ARENA PHARMACEUTICALS INC
Form 8-K
January 03, 2012

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the

Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): January 3, 2012

Arena Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**000-31161**	**23-2908305**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

6166 Nancy Ridge Drive, San Diego, California 92121

(Address of principal executive offices) (Zip Code)

858.453.7200

(Registrant s telephone number, including area code)

N/A

(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

¨ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

¨ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

¨ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

¨ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

In this report, Arena Pharmaceuticals, Arena, Company, we, us and our refer to Arena Pharmaceuticals, Inc., unless the context otherwise provides.

Item 8.01 Other Events.

Submission of Response to Lorcaserin Complete Response Letter

On January 3, 2012, we and Eisai Inc. announced that we have submitted our response to the Complete Response Letter, or CRL, issued by the US Food and Drug Administration, or FDA, following its review of the lorcaserin New Drug Application, or NDA. Lorcaserin is intended for weight management, including weight loss and maintenance of weight loss, in patients who are obese (Body Mass Index, or BMI, ≥30) or patients who are overweight (BMI ≥27) and have at least one weight-related co-morbid condition. The FDA received our submission on December 27, 2011, and we expect that later this month the FDA will confirm its acceptance of the response and assign a new Prescription Drug User Fee Act, or PDUFA, date.

Our response to the lorcaserin CRL includes data and analyses that were not incorporated in the original NDA, including the results of our Phase 3 BLOOM-DM (Behavioral modification and Lorcaserin for Overweight and Obesity Management in Diabetes Mellitus) clinical trial, which evaluated lorcaserin for weight loss in patients with type 2 diabetes. The additional information also includes data and analyses from activities intended to address tumors observed in a two-year lorcaserin rat carcinogenicity study, cell culture experiments intended to further refine serotonin subtype 2 receptor activity and rat studies designed to further assess abuse potential.

Below is an overview of the data from our recently completed mechanistic studies relating to the mammary tumors observed in the two-year lorcaserin rat carcinogenicity study and additional information on lorcaserin s serotonin subtype 2 receptor activity. These are summaries of the results and analysis, and it is important to note that the FDA or others may analyze or weigh the data differently.

Studies Intended to Investigate the Mechanism of Mammary Tumors in Rats

We recently completed a series of studies that were conducted to investigate the mechanism underlying mammary tumors that were observed in female rats during a two-year lorcaserin carcinogenicity study that was included in the original lorcaserin NDA.

As outlined below, in a three-month study of intact female rats, lorcaserin persistently increased pituitary prolactin content, transiently increased plasma prolactin, and caused changes in mammary histomorphology that are consistent with prolactin stimulation in rats. We believe that this study demonstrates a link between lorcaserin, increased prolactin, and mammary changes that can precede hormone-mediated mammary tumors in rats. As also outlined below, the results of our blockade studies of one-month and shorter duration suggest that lorcaserin-mediated effects on the rat mammary gland are dependent on pituitary prolactin.

Study Background

We believe the previously reported re-adjudication by an independent Pathology Working Group, or PWG, and related analyses establish a safety margin of 24-fold between human lorcaserin exposures at the expected recommended maximum dose and exposures in female rats at the highest dose not associated with an increase in mammary adenocarcinoma, which are malignant tumors, in the two-year rat carcinogenicity study. The re-adjudication did not establish a safety margin for mammary fibroadenomas, which are benign tumors, as these tumors were increased over control in female rats at all lorcaserin doses tested.

In addition to the activities related to the PWG re-adjudication, we conducted a series of studies that were designed to investigate the mechanism by which the benign and malignant tumors formed. The studies sought to demonstrate a link between lorcaserin, prolactin and mammary tumor development in rats. Interpretation of the results included a comparison of lorcaserin s effects to those of another drug that increases prolactin and causes mammary tumors in rats.

The studies can be categorized as follows:

- short-term pilot experiments designed to optimize methods for measuring or detecting prolactin in plasma, the pituitary gland and the mammary gland;
- three-month studies in rats to investigate changes in plasma and tissue prolactin and mammary gland morphology; and
- studies of one-month and shorter duration in female rats to determine whether lorcaserin-mediated changes in the mammary gland could be prevented by blocking prolactin action or prolactin release.

In most of the experiments, a positive control drug (perphenazine, a dopamine-2 receptor blocker) that is known to increase circulating prolactin and to cause mammary tumors in rats was included.

Three-Month Studies

After optimizing methodology in the pilot experiments, we conducted a three-month study of female rats. Pituitary prolactin content was measured after dosing vehicle, lorcaserin or perphenazine for 7, 28, 60 and 90 days, and plasma prolactin concentrations were measured at various time points throughout the study. Lorcaserin at all doses tested (10, 30 and 100 mg/kg/day) increased pituitary prolactin content relative to vehicle control at all time points, and these increases were statistically significant for all lorcaserin doses at Day 90. Lorcaserin also statistically significantly increased plasma prolactin compared to vehicle control at 20 hours after dosing for up to ten days at the high dose.

We evaluated lorcaserin s effect on mammary tissue using several different techniques. Mammary whole mount preparations were used to look at the morphology of the gland with a focus on changes that could precede the development of tumors. Mammary sections were also examined microscopically using hematoxylin and eosin, or H&E, staining to evaluate

histopathology. Proliferating cell nuclear antigen, or PCNA, immunostain was performed to quantify nuclear proliferation, and prolactin immunostain was used to evaluate the prolactin content of the mammary gland.

In the mammary whole mount preparations, lorcaserin was associated with decreases in mammary gland terminal ducts and increases in lobular structures. Decreases in terminal ducts typically occur under prolactin stimulation as these structures develop into progressively more complex lobular structures (from type 1 to type 3) needed for milk production. The increase in type 2 lobules was statistically significant at Day 28 at the lorcaserin high dose, and decreases in terminal ducts and increases in type 1 lobules and total lobular structures were statistically significant at Day 90 at the low and high lorcaserin doses. These types of changes can precede prolactin-mediated mammary tumors in rats.

H&E staining showed that lorcaserin at the high dose statistically significantly increased the proportion of animals with mammary secretory product (believed to be milk) as compared to vehicle control at Day 28. This increase in secretory product is another marker of prolactin stimulation.

Low-dose lorcaserin statistically significantly increased PCNA staining at Day 90, and mid-dose lorcaserin increased the signal at Day 28. High-dose lorcaserin did not statistically significantly affect PCNA staining in this study.

We did not observe changes in circulating progesterone, estradiol or luteinizing hormone in lorcaserin dose groups that we believe are sufficient to explain the observed changes in mammary morphology.

The positive control, perphenazine, caused statistically significant elevations of plasma prolactin at all time points, more pronounced morphological changes at Days 28 and 90 and statistically significantly decreased pituitary prolactin content at Days 28 and 90. Perphenazine also increased lobular hyperplasia in H&E sections and increased PCNA immunostaining of mammary tissue on Days 28 and 90.

A smaller study in male rats did not show consistent effects on pituitary or plasma prolactin or mammary morphological changes with lorcaserin or perphenazine treatment. Since the positive control had no effect relative to control, this experiment does not contribute to our interpretation of the prolactin hypothesis.

Blockade Studies of One-Month and Shorter Duration

We also performed studies that utilized agents or procedures to block prolactin release or action.

In one study, lorcaserin (30 mg/kg/day) or vehicle was administered for 10 days to female rats that had undergone pituitary ablation to eliminate prolactin production the hypophysectomized group and to an intact control group. Approximately 10 days after the dosing period, lorcaserin increased mammary lobular hyperplasia in the intact control group that was statistically significantly greater than vehicle. Hypophysectomy prevented the lorcaserin-mediated increase in mammary lobular hyperplasia. The results of this study provide evidence that the lorcaserin-

induced mammary lobular hyperplasia a finding that can precede mammary tumor formation in female rats was dependent on the pituitary gland. Lorcaserin did not increase mammary PCNA staining or mammary prolactin content in this study.

In another prolactin blockade study, female rats received lorcaserin (100 mg/kg/day) or perphenazine for one month with or without simultaneous administration of a compound (a peptide called S179D) that blocks the prolactin receptor. Lorcaserin and perphenazine statistically significantly increased mammary tissue staining with PCNA, a marker of cellular proliferation. This effect was partially prevented by S179D for both compounds, and with statistical significance for lorcaserin, providing evidence that the proliferative effect of lorcaserin on the rat mammary gland was mediated through prolactin action. Increases in mammary hyperplasia observed with both lorcaserin and perphenazine were not inhibited by S179D.

Serotonin Subtype 2 Receptor Activity

As part of our response to the CRL, and based on the FDA s suggestion, we supplemented our original receptor pharmacology data by investigating lorcaserin s functional activity at the three serotonin subtype 2 receptors (2A, 2B and 2C) in the absence of receptor reserve. These experiments, which eliminated spare receptors, confirmed that lorcaserin has greater potency at the serotonin 2C receptor than at the 2A or 2B receptor subtypes; in these experiments, lorcaserin was 14 times less potent at 2A and 61 times less potent at 2B receptors than at 2C receptors.

Forward-Looking Statements

Certain statements in this Form 8-K are forward-looking statements that involve a number of risks and uncertainties. Such forward-looking statements include statements about the advancement, therapeutic indication and use, safety, efficacy, tolerability, mechanism of action, and potential of lorcaserin; the response to the CRL for the lorcaserin NDA, including confirmation of acceptance, assignment of a PDUFA date, the FDA s review, and addressing issues raised in the CRL; the data and studies, analyses and other activities included in such response, including their significance and what they were intended to address, refine and assess; the results and analysis of the rat mechanistic studies, including our interpretation and the significance of their results; and the involvement of prolactin in rat mammary tumors. For such statements, we claim the protection of the Private Securities Litigation Reform Act of 1995. Actual events or results may differ materially from our expectations. Factors that could cause actual results to differ materially from the forward-looking statements include, but are not limited to, the following: the timing of regulatory review, including the assignment of a PDUFA date, and approval is uncertain; nonclinical and clinical data is voluminous and detailed, and regulatory agencies may interpret or weigh the importance of data differently and reach different conclusions than we or others, request additional information, have additional recommendations or change their guidance or requirements before or after approval; data and other information related to lorcaserin and our other research and development programs may not meet safety or efficacy requirements or otherwise be sufficient for regulatory review or approval; our submission of a marketing authorization application for regulatory approval of lorcaserin may not be submitted when anticipated, if at all; unexpected or unfavorable new data; risks related to commercializing new products; our ability to obtain and defend our patents; the timing, success and cost of our research and development programs; results of clinical trials and other studies are

subject to different interpretations and may not be predictive of future results; clinical trials and other studies may not proceed at the time or in the manner expected or at all; our ability to obtain adequate funds; risks related to relying on collaborative agreements; the timing and receipt of payments and fees, if any, from collaborators; and satisfactory resolution of pending and any future litigation or other disagreements with others. Additional factors that could cause actual results to differ materially from those stated or implied by our forward-looking statements are disclosed in our filings with the Securities and Exchange Commission. These forward-looking statements represent our judgment as of the time of the filing of this Form 8-K. We disclaim any intent or obligation to update these forward-looking statements, other than as may be required under applicable law.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: January 3, 2012

Arena Pharmaceuticals, Inc.

By: /s/ Steven W. Spector
Steven W. Spector
Senior Vice President, General Counsel and Secretary