BLOSSOM:

Behavioral Modification and Lorcaserin Second Study for Obesity Management

*A 52-Week, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Safety and Efficacy of Lorcaserin Hydrochloride in Overweight and Obese Patients*

**Why is this research study being done?**

We are studying an “investigational” drug, lorcaserin hydrochloride (“lorcaserin”), formerly known as APD356. An investigational drug is one that has not been approved by the United States (US) Food and Drug Administration (FDA) for sale. Arena Pharmaceuticals, the company that makes lorcaserin is sponsoring (paying for) this study.

Your main study visits will be conducted at the MGH Weight Center. The clinic is located at 50 Staniford St, 4th Floor, Boston, MA 02114.

This is the eleventh study using lorcaserin in humans. It’s the eighth study in which lorcaserin pills are given to obese patients for more than one day. More than 4300 volunteers have taken part in studies of lorcaserin so far. The studies have ranged from single doses up to 52 weeks of dosing.

The main purpose of this study is to find out the effects of lorcaserin in obese and overweight subjects who have one or more complications caused by their weight. Another purpose of this study is to gather information about how safe lorcaserin is.

We will also use a placebo in this study. A placebo looks exactly like the active study drug but contains no active ingredients. Placebos help us know if the study results are from the study drug or from other reasons. Subjects in this study will take study drug or placebo and will also follow a diet and exercise program for one year.

We expect to enroll about 40 subjects at MGH, out of a total study enrollment of about 3000 subjects. This study will take place at about 100 different medical centers across the US.

**Background Information: Other obesity drugs**

Lorcaserin is being developed as a possible treatment for obesity. More than 1 billion individuals worldwide are overweight. At least 300 million of these people are obese. This is more than 20% of the world population. In the U.S., about 30% of adults and 15% of children and adolescents are considered obese and many more are overweight.
Obesity can lead to other diseases and conditions. These include high blood pressure, high cholesterol, diabetes, sleep disorders, arthritis, and some cancers. The treatment of obesity includes diet and exercise programs, treatment with drugs, and surgery (for some extreme cases).

Only two prescription drugs are currently approved in the U.S. for the chronic treatment (longer than 12 weeks) of obesity. These drugs are sibutramine (Meridia®) and orlistat (Xenical). Also, phentermine is approved in the U.S. for short-term use (less than 12 weeks). Phentermine is sold in the U.S. under the brand names Adipex® and Ionamin®. However, use of these drugs is limited. They work only moderately well and have unwanted side effects. Side effects include increased blood pressure (Meridia), stomach and intestinal side effects (Xenical), and possible addiction (phentermine).

Lorcaserin is meant to be used along with diet and exercise to achieve weight loss. Lorcaserin works in a way that is similar to two older appetite-suppressing drugs. Those drugs are called fenfluramine and dexfenfluramine. In 1997, fenfluramine (Pondimin®) and dexfenfluramine (Redux®) were withdrawn from the market in the US due to safety concerns. These concerns included damage to heart valves and pulmonary hypertension. Lorcaserin was designed to try to overcome these dangerous side effects but to retain the weight loss effects.

At this time, we don’t fully understand the cause of the side effects that made Pondimin® and Redux® unsafe. We also don’t fully understand the side effects of lorcaserin itself. For this reason, we cannot be sure that the harmful effects have been eliminated. You may experience side effects, which you should report to your study doctor.

**How long will I take part in this research study?**

This research study begins with a 6-week screening period to see if you qualify for the study. After screening, there is a 52 week dosing period, when you will take the study drug. You will make at least 2 outpatient visits during the screening period and at least 15 outpatient visits during the dosing period. Your study doctor may ask you to make extra visits for safety reasons.

We will also make a follow-up telephone call to you about 4 weeks after your last visit to check on your health.
What are the risks and possible discomforts from being in this research study?

Risks of Lorcaserin

All medications may cause side effects. There may be side effects from taking lorcaserin hydrochloride that are not yet known. The study doctor and the sponsor will tell you right away about any new side effects that occur, so that you can decide whether to stay in this study.

There is only limited information available regarding the side effects of lorcaserin in humans.

Lorcaserin may cause drowsiness. You should exercise caution and not drive, operate machinery, or engage in other activities requiring mental alertness until you know how the study drug will affect you.

In the first study with lorcaserin, up to 20 mg was associated with side effects of headache, dizziness, blurred vision and lightheadedness. Gastrointestinal effects (nausea, vomiting, and indigestion) were reported.

At a dose of 40 mg, a few subjects experienced mild euphoria (exaggerated feeling of wellbeing). One subject had symptoms of euphoria and intoxication (feeling drunk). These were followed by disorientation (feeling very confused), feelings of hot and cold, and a possible hallucination (seeing or hearing things that aren’t real). You will not take more than 10 mg at a time in this study.

In the second study with lorcaserin, daily doses of up to 20 mg were taken for 14 days. The most common side effects were headache, drowsiness, lightheadedness, nausea, and vomiting. All of these symptoms tended to occur only once, were mild or moderate in intensity, and lasted for hours rather than days.

In the third study with lorcaserin, doses of 1, 5, and 15 mg once a day were taken for 4 weeks. The most common side effects were headache, drowsiness, lightheadedness, and nausea.

In the fourth study with lorcaserin, subjects took doses of 10 mg once a day, 15 mg once a day, or 10 mg twice a day for 12 weeks. The most common side effects reported were headache, lightheadedness, dry mouth, fatigue, diarrhea, nausea, and vomiting. One woman developed depression after taking lorcaserin 10 mg twice a day for about 6 weeks. Another woman who had never before had a seizure experienced a seizure after taking lorcaserin 10 mg twice a day for about 6 weeks. We do not know if these events are related to taking lorcaserin.

Some predictions can be made from animal studies with lorcaserin and from human studies of other drugs similar to lorcaserin. Lorcaserin is a member of a group of drugs known as serotonin agonists. A serotonin agonist stimulates serotonin receptors, located in the part of the brain called the hypothalamus, which helps regulate satiety (how full
you feel) and influences metabolic rate (how much food your body needs).

**Potential Brain Effects**

Effects on the brain were the most frequently seen side effects of lorcaserin in animals. These brain effects in animals included decreased activity, sleeplessness, and vomiting. In some animals at high doses the brain effects were severe, and led to fits (for example, seizures and convulsions). These effects in animals were related to the amount of drug given. They were seen only at high doses (much higher than doses in this study). Such effects, along with headaches and distorted thinking (hallucinations) have also been seen with other serotonin agonists (drugs similar to lorcaserin) in humans.

As with any drug that activates the serotonin system, there is a risk of developing “serotonin syndrome.” This syndrome results from excessive amounts of serotonin released in the brain. It can be fatal if not treated promptly. Please report any adverse (bad or unwanted) feelings you may have to the study staff immediately. Adverse feelings may include headaches, nausea or other occasions where you feel sick. The sponsor does not expect that lorcaserin will cause serotonin syndrome. Studies in animals appear to show that the drug does not cause an increase in serotonin in the brain. However, the effects of lorcaserin in humans are not fully known.

**Potential Heart and Lung Effects**

Some serotonin agents that were used to treat obesity caused heart valve changes. In a few extreme cases, these changes meant the patient had to have an operation to fix their heart valves. In addition, these same drugs may have caused a condition called "pulmonary artery hypertension (PAH)". PAH occurs when the pressure in one of the main blood vessels leading to the lungs becomes much higher than normal. PAH is a life-threatening condition, and there is no known treatment for it. These drugs are no longer given to patients for any health condition.

Changes to heart valves caused by other drugs will generally respond to treatment with medication if discovered early enough. We require subjects to have echocardiogram tests in this study to watch for these changes. In rare cases with other drugs like fenfluramine, patients have had to have an operation to repair their heart valves.

No apparent drug-related changes in heart valves have been seen in studies of lorcaserin with animals or people to date. Likewise, no apparent drug-related increases in pulmonary arterial pressure have been observed to date.

**Other Potential Drug Effects**

In some animals given lorcaserin, spontaneous erections of the penis were seen. These always settled spontaneously. This effect has not been observed in human research studies of lorcaserin to date. However, the condition could require medical treatment if it occurred and did not resolve spontaneously.

At the highest doses tested, minor changes occurred in the lungs, liver, and kidneys of
animals. You will be monitored during the study for any signs/evidence of this.

Some rats given lorcaserin at very high doses for 6 months or up to a year or more developed tumors of the breast in an ongoing two year study. Breast tumors occur commonly in rats that receive certain drugs that act on the brain. This finding is thought to be limited to rats and of questionable importance for humans. Several drugs have been approved with this finding, including a sleep drug. Mice and monkeys have not developed breast tumors when given lorcaserin.

A small number of rats in this same ongoing two year study that were given very high doses of lorcaserin were found to have brain tumors. The type of brain tumor that was found occurs naturally in a small percent of rats that do not receive any drug.

There may be side effects other than those described in this consent form. We will closely monitor your health throughout the study. There will be regular checks of your vital signs [blood pressure, heart rate (how fast your heart is beating), and body temperature]. We will also do ECGs and blood and urine tests. If there are any concerns about these, they will be discussed with you. Repeat tests may be necessary for your welfare and safety.

**Other Possible Effects**

You could also have an allergic reaction to the study drug. This could be mild, or even fatal. For your safety, you must tell your study doctor about your past and present medical events. Tell your study doctor about any allergies you have and about all medications and drugs you now take. This includes over-the-counter drugs and herbal or food supplements.

As with all medications, if you fail to follow dosage instructions, this may result in unwanted side effects and may be dangerous for your health.

There are no known risks associated with echocardiograms. You may feel a little uncomfortable lying still on your back during the test.

The most common side effects of blood drawing include mild discomfort or feeling faint. A bruise may form where the needle enters your vein. Other risks may include bleeding from and infection at the puncture site. If an infection develops, it can be treated. The total amount of blood to be collected for the entire study will be less than the amount you would give in donating blood (less than 2 cups).

There are no known side effects from the ECG procedure other than local skin irritation or itching. It may be necessary to shave small areas of the chest for the attachment of disposable sticky pads.

Fasting may cause dizziness, headaches, stomach discomfort, or fainting.
You must not take part in another research study while taking part in this study. If you have recently taken part in a research study, please tell the study coordinator.

**What are the possible benefits from being in this research study?**

You may not receive any personal medical benefit. There are health benefits to losing weight, but you are not guaranteed to lose weight during this study. The only direct benefit to you will be the evaluation and review of your health by the examining study doctor.

You may receive some benefit from taking part in the Arena® Healthy Lifestyles Program, a weight management program designed specifically for this study. The knowledge and materials you gain from this program may benefit you; even after your study participation is complete.

In addition, the information learned from this study as a result of your participation may benefit others in the future.

**What other treatments or procedures are available for my condition?**

This is a research study and is not the same as treatment or therapy. If you do not qualify for the study, or choose not to take part in this study, your doctor can discuss other treatments with you. These may include diet and exercise programs, other drugs (including sibutramine, orlistat and phentermine), a combination, or even surgery for some cases.

**For Additional Information, please call the study coordinator at 617-724-9616**