September 22, 2012

Zafgen Announces Additional Weight Loss and Cardiometabolic Data from Phase 1b Studies of Beloranib in Obesity at Obesity 2012, the 30th Annual Scientific Meeting of The Obesity Society

Findings Show Treatment with Beloranib Resulted in Rapid Weight Loss, Corresponding Reductions in Multiple Cardiovascular Risk Factors in Severely Obese Subjects

San Antonio, September 22, 2012 – Zafgen, Inc., a leading biopharmaceutical company dedicated to addressing the unmet needs of severely obese patients, today announced new data from two Phase 1b studies of beloranib, a selective inhibitor of methionine aminopeptidase 2 (MetAP2), which showed rapid weight loss, reductions in body fat, and improvements in cardiovascular disease risk markers in severely obese women. These results were achieved with both the intravenous (IV) and subcutaneous administration of beloranib. The data were presented in a poster session at Obesity 2012, the 30th Annual Scientific Meeting of The Obesity Society in San Antonio on September 22, 2012 at noon CST.

With these latest findings, there are now three independent studies showing that treatment with beloranib resulted in identical weight loss and was well-tolerated. Beloranib, a novel obesity therapy that utilizes a unique mechanism of action, is being studied for its ability to restore balance between the production and utilization of fat.

“Consistent results showing rapid and substantial weight loss in three independent placebo-controlled and doubleblinded studies raise our confidence in beloranib as an obesity therapeutic,” said Tom Hughes, PhD, president and CEO of Zafgen. “The latest findings also validate the transition from intravenous administration, which we employed to establish proof of concept, to a subcutaneous form that is more convenient for patients and paves the way to larger trials.”

Both Phase 1b trials presented at Obesity 2012 were randomized, double-blind, placebo-controlled studies to evaluate the safety, tolerability and metabolic effects of twice-weekly administered beloranib in severely obese women. In one trial, beloranib was administered intravenously (IV); the second trial involved subcutaneous administration. Patients in both studies were allowed to eat normally and were not counseled to change their exercise habits.

The first poster presentation authored by Dr. Dennis Kim, Chief Medical Officer of Zafgen, showed that after four weeks of treatment, the fixed dosing regimen of IV beloranib was generally well-tolerated, resulted in rapid body weight (BW) loss, improved body composition and cardiometabolic risk markers and reduced hunger. Patients were obese women with mean (SEM) age 45.7 (2.6) yr, body weight (BW) 104.9 (4.0) kg, and BMI 39.5 (1.1) kg/m2, who were enrolled into each of the 3 arms of the trials (N=6 in 3.0 mg, 5 in 6.0 mg, and 5 in placebo arm). Results are based on the per-protocol population (n=6, 3, and 5 for 3.0 mg, 6.0 mg, and placebo, respectively) completing the trial.

After four weeks, subjects on 3.0 mg beloranib lost an average of 4.7 kg from baseline (P=0.0008), 6.0 mg beloranib lost 6.7 kg (p=0.0013) vs. a gain of 0.2 kg for placebo. Body composition measurements were consistent with reduced adipose tissue mass. Despite the fact that they lost weight, hunger tended to be reduced (-28% with 3.0 mg, -52% with 6.0 mg, vs. -2% with placebo). The cardiovascular disease risk markers LDLc (Low-Density Lipoprotein cholesterol) and CRP (C-Reactive Protein, an inflammatory marker), decreased significantly in the two beloranib groups vs. placebo. Blood pressure (BP) and glucose did not change with treatment. Doses less than 6.0 mg appearto have clinical utility in balancing effectiveness and tolerability.

The most frequent adverse events (AEs) were mild diarrhea, nausea, headache, dizziness, infusion site injury, and mild-to-moderate sleep disturbance (resulting in two drop-outs from the 6.0 mg group). There were no clinically significant abnormal laboratory or ECG findings.

The second poster (in the Late Breaking Abstract Poster Session) presented by Dr. Dennis Kim demonstrated thatsubcutaneously administered beloranib appeared safe and showed dose responsive weight loss over four weeks. Beloranib treatment was generally well-tolerated by subcutaneous administration, resulted in rapid BW loss, improved sense of hunger and cardiovascular disease risk markers. Patients were white women (mean age 46.0 - 49.9 yr, BW 92.0 - 98.4 kg, and BMI 34.0 - 36.4 kg/m2 across the treatment groups).

Obese women were randomized to 1.0 mg (n=6), 2.0 mg (n=6), or 4.0 mg (n=7) of SC beloranib vs. placebo (N=6) twice-weekly for four weeks. BW, PK (pharmacokinetics) and cardiometabolic biomarkers were measured. Results are based on the per-protocol population (n=6, 5, 4, 6 for 1.0, 2.0, 4.0 mg, and placebo, respectively).

After four weeks, subjects on 1.0 mg, 2.0 mg, or 4.0 mg lost an average of 4.3 kg, 4.2 kg, and 6.1 kg vs. 1.2 kg for placebo (all p<0.001). LDLc, and CRP decreased significantly in all beloranib groups vs. placebo (p<0.05). Hunger tended to be reduced

on beloranib (-42% for 1 mg, -45% for 2 mg, -46% for 4mg, vs. -22% for placebo). Systolic and Diastolic Blood Pressure tended to decrease with beloranib vs. placebo. Subcutaneous beloranib demonstrated reduced peak drug levels (Cmax) with ~100% bioavailability compared to IV beloranib. Subcutaneous doses of beloranib less than 4.0 mg appear to have clinical utility in balancing effectiveness and tolerability.

The most common adverse events (AEs) with higher incidence during beloranib treatment vs. placebo were decreased appetite, vivid dreams, and sleep disturbance (resulting in three drop-outs from the 4.0 mg group). There were no severe AEs, serious AEs, or deaths. There were no clinically significant abnormal laboratory or ECG findings.

“We are excited about these latest results which reinforce the promise of beloranib as a treatment for patients who have limited options,” said Dr. Dennis Kim. “We are looking forward to expanding our clinical development program to include more patients who can potentially benefit from the rapid weight loss and reduction in cardiovascular risk factors we have seen with beloranib.”

About Fat Metabolism
Research continues to show that obese and lean individuals metabolize fat differently. Studies indicate that once a person becomes obese, the body undergoes certain metabolic changes and is “programmed” to make and store more fat, making it much more difficult to reduce body weight. These metabolic adaptations that take place in obese people impair the normal release and breakdown of fatty acids from adipose tissue. Simultaneously, the body becomes much more efficient in diverting calories from food and storing them as fat.

About Beloranib
Beloranib is the first compound in its class that works by targeting a key enzyme called methionine aminopeptidase 2 (MetAP2) that controls the production and utilization of fatty acids. Inhibitors of MetAP2 reduce the production of new fatty acid molecules by the liver and help to convert stored fats into useful energy. Beloranib is being developed as a twice-weekly subcutaneous injection for severe obesity. Zafgen holds exclusive worldwide rights (exclusive of Korea) for development and commercialization of beloranib.

About Zafgen, Inc.
Zafgen is an innovative company dedicated to addressing the unmet need of severely obese patients by bringing beloranib, a first-in-class novel medicine, to market. Founded in 2005 as a virtual company, Zafgen brings together leading experts in obesity and metabolic disease to address the underserved and growing population of patients who are severely obese. Zafgen’s singular focus is on advancing novel therapeutics for patients suffering from severe obesity and obesity-related disorders. The company is located in Cambridge, MA. For more information, visit zafgen.com.