



## **Arena Pharmaceuticals Announces Results of its Phase 1b Safety Study for its Novel Anti-Obesity Compound**

SAN DIEGO, Nov. 30 /PRNewswire-FirstCall/ -- Arena Pharmaceuticals, Inc. (Nasdaq: ARNA) announced today results from the dosing phase of its Phase 1b clinical trial of APD356, an orally administered small molecule designed to regulate satiety (and perhaps metabolism) for the treatment of obesity. APD356 is a selective agonist of 5-HT<sub>2C</sub> serotonin receptors, which are concentrated in the hypothalamus, an area of the brain believed to play an important role in regulating food intake and metabolism.

The Phase 1b clinical trial of APD356 was a randomized, double-blinded, placebo-controlled, multiple-dose, dose-escalation study designed to evaluate the safety of APD356 at steady state drug levels during repeated daily dosing for 14 days. Highlights of the Phase 1b study include:

- \* APD356 was well tolerated.
- \* Side effects were similar to placebo at the 3 and 10 mg doses of APD356, but tended to occur more frequently than placebo at the 20 mg dose. The most common side effects, occurring primarily at the 20 mg dose, were headache, nausea and vomiting. These side effects were generally mild in nature.
- \* APD356 continued to demonstrate predictable pharmacokinetic behavior; time to maximum plasma concentration (T<sub>max</sub>) was approximately two hours after dose administration, estimated plasma half-life (t<sub>1/2</sub>) was about 10 hours, and steady state plasma levels were achieved by day five.

"These results are consistent with our expectations of APD356 based on the Phase 1a trial and preclinical data, and support our intention to initiate a Phase 2 trial examining weight loss as the primary endpoint," stated William Shanahan, M.D., Arena's Vice President and Chief Medical Officer. "We are currently on track to begin dosing APD356 in a Phase 2, multiple-dose, 28-day trial of 400 obese volunteers by year's end. We plan to compare daily doses of 1, 5, and 15 mg of APD356 to placebo."

Doses for the Phase 2 trial were chosen to bracket the 10 mg dose previously shown in the Phase 1a trial to demonstrate a pharmacologic signal (a reduction in meal size) with a single dose. The 1 mg dose was chosen as the lowest dose because Arena believes that a 1 mg dose has the potential to produce therapeutic drug levels in the CNS if APD356, as observed in rats, achieves higher concentrations in human brain than in blood.

The Phase 1b clinical trial enrolled 27 subjects (15 males and 12 females) with an average BMI of 31 (+/- 6), and a BMI range of 25 to 58. Participants were administered 3, 10 and 20 mg doses of APD356 or placebo in successive cohorts of 9 subjects (6 APD356, 3 placebo) and were kept within a Phase 1 unit. Participants were instructed to maintain their usual exercise patterns, and were offered sufficient food to maintain their desired intake levels.

APD356 was well tolerated; there were no severe or serious adverse events reported, no withdrawals due to an adverse event, and no reports of euphoria, dysphoria, or disorientation. APD356 continued to demonstrate very predictable pharmacokinetic behavior, similar to that found in the Phase 1a trial of APD356. The maximum plasma concentration (C<sub>max</sub>) and exposures (AUC<sub>0-24</sub> and AUC<sub>0-inf</sub>) increased dose proportionately with increasing doses of APD356. There were no apparent gender differences in pharmacokinetic parameters.

Based on a comparison of Day 14 echocardiograms with those taken at screening, there was no evidence of a drug effect on heart valves or pulmonary artery pressure. As part of the follow-up phase of the trial, results will be obtained from longer-term echoes (performed at 2 months and 3 months post dosing) to confirm continued absence of drug effect.

This Phase 1b study was designed as a safety study and was not meant to detect significant weight change between treatment groups. As expected with a small number of participants in an artificial setting, considerable variations in weight change within each group were noted, and, when compared with placebo, none of the mean changes in weight in the active arms were statistically significant.

About APD356

Obesity and metabolic syndrome are conditions that affect tens of millions of adults and children and pose a serious long-term threat to their health and welfare. In the previous Phase 1a single-dose clinical trial, evidence of a pharmacological effect on food intake was seen with a single 10 mg dose of APD356. The 10 mg dose was well tolerated, and produced peak drug levels in blood that are some 20-fold greater than the in vitro EC50 for the 5-HT2C receptor, the pharmacologic target for APD356. Dose escalation was stopped after the 40 mg dose due to CNS side effects consistent with a high dose of a serotonergic drug. APD356 was pharmacokinetically well behaved, with minimal inter-subject variability, excellent dose proportionality and a half-life suitable to once daily dosing. Food did not affect the amount of APD356 that was absorbed, which suggests that it can be taken before or after a meal.

In animal models of obesity, APD356 reduced body weight and food intake, which, Arena believes, is due to the compound's ability to regulate satiety and perhaps metabolism. Arena's in vivo experiments showed that APD356 selectively reduced fat mass in obese animals, while leaving lean body mass unchanged, a very desirable outcome. Stimulation of the 5-HT2C receptor is thought to play an important role in weight loss. APD356 has approximately 100-fold selectivity in vitro for the 5-HT2C receptor relative to the 5-HT2B receptor, the receptor primarily implicated in the cardiac valvulopathy observed with non-selective serotonergic drugs. In addition, APD356 has approximately 15-fold selectivity in vitro for the 5-HT2C receptor versus the 5-HT2A receptor, the central nervous system (CNS) receptor thought to be primarily responsible for most of the CNS adverse effects of non-selective serotonergic agents. It is hypothesized that its selectivity will allow APD356 to be dosed at a well-tolerated level that will induce clinically relevant weight loss while avoiding the cardiovascular side effects observed with non-selective serotonergic agents.

#### About Arena Pharmaceuticals

Arena is a biopharmaceutical company focusing on the discovery, development and commercialization of drugs in four major therapeutic areas: metabolic, cardiovascular, inflammatory and central nervous system diseases. Arena is developing a broad pipeline of compounds that act on an important class of drug targets called G protein-coupled receptors, or GPCRs, and that are being developed using Arena's proprietary technologies, including CART™ (Constitutively Activated Receptor Technology) and Melanophore. Arena also has research collaborations with Merck, Fujisawa, Taisho and TaiGen for products in a number of different indications. For additional information about Arena, visit their website at <http://www.arenapharm.com>.

#### Forward-Looking Statements

Certain statements in this press release are forward-looking statements that involve a number of risks and uncertainties. Such forward-looking statements include statements relating to the selectivity and therapeutic applications of APD356, about when and whether Arena expects to continue further clinical testing on APD356 and about Arena's strategy, technologies, pre-clinical and clinical programs, and ability to identify and develop drugs, as well as other statements that are not historical facts. For such statements, Arena claims the protection of the Private Securities Litigation Reform Act of 1995. Actual events or results may differ materially from Arena's expectations. Factors that could cause actual results to differ materially from the forward-looking statements include, but are not limited to, the timing, success and cost of Arena's research, out-licensing endeavors and clinical studies, Arena's ability to obtain additional financing, and the timing and receipt of payments and fees, if any, from Arena's collaborators. Additional factors that could cause actual results to differ materially from those stated or implied by Arena's forward-looking statements are disclosed in Arena's SEC reports, including Arena's most recent quarterly report on Form 10-Q. These forward-looking statements represent Arena's judgment as of the date of this release. Arena disclaims any intent or obligation to update these forward-looking statements.

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