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Zafgen Presents New Data from the Phase 3 bestPWS Study Evaluating Beloranib in Prader-Willi Syndrome at ENDO 2016

--bestPWS Study is the first Phase 3 pivotal trial to show significant weight-loss and improvement in hyperphagia-related behaviors in PWS patients--

--Beloranib was associated with improvement in total cholesterol, LDL cholesterol and other markers of cardiometabolic risk --

--Beloranib demonstrated a statistically significant reduction in fat mass at both 1.8 mg and 2.4 mg dose levels--

BOSTON, April 03, 2016 (GLOBE NEWSWIRE) -- Zafgen Inc. (Nasdaq:ZFGN), a biopharmaceutical company dedicated to significantly improving the health and well-being of patients affected by obesity and complex metabolic disorders, today announced new data from the bestPWS ZAF-311 study, a pivotal, double-blind, placebo-controlled Phase 3 trial evaluating the safety and efficacy of beloranib, a MetAP2 inhibitor, in patients with Prader-Willi syndrome (PWS) during the six-month randomized treatment period. Data presented today during ENDO 2016, the Endocrine Society's 98th Annual Meeting & Expo, showed that beloranib was associated with improvement in total cholesterol, LDL cholesterol and other cardiometabolic risk factors, and a reduction in fat mass when compared to placebo.

As previously reported, the bestPWS study achieved its co-primary efficacy endpoints, as beloranib demonstrated a statistically significant reduction in both body weight and hyperphagia-related behaviors, making it the first investigational drug to demonstrate a positive impact on these two hallmark challenges of PWS.

"These data further support the efficacy profile of beloranib in PWS, and advance our understanding of the potential of our MetAP2 inhibitor platform to impact metabolic disorders," stated Thomas Hughes, Ph.D., Chief Executive Officer of Zafgen. "We believe these data also provide greater perspective on the benefit/risk relationship of beloranib in this high-risk patient population and we look forward to discussing these results with the FDA."

PWS is the most common genetic cause of life-threatening obesity. Hyperphagia, pathologic hunger-related behaviors, dominates the lives of individuals with PWS, driving patients to engage in problematic behaviors which can lead to bodily injury, choking, and stomach rupture. Patients with PWS also have higher rates of psychiatric conditions including aggression, anxiety and psychosis. Compounding the obesity in PWS is markedly low metabolism, abnormal body composition with higher fat mass and low lean mass, and higher risk for cardiopulmonary and metabolic co-morbidities, all of which contribute to a higher risk of obesity-related mortality.

"Prader-Willi syndrome is a life-limiting and life-threatening condition with no available treatment options that significantly impact affected individuals and their families," said Merlin G. Butler, M.D., Ph.D., FFACMG, Professor of Psychiatry, Behavioral Sciences and Pediatrics, Director, Division of Research and Genetics, Departments of Psychiatry & Behavioral Sciences and Pediatrics at the University of Kansas Medical Center. "In addition to the reduction in body weight and decrease in excessive eating behaviors previously reported from this study, the data presented today demonstrate important reductions in cardiometabolic risk factors and further support a strong rationale for continued evaluation of beloranib as a potential treatment for PWS."

BestPWS ZAF-311 Efficacy and Safety Results

In the bestPWS ZAF-311 study, 107 patients were randomized to receive twice-weekly subcutaneous injections of either 2.4 mg or 1.8 mg of beloranib or placebo. Seventy-four patients completed the full 26 weeks of treatment per the study protocol, and 27 patients completed at least 75 percent of the randomized treatment period prior to the suspension of dosing in the trial in October 2015. There were six patients who discontinued early. The co-primary efficacy endpoints for this trial were improvement in hyperphagia-related behaviors and reduction in body weight. Secondary endpoints in this trial included improvement in total body fat mass and improvement in lipids and markers of cardiometabolic risk (TC and LDL). Patients in the trial were on average 20 years old, had an average BMI of 40 kg/m^2, an average body weight of 100 kg, an average fat mass of 51 kg and an average hyperphagia total score of 16.9, consistent with moderate to severe hyperphagia, at the beginning of randomized treatment. These baseline characteristics were well-balanced across treatment arms. In agreement with the FDA, Zafgen has analyzed the data using a mixed model repeated measures (MMRM) approach to account for missing endpoint data from the patients who did not complete the randomized treatment period of the trial.

Co-primary Endpoints

	Average Weight at Baseline (kg)[1]	Percent Change in Body Weight[1]	Placebo-adjusted Change in Body Weight[1]	p-value
2.4 mg beloranib (n=37)	105.7	-5.30%	-9.45%	<0.0001
1.8 mg beloranib (n=36)	97.5	-4.05%	-8.20%	<0.0001
Placebo (n=34)	100.9	+4.15%		

[1]Endpoint results shown are Least Squares mean values.

Patients in the ZAF-311 trial were markedly obese at baseline. Patients randomized to receive placebo displayed substantial (4.15%) increase in body weight over the course of the six months of randomized treatment. Body weight gain in this patient population was anticipated, and typically occurs throughout life generally due to a lack of effective treatments for managing obesity. Patients treated with beloranib, in contrast to placebo, experienced a reduction in weight, with the 2.4 mg dose arm displaying a 5.3 percent reduction from baseline, with a placebo-adjusted weight loss of 9.45 percent.

	Average Hyperphagia Questionnaire (HQ-CT) Total Score at Baseline	Unit Change in HQ-CT Total Score[1]	Placebo-adjusted Change in HQ-CT Total Score[1]	p-value
2.4 mg beloranib (n=37)	18.3	-7.4	-7.0	0.0001
1.8 mg beloranib (n=36)	17.4	-6.7	-6.3	0.0003
Placebo (n=34)	15.0	-0.4		

[1]Endpoint results shown are Least Squares mean values.

The HQ-CT is a PWS-specific study instrument that provides an assessment by caregivers of the food-seeking behaviors exhibited by patients. The scale provides a composite value from nine questions, each rated on a scale of zero to four units (total range of score of zero to 36). Patients in the ZAF-311 trial were enrolled only if their baseline HQ-CT total score was greater than 12 units, representing moderate-to-severe hyperphagia related behaviors at baseline. While hyperphagia-related behaviors were stable over six months of treatment in the placebo arm, both the 2.4 mg and 1.8 mg beloranib arms showed highly statistically significant reductions in HQ-CT total score, indicative of reduced hunger-associated behaviors.

Secondary Endpoints

In this study, beloranib was associated with improvements in total cholesterol and LDL cholesterol as well as other markers of cardiometabolic risk compared to placebo. The mean change in HDL cholesterol and triglycerides showed no significant change from baseline for each treatment arm. The reduction in leptin levels and increase in adiponectin levels seen in PWS patients receiving both dose levels of beloranib is consistent with altered fatty acid mobilization and lipid utilization.

	Change in LDL Cholesterol (mg/dl)[1]	Change in Total Cholesterol (mg/dl)[1]	Change in Leptin (µg/L)[1]	Change in Adiponectin (µg/L)[1]	Percent Change in CRP[2]
Mean at Baseline	101	174	6.9	4.6	7.6 µg/mL
2.4 mg beloranib (n=37)	-17.8**	-18.0*	-24.0**	+1.9**	-53%**
1.8 mg beloranib (n= 36)	-16.6**	-17.2*	-20.7**	+1.7**	-56%**
Placebo (n=34)	+1.8	+1.3	+6.9	-0.5	+2.5%

[1]Endpoint results shown are Least Squares mean values.

[2]Endpoint results are Geometric Least Squares mean values.

*p<0.001 compared to placebo

** p<0.0001 compared to placebo

Body composition was measured using dual-energy X-ray absorptiometry (DXA) scan. Patients treated with beloranib demonstrated a significant reduction in total body mass and fat mass at both the 1.8 mg and 2.4 mg doses of beloranib.

Lean body mass was minimally changed from baseline with a 0.5 kg loss in the 1.8 mg beloranib arm, a 0.7 kg loss in the 2.4 mg beloranib arm and an increase of 0.7 kg in the placebo arm. Approximately 90 percent of loss in total body mass with beloranib was due to loss of body fat, indicating preferential loss of fat with minimal change in lean mass.

	Change in Total Body Mass[1]	Fat Mass Change (kg)[1]	Percentage Change in Fat Mass[1]
2.4 mg beloranib (n=37)	-5.7%*	-5.0*	-9.8%*
1.8 mg beloranib (n=36)	-2.9%*	-2.5*	-4.5%*
Placebo (n=34)	+ 3.4%	+ 2.6	+ 5.9%

[1]Endpoint results shown are Least Squares mean values.
*p<0.0001 compared to placebo

The most common adverse events (AEs) in this study were injection site bruising, aggression, and hyperphagia, generally of mild severity and transient in nature. Of these, only injection site bruising was notable as being reported more frequently in patients taking beloranib compared to placebo. There were a total of five serious adverse events (SAEs); aggression (placebo, 2.4 mg beloranib), ankle fracture (placebo), mental status change (1.8 mg beloranib), and pulmonary embolism (1.8 mg beloranib). Four patients withdrew due to adverse events in the 1.8 mg beloranib treatment group (abnormal behavior, anxiety, mental status changes, and pulmonary embolism) and two patients in the 2.4 mg beloranib group (injection site pain and psychotic disorder). Many of these adverse events, specifically psychiatric disorders, are commonly observed as background comorbidities in PWS patients. At the end of the randomized treatment period, there were no clinically significant abnormal patterns regarding laboratory values, vital signs, or electrocardiography (ECG) findings. As previously disclosed, across the completed trials comprising the beloranib clinical program, there has been an association of venous thromboembolic events reported in patients treated with beloranib versus placebo, including one fatal case of pulmonary embolism (1.8 mg beloranib) during the randomized portion of the bestPWS study that was reported in October 2015. No other venous thromboembolic events were reported during the blinded randomized portion of the bestPWS study. As previously reported, a second patient death associated with pulmonary embolism (2.4 mg beloranib) and two cases of deep vein thrombosis (1.8 mg and 2.4 mg beloranib) occurred during the open-label extension portion of the bestPWS study. No other deaths have occurred over the course of the beloranib program.

Zafgen plans to present to the FDA the data from the ZAF-311 clinical trial, and previously reported data from the ZAF-203 Phase 2b clinical trial of beloranib in obesity complicated by type 2 diabetes, as well as a proposal for a risk mitigation strategy for beloranib in PWS in an effort to resolve the full clinical hold the FDA placed on the beloranib IND in December 2015.

About Beloranib
Beloranib is a novel, first-in-class injectable small molecule therapy that works by inhibiting MetAP2, an enzyme that modulates the activity of key cellular processes that control metabolism. Once a person becomes obese, the body undergoes certain metabolic changes and becomes "programmed" to create and store more fat, making it much more difficult to reduce body weight. Beloranib is believed to help reduce hunger and restore balance to fat metabolism, enabling calories to once again be used as a productive energy source. Because beloranib works beyond just regulating hunger through the hypothalamus, it has the potential to be used in a variety of complex metabolic disorders such as Prader-Willi syndrome and hypothalamic injury associated obesity. Zafgen holds exclusive worldwide rights (exclusive of South Korea) for the development and commercialization of beloranib. Zafgen exclusively licensed beloranib from Chong Kun Dang Pharmaceutical Corporation (CKD Pharma) of South Korea.

About Prader-Willi Syndrome (PWS)
Prader-Willi syndrome (PWS), is the most common known genetic cause of life-threatening obesity. A dysfunctional signaling to the hypothalamus results in constant and unrelenting perception of starvation, driving patients with PWS to engage in problematic hunger-related behaviors, known as hyperphagia, and to gain excessive weight. As a result, many of those affected with PWS become morbidly obese and suffer significant mortality. Currently, there is no cure for this disease. Although the cause of PWS is complex, it results from a deletion or loss of function of a cluster of genes on the 15th chromosome. PWS typically causes low muscle mass and function, short stature, incomplete sexual development, and a chronic feeling of hunger that, when coupled with a metabolism that utilizes drastically fewer calories than normal, can lead to excessive eating and life-threatening obesity. PWS occurs in males and females equally and in all races, with the same incidence around the world. Prevalence estimates have ranged from 1:8,000 to 1:50,000. Patients with PWS have a shortened life expectancy of approximately 32 years, as a result of an estimated three percent annual death rate for the PWS population. Common causes of mortality in PWS include respiratory disease, cardiac disease, infection, choking, gastric rupture, and pulmonary embolism.

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 is also developing ZGN-839, a liver-targeted MetAP2 inhibitor, for the treatment of nonalcoholic steatohepatitis, or NASH, and abdominal obesity, as well as second-generation MetAP2 inhibitors, which may be developed for the treatment of 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 PWS and obesity caused by hypothalamic injury, including craniopharyngioma-associated obesity, Zafgen's expectations regarding the use of other MetAP2 inhibitors as treatments for other forms of severe obesity, including severe obesity in the general population, Zafgen's expectations with respect to the timing and success of its non-clinical studies and clinical trials of beloranib and its other product candidates, the expected requirements and timing of additional requirements for planned clinical trials, and the need for additional clinical trials and pre-clinical studies, and Zafgen's 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 obtain a release of the full clinical hold that the FDA placed on the investigational new drug application for beloranib, Zafgen's ability to successfully demonstrate the efficacy and safety of beloranib and its other product candidates, the pre-clinical and clinical results for beloranib and its other product candidates, which may not support further development and marketing approval, actions of regulatory agencies, which may affect the initiation, timing and progress of pre-clinical studies and clinical trials, Zafgen's ability to obtain, maintain and protect 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 Zafgen's most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission, 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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