SAE or any unexpected AE according to ICH guidelines.

13 PROTOCOL MANAGEMENT AND ADMINISTRATIVE CONSIDERATIONS

13.1 Study documentation

The PI and study staff have the responsibility of maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be available for inspection by Arena, representatives of Arena, the IRB, and regulatory authorities (i.e., FDA or international regulatory authorities) at any time, and should consist of the following elements:

Patient files, containing the completed case report forms (CRFs), supporting source documentation from the medical record including laboratory data and the VICF;

Regulatory files, containing the protocol with all amendments and Investigator signature pages, copies of all other regulatory documentation, and all correspondence between the site and the IRB and Sponsor; and Drug accountability files, including a complete account of the receipt and disposition of the study medication (test article).

Records are to be available for 2 years after marketing application approval, or if the application is not approved or never submitted, 2 years after the last shipment and delivery of the material and the appropriate competent regulatory authorities are notified. Arena will provide written notification when it is appropriate for the Investigator(s) to discard the study-specific documents referenced above.

13.2 Protocol interpretation and compliance

To ensure accurate interpretation and implementation of the study, the procedures and endpoints defined in the protocol will be carefully reviewed by the PI and his or her staff prior to the time of study initiation. The Sponsor and PI will follow all reasonable means to resolve any differences of opinion of matters of eligibility, toxicity and other endpoints. In the event that a resolution cannot be reached then one or both parties may seek to terminate the study following the provisions outlined in the Clinical Trials Agreement.

13.3 Study monitoring

Representatives from Arena Pharmaceuticals, Inc. or contracted monitor will visit the study center periodically to monitor adherence to the protocol, compliance with ICH guidelines, adherence to applicable FDA regulations, and the maintenance of adequate and accurate clinical records. Case reports forms will be reviewed to ensure that key safety and efficacy data are collected and recorded as specified by the protocol. The Arena representatives and contracted monitor will be permitted to access patients' complete medical records, laboratory data, and other source documentation as needed to monitor the trial appropriately.

14 PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study as outlined in the protocol entitled, “Behavioral modification and Lorcaserin for Overweight and Obesity Management (BLOOM), A 104-Week, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Safety and Efficacy of Lorcaserin Hydrochloride in Obese Patients,” in accordance with the guidelines and all applicable government regulations including Part 54: Financial Disclosure by Clinical Investigators. These guidelines and regulations include, but are not limited to:

- Permission to allow the sponsor, or designee, and the FDA or other regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures patient confidentiality. If this study is to be inspected by a regulatory agency, the sponsor and ICON should be notified as soon as possible.
- Submission of the proposed clinical investigation, including the protocol and the consent form, to a duly constituted IRB for approval, and acquisition of written approval for each prior to the use of the test article.
- Use of written informed consent that is obtained prior to administration of test article or any non-routine procedures that involve risk, and that contains all the elements of consent as specified in the federal regulations and has been previously approved by the sponsor and the IRB.
- Submission of any proposed change in or deviation from the protocol to the IRB using a signed formal amendment document approved by the sponsor. Any proposed changes or deviations from the protocol require that the informed consent also reflect such changes or deviations and that the revised informed consent be approved by the IRB.
- Documentation and explanation of individual protocol deviations on the appropriate CRF page or in letters to the sponsor.
- Reports of SAEs to the ICON Medical Monitor within 24 hours by telephone and a written report of the SAE within 72 hours after the investigator’s initial receipt of the information.
- Submission of reports of SAEs, as outlined in the protocol, to the IRB within 15 calendar days of their disclosure.
- Submission of timely progress reports to the IRB and sponsor at appropriate intervals on a schedule determined by the IRB.
- Maintenance of appropriate records: Federal regulations require an investigator to prepare and maintain adequate and accurate case histories designed to record all observations and other data (such as test article accountability) pertinent to the investigation on each individual enrolled in the study. These records must be maintained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

In addition, I agree to provide all the information requested in the CRF in a manner to assure legibility and accuracy. To this end, I shall carefully follow the instructions for completing CRFs.

I also agree that all information provided to me by the sponsor, including protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be related in confidence to the IRB. I also understand that reports of information about the study or its progress will not be provided to anyone not involved in the study other than to the PI, or in confidence to the IRB or to the FDA or other legally constituted authority.

Principal Investigator

Date

Printed Name

15 APPENDICES

Appendix A – Body Mass Index Table

Appendix B – Echocardiography Procedures

Appendix C – Arena[®] Healthy Lifestyle Program

Appendix D – Binge Eating Scale

Appendix E – Beck Depression Inventory - II

Appendix F – Impact of Weight Questionnaire - Lite (IWQOL-Lite)

APPENDIX A – BODY MASS INDEX TABLE

Height (inches)	<i>Body Mass Index (kg/m²)</i>																											
	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
	Body Weight (pounds)																											
58	129	134	138	143	148	153	158	162	167	172	177	181	186	191	196	201	205	210	215	220	224	229	234	239	244	248	253	258
59	133	138	143	148	153	158	163	168	173	178	183	188	193	198	203	208	212	217	222	227	232	237	242	247	252	257	262	267
60	138	143	148	153	158	163	168	174	179	184	189	194	199	204	209	215	220	225	230	235	240	245	250	255	261	266	271	276
61	143	148	153	158	164	169	174	180	185	190	195	201	206	211	217	222	227	232	238	243	248	254	259	264	269	275	280	285
62	147	153	158	164	169	175	180	186	191	196	202	207	213	218	224	229	235	240	246	251	256	262	267	273	278	284	289	295
63	152	158	163	169	175	180	186	191	197	203	208	214	220	225	231	237	242	248	254	259	265	270	278	282	287	293	299	304
64	157	163	169	174	180	186	192	197	204	209	215	221	227	232	238	244	250	256	262	267	273	279	285	291	296	302	308	314
65	162	168	174	180	186	192	198	204	210	216	222	228	234	240	246	252	258	264	270	276	282	288	294	300	306	312	318	324
66	167	173	179	186	192	198	204	210	216	223	229	235	241	247	253	260	266	272	278	284	291	297	303	309	315	322	328	334
67	172	178	185	191	198	204	211	217	223	230	236	242	249	255	261	268	274	280	287	293	299	306	312	319	325	331	338	344
68	177	184	190	197	203	210	216	223	230	236	243	249	256	262	269	276	282	289	295	302	308	315	322	328	335	341	348	354
69	182	189	196	203	209	216	223	230	236	243	250	257	263	270	277	284	291	297	304	311	318	324	331	338	345	351	358	365
70	188	195	202	209	216	222	229	236	243	250	257	264	271	278	285	292	299	306	313	320	327	334	341	348	355	362	369	376
71	193	200	208	215	222	229	236	243	250	257	265	272	279	286	293	301	308	315	322	329	338	343	351	358	365	372	379	386
72	199	206	213	221	228	235	242	250	258	265	272	279	287	294	302	309	316	324	331	338	346	353	361	368	375	383	390	397
73	204	212	219	227	235	242	250	257	265	272	280	288	295	302	310	318	325	333	340	348	355	363	371	378	386	393	401	408
74	210	218	225	233	241	249	256	264	272	280	287	295	303	311	319	326	334	342	350	358	365	373	381	389	396	404	412	420
75	216	224	232	240	248	256	264	272	279	287	295	303	311	319	327	335	343	351	359	367	375	383	391	399	407	415	423	431
76	221	230	238	246	254	263	271	279	287	295	304	312	320	328	336	344	353	361	369	377	385	394	402	410	418	426	435	443

APPENDIX B - ECHOCARDIOGRAPHY PROCEDURES

[Redacted—information proprietary to echocardiography core facility]

APPENDIX C – ARENA[®] HEALTHY LIFESTYLE PROGRAM

Program Overview

The Behavioral Health Solutions (BHS) division of Johnson & Johnson Health Care Systems Inc. (JJHCS) has extensive experience in designing, implementing, training, and evaluating high-risk behavioral intervention programs. Arena has employed BHS services to customize a program, the Arena Healthy Lifestyle Program, specifically for use in this study.

All subjects in this clinical research trial will participate in a standardized behavioral weight management program. The program framework is based on a one-to-one counseling model in which subjects will meet with a trained Program Counselor at each study visit as indicated in the Schedule of Events for Year 1 and Year 2 (Table 7, Table 8). The visit objectives and materials will be standardized across all study sites. The discussion topics will focus on healthy eating, physical activity, and lifestyle changes that will facilitate weight loss and weight maintenance.

The objectives of this program are as follows:

- Develop a moderate-intensity weight management program for all APD356 study participants
- Standardize the weight management program across all study sites
- Maximize patient recruitment and retention
- Maintain counselor motivation

The initial counseling visit will take place on the day of randomization. The initial counseling visit occurs at the time of randomization, will be approximately 1 hour in length, and includes a Baseline Interview with the patient, assessment of the patient's dietary habits and activity level, and calculation of the calorie requirement. The prescribed diet will be approximately 600 calories less per day than the patient's calculated Estimated Energy Requirement (EER). The EER will be calculated using WHO criteria with a fixed activity factor of 1.3 for most patients. However, for patients who engage in ≥ 1 hour /day aerobic exercise, an activity factor of 1.4 will be used based on the counselors baseline interview.

Between visits, patients will be asked to complete a food and activity log which they will return at each study visit for assessment by the counselor for compliance with the program. Non-compliance will be addressed by the counselor as appropriate through additional discussion, education, and materials.

At each subsequent study visit, the program will guide the counselor and patient through various pre-selected topics related to successful long-term weight management programs. Sample topics include Preparing for Change, Embracing Physical Activity, Practical Portions, Keeping Slips from Becoming Setbacks, Dining Out, and other relevant topics to keep patients informed and motivated.

Counselor Training

Each site will allocate a person (or persons) to perform the counselor role. Ideally the counselor will be qualified by professional training (i.e., Registered Dietitians). Each counselor will be asked to

attend the Investigator's Meeting which includes an intensive 4-hour workshop designed and implemented by BHS. The workshop will include the following:

- Objectives and Key Program Components
- Counselor Roles and Responsibilities
- Overview Materials and Counseling Sessions Topics
 - Assess materials
 - Review Delivery Strategies
 - Practice Calorie deficit protocol
 - Observe "Therapeutic Partnership" Role-play
- Counseling Intervention Elements
 - SMART Goals practice
 - Overview of STAGE appropriate goals
 - Best Practices for Counselors
 - Case studies with counseling plans
 - Application: trio role plays with feedback
- Action Planning
 - Individual Counselor Action Plan
 - Site Counselors "Success Circles" Action Plans
 - Web-site preview
 - Ordering Materials
 - Contact information

Upon completion of the workshop, each counselor will receive a certificate of completion. Only counselors who have been officially trained by BHS will be allowed to administer the program to patients.

As with any long-term study, it is anticipated that additional training for new staff will be required. The ICON study monitor will notify BHS when additional training is needed for a particular site. BHS will develop and administer a training program that can be administered via distance learning, onsite, or a combination of training modes, as needed. A record of this training will be maintained by BHS and provided to ICON throughout the study.

To facilitate additional outreach and information sharing with the site counselors, a website accessible only to certified counselors will be maintained by BHS. Content of the website will parallel topics that are provided in the hard copy materials. The website content will include the following:

- Quarterly tips
- Articles by Experts
- Training Materials
- Program Materials Reorder

The above list is not all inclusive of the intended website content, but provided as an example of the types of content that will be included.

Program Quality Assurance

Arena recognizes the importance of maintaining a quality and consistent behavioral program throughout the course of the study. Prior to initiation of the study, all sites will be consistently trained and counselors certified at conclusion of the Counselor Training Workshop. Ongoing quality assurance will be assessed by ICON study monitors who will review, at a minimum, quarterly with each site a quality checklist as provided by BHS. Compliance with the program will be documented in the corresponding monitoring report. Deficiencies will be communicated to BHS and Arena and addressed proactively, as needed.

APPENDIX D – BINGE EATING SCALE (SAMPLE ONLY)

Instructions: Below are groups of numbered statements. Read all of the statements in each group and completely fill in the bubble for the one that best describes the way you feel about the problems you have controlling your eating behavior.

Ref: Gormally, J., Black, S., Daston, S., & Rardin, D. (1982). The assessment of binge eating severity among obese persons. *Addictive Behaviors*, 7, 47-55.

Statement	SC ONLY
1)	
<input type="checkbox"/> I don't feel self-conscious about my weight or body size when I am with others	0
<input type="checkbox"/> I feel concerned about how I look to others, but it normally does not make me feel disappointed about myself	0
<input type="checkbox"/> I do get self-conscious about my appearance and weight which makes me feel disappointed in myself	1
<input type="checkbox"/> I feel very self conscious about my weight, and frequently I feel intense shame and disgust with myself. I try to avoid social contacts because of my self-consciousness	3
2)	
<input type="checkbox"/> I don't have any difficulty eating slowly in the proper manner	0
<input type="checkbox"/> Although I seem to "gobble down" foods, I don't end up feeling stuffed because of eating too much	1
<input type="checkbox"/> At times, I tend to eat quickly and then I feel uncomfortable afterwards.	2
<input type="checkbox"/> I have a habit of bolting down my food without really chewing it. When this happens I usually feel uncomfortably stuffed because I've eaten too much.	3
3)	
<input type="checkbox"/> I feel capable to control my eating urges when I want to.	0
<input type="checkbox"/> I feel that I have failed to control my eating more than the average person	1
<input type="checkbox"/> I feel utterly helpless when it comes to feeling in control of my eating urges.	3
<input type="checkbox"/> Because I feel so helpless about controlling my eating, I have become very desperate about trying to get in control.	3

- 4)
- I don't have the habit of eating when I'm bored. 0
 - I sometimes eat when I'm bored, but often I'm able to "get busy" and get my mind off food. 0
 - I have a regular habit of eating when I'm bored, but occasionally, I can use some other activity to get my mind off eating. 0
 - I have a strong habit of eating when I'm bored. Nothing seems to help me break the habit. 2
- 5)
- I'm usually physically hungry when I eat something. 0
 - Occasionally, I eat something on impulse even though I really am not hungry. 1
 - I have the regular habit of eating food that I might not really enjoy, to satisfy a hungry feeling, even though physically I don't need the food. 2
 - Even though I'm not physically hungry, I get a hungry feeling in my mouth that only seems to be satisfied when I eat a food, like a sandwich, that fills my mouth. Sometimes, when I eat the food to satisfy my mouth hunger, I then spit the food out so I won't gain weight. 3
- 6)
- I don't feel any guilt or self-hate after I overeat. 0
 - After I overeat, I occasionally feel guilt or self-hate. 1
 - Almost all the time I experience strong guilt or self-hate after I overeat. 3
- 7)
- I don't lose total control of my eating when dieting even after periods when I overeat. 0
 - Sometimes, when I eat a "forbidden food" on a diet, I feel like I "blew it" and eat even more. 2
 - Frequently, I have the habit of saying to myself, "I've blown it now, why not go all the way," when I overeat on a diet. When that happens I eat even more. 3

-
- I have a regular habit of starting strict diets for myself, but I break the diets by going on an eating binge. My life seems to be either a “feast” or a “famine”. 3
- 8)**
- I rarely eat so much food that I feel uncomfortably stuffed afterwards. 0
- Usually about once a month, I eat such a quantity of food, I end up feeling very stuffed. 1
- I have regular periods during the month when I eat large amounts of food, either at mealtime or at snacks. 2
- I eat so much food that I regularly feel quite uncomfortable after eating and sometimes a bit nauseous. 3
- 9)**
- My level of calorie intake does not go up very high or go down very low on a regular basis. 0
- Sometimes after I overeat, I will try to reduce my caloric intake to almost nothing to compensate for the excess calories I’ve eaten. 1
- I have a regular habit of overeating during the night. It seems that my routine is not to be hungry in morning but to overeat in the evening. 2
- In my adult years, I have had weeklong periods where I practically starve myself. This follows periods when I overeat. It seems I live a life of either “feast” or “famine.” 3
- 10)**
- I usually am able to stop eating when I want to. I know when “enough is enough”. 0
- Every so often, I experience a compulsion to eat which I can’t seem to control. 1
- Frequently I experience strong urges to eat which I seem unable to control, but at other times I can control my eating urges. 2
- I feel incapable of controlling urges to eat. I have a fear of not being able to stop eating involuntarily. 3

- 11)**
- I don't have any problem stopping eating when I feel full. 0
 - I usually can stop eating when I feel full but occasionally overeat, leaving me feeling uncomfortably stuffed. 1
 - I have a problem stopping eating once I start and usually I feel uncomfortable stuffed after I eat a meal. 2
 - Because I have a problem not being able to stop eating when I want, I sometimes have to induce vomiting to relieve my stuffed feeling. 3
- 12)**
- I seem to eat just as much when I'm with others (family, social gatherings) as when I'm by myself. 0
 - Sometimes when I'm with other persons, I don't eat as much as I want to eat because I'm self-conscious about my eating. 1
 - Frequently, I eat only a small amount of food when others are present, because I'm very embarrassed about my eating. 2
 - I feel so ashamed about overeating that I pick times to overeat when I know no one will see me. I feel like a "closet eater". 3
- 13)**
- I eat three meals a day with only an occasional between meal snack. 0
 - I eat three meals a day, but I also normally snack between meals. 0
 - When I am snacking heavily, I get in the habit of skipping regular meals. 2
 - There are regular periods when I seem to be continually eating, with no planned meals. 3
- 14)**
- I don't think much about trying to control unwanted eating urges. 0
 - At least some of the time, I feel my thoughts are preoccupied with trying to control my eating urges. 1
 - I feel that frequently I spend much time thinking about how much I ate or about not trying to eat any more. 2
 - It seems to me that most of my waking hours are preoccupied by thoughts about eating or not eating. I feel like I'm constantly struggling not to eat. 3

15)

- I don't think about food a great deal. 0
- I have strong cravings for food but they last only for brief periods of time. 1
- I have days when I can't seem to think about anything else but food. 2
- Most of my days seem to be preoccupied with thoughts about food; I feel like I live to eat. 3

16)

- I usually know whether or not I'm physically hungry. I take the right portion of food to satisfy me. 0
- Occasionally, I feel uncertain about knowing whether or not I'm physically hungry. At these times it's hard to know how much food I should take to satisfy me. 1
- Even though I might know how many calories I should eat, I don't have any idea what is a "normal" amount of food for me. 2

APPENDIX E – BECK DEPRESSION INVENTORY – II (SAMPLE ONLY)

Ref: Beck, AT, CH Ward, M Mendelson, J Mock, and J Erbaugh. 1961. An inventory for measuring depression. Arch Gen Psychiatry 4: 561-571.

Ref: Beck, AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. J Clin Psychol. 1984 Nov; 40(6):1365-7.

[CONTENT OF BDI-II QUESTIONNAIRE REDACTED—COPYRIGHTED MATERIAL]

**APPENDIX F – IMPACT OF WEIGHT QUESTIONNAIRE - LITE (IWQOL-LITE) –
(SAMPLE ONLY)**

Ref: Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity. *Obesity Res.* 2001;9:102-11.

Ref: Kolotkin RL, Crosby RD. Psychometric evaluation of the Impact of Weight on Quality of Life-Lite Questionnaire (IWQOL-Lite) in a community sample. *Quality of Life Research.* 2002;11(2):157-71.

[CONTENT OF IWQOL-LITE REDACTED—COPYRIGHTED MATERIAL]

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