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## **Zafgen Announces Positive Results From Phase 2 Clinical Trial of Beloranib in Hypothalamic Injury Associated Obesity**

BOSTON, Jan. 7, 2015 (GLOBE NEWSWIRE) -- Zafgen (Nasdaq:ZFGN), a biopharmaceutical company dedicated to significantly improving the health and well-being of patients affected by obesity and complex metabolic disorders, announced today that ZAF-221, a randomized, double-blind, placebo-controlled Phase 2 clinical trial of beloranib, a MetAP2 inhibitor, in 14 adults with hypothalamic injury associated obesity, or HIAO, met the primary efficacy endpoint of weight reduction ( $p = 0.01$ ). In addition, beloranib treatment was well-tolerated and improved cardiovascular disease risk factors.

HIAO is a rare form of medically induced obesity resulting from damage to the hypothalamus following resection of central nervous system tumors such as craniopharyngioma. The hypothalamus is a homeostatic control center in the brain that provides oversight of multiple hormonal systems, metabolic rate, hunger, and satiety. Patients affected by HIAO fail to regulate metabolism and food intake normally, resulting in rapid and intractable weight gain, treatment resistant severe obesity, and associated co-morbidities.

"We are extremely pleased with these results, which differentiate beloranib from other weight loss agents. Beloranib's impact to restore balance to production and utilization of fat is further validated with these findings," said Dennis Kim, M.D., Chief Medical Officer of Zafgen. "With these results in hand, we plan to pursue HIAO as an extension of our work in Prader-Willi syndrome, or PWS. We believe beloranib shows tremendous potential to improve the lives of those impacted by HIAO and PWS, and for whom there are limited effective pharmaceutical alternatives. In 2015, we aim to establish the regulatory path for a registration program with U.S. and EU regulatory authorities."

"We are delighted by these clinical results that provide additional evidence for our hypothesis about beloranib's mechanism and establish the drug's unique extra-hypothalamic mode of action. Along with PWS and severe obesity in the general population, HIAO is the third indication for which we have established proof of concept for beloranib," said Thomas Hughes, Ph.D., Chief Executive Officer of Zafgen. "We are enthusiastic to continue development of beloranib for the treatment of patients with severe and complex forms of obesity."

Beloranib, a first-in-class MetAP2 inhibitor, that has demonstrated the potential to address weight loss and hunger reduction in patients with obesity, is being studied for the treatment of multiple indications. ZAF-221 was a randomized, double-blind, placebo controlled study of twice-weekly subcutaneous injections of 1.8 mg beloranib or placebo in patients with HIAO to evaluate weight reduction and safety over four weeks, followed by an optional four week open-label extension. Beloranib treatment resulted in mean weight loss of 3.4 kg and 6.2 kg in patients with HIAO after four and eight weeks of treatment with beloranib, respectively, in contrast to 0.3 kg mean weight loss in patients treated with placebo for four weeks ( $p = 0.01$ ). Improvements in cardiovascular disease risk factors of lipids and inflammation (measured by C-reactive protein) were also observed. Beloranib 1.8 mg was well tolerated in this population, with no serious or severe adverse events reported. Safety measures such as laboratory, electrocardiogram, and vital sign measurements revealed no signals of concern, and all subjects randomized to beloranib completed the trial. This trial enrolled 14 obese patients (nine women and five men) who were confirmed by magnetic resonance imaging (MRI) to have had hypothalamic injury.

"These data represent a significant step forward in understanding the role of MetAP2 inhibition as a useful therapeutic approach to treating complex forms of obesity characterized by hypothalamic dysfunction," said Professor Joseph Proietto, Head of Weight Control Clinic, Austin Health, Melbourne, Australia. "These results are innovative, as they represent an exceptional level of success in the pharmaceutical treatment of HIAO, and are very encouraging for our field, as well as for these patients who remain largely beyond the reach of currently marketed pharmaceutical agents."

### **About Beloranib**

Beloranib is a novel, first-in-class injectable small molecule therapy with a unique mechanism of action that reduces hunger while stimulating the use of stored fat as an energy source. Beloranib is a potent inhibitor of methionine aminopeptidase 2, or MetAP2, an enzyme that modulates the activity of key cellular processes that control metabolism. MetAP2 inhibitors work, at least in part, by directing MetAP2 binding to cellular stress mediators, and, thus, reducing the tone of signals that drive lipid synthesis by the liver and fat storage throughout the body. In this manner, MetAP2 inhibition increases metabolism of fat as an energy source. Zafgen holds exclusive worldwide rights (exclusive of South Korea) for the development and commercialization of beloranib. Zafgen exclusively licensed beloranib from Chong Kun Dang (CKD) Pharmaceutical Corp. of South Korea.

### **About Hypothalamic Injury-Associated Obesity (HIAO)**

HIAO is most commonly caused by damage incurred during removal of a central nervous system tumor called craniopharyngioma but it can also result from less common types of hypothalamic injury such as strokes, brain trauma, or radiation therapy to the brain. Craniopharyngioma is a rare form of benign brain tumor that occurs most commonly during childhood and infiltrates near the optic nerve, pituitary gland and the hypothalamus. Treatment of these tumors commonly involves surgical removal of the tumor mass, followed by radiation treatment, which results in disruption or removal of neighboring structures including the hypothalamus. Post-treatment hypothalamic dysfunction results in hyperphagia and significant obesity in up to 50% of these patients, resulting in a variety of co-morbid conditions and a deteriorated quality of life. Craniopharyngioma-associated obesity occurs in males and females equally and in all races, with the same incidence around the world. The incidence estimates have ranged from 0.13 to 0.17 per 100,000 per year, or approximately 400 to 500 new cases per year in the United States and 650 to 850 new cases per year in the European Union.

## About Zafgen

Zafgen (Nasdaq:ZFGN) is a biopharmaceutical company dedicated to significantly improving the health and well-being of patients affected by obesity and complex metabolic disorders. Zafgen is focused on developing novel therapeutics that treat the underlying biological mechanisms through the MetAP2 pathway. Beloranib, Zafgen's lead product candidate, is a novel, first-in-class, twice-weekly subcutaneous injection being developed for the treatment of multiple indications, including severe obesity in two rare diseases, Prader-Willi syndrome and obesity caused by hypothalamic injury, including craniopharyngioma-associated obesity; and severe obesity in the general population. Zafgen aspires to improve the lives of patients through targeted treatments and has assembled a team accomplished in bringing therapies to patients with both rare and prevalent metabolic diseases.

## Safe Harbor Statement

Various statements in this release concerning Zafgen's future expectations, plans and prospects, including without limitation, Zafgen's expectations regarding beloranib as a treatment for HIAO, Prader-Willi syndrome, and severe obesity in the general population, its expectations with respect to the timing and success of its clinical trials, the expected requirements and timing of additional clinical trials and pre-clinical studies, and its plans regarding commercialization of beloranib may constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995 and other federal securities laws. Forward-looking statements can be identified by terminology such as "anticipate," "believe," "could," "could increase the likelihood," "estimate," "expect," "intend," "is planned," "may," "should," "will," "will enable," "would be expected," "look forward," "may provide," "would" or similar terms, variations of such terms or the negative of those terms. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including, without limitation, Zafgen's ability to successfully demonstrate the efficacy and safety of its product candidates, the pre-clinical and clinical results for its product candidates, which may not support further development, actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials, obtaining, maintaining and protecting its intellectual property, Zafgen's ability to enforce its patents against infringers and defend its patent portfolio against challenges from third parties, competition from others developing products for similar uses, Zafgen's ability to manage operating expenses, Zafgen's ability to obtain additional funding to support its business activities and establish and maintain strategic business alliances and new business initiatives, Zafgen's dependence on third parties for development, manufacture, marketing, sales and distribution of products, the outcome of litigation, and unexpected expenditures, as well as those risks more fully discussed in the section entitled "Risk Factors" in the final prospectus related to Zafgen's initial public offering filed with the Securities and Exchange Commission pursuant to Rule 424(b) of the Securities Act, as well as discussions of potential risks, uncertainties, and other important factors in Zafgen's subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Zafgen's views only as of today and should not be relied upon as representing its views as of any subsequent date. Zafgen explicitly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

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