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Zafgen Presents Data on a New Class of Medicines to Treat Obesity at the American Diabetes Association Annual Meeting

Data Show Treatment with MetAP2 Inhibitor Eliminates Excess Body Fat through Regulation of Fat Metabolism and Food Intake and Normalizes Glucose Tolerance in Preclinical Models

CAMBRIDGE, Mass., June 26, 2010 – Zafgen, Inc., a pharmaceutical company pioneering novel obesity therapeutics to help the body regain and sustain a lean, healthy state by targeting imbalances in fat metabolism, today announced data on ZGN-201, a prototype methionine aminopeptidase 2 inhibitor (MetAP2), for the treatment of obesity. Preclinical studies demonstrate MetAP2 inhibition eliminates excess body weight through the regulation of fat metabolism and food intake, and normalizes glucose tolerance in animal models. These findings are significant as they show for the first time the long-term weight- and glucose-lowering effects of MetAP2 inhibitors in rodent and non-rodent models of obesity, supporting their potential for treatment of human obesity and its related metabolic disorders. MetAP2 inhibitors work by reestablishing balance to the ways the body processes fat, leading to substantial loss of body weight and improved glucose tolerance. The data will be presented tomorrow in two separate poster sessions at the American Diabetes Association's 70th Scientific Sessions® in Orlando, Fla.

"We are very encouraged by these findings as they demonstrate the efficacy and tolerability of MetAP2 inhibitor treatment in two long-term preclinical studies in multiple animal models," said Thomas Hughes, Ph.D., president and chief executive officer, Zafgen, Inc. "Our approach is focused on overcoming metabolic adaptations that may hinder weight loss in people by inhibiting the enzymatic activity of MetAP2. By acting on a peripheral target, our program distinguishes itself from most other drugs in development that rely on reducing food intake by targeting the brain, and it provides an exciting new way to potentially treat obesity. We look forward to the results of our ongoing Phase 1 clinical trial assessing safety, tolerability and weight loss using our first generation MetAP2 inhibitor ZGN-433. This is the first 'proof of concept' study to be performed with a MetAP2 inhibitor in obese humans, and will help to determine whether the approach has the potential to be developed as a pharmacological alternative to bariatric surgery."

The preclinical studies presented in Orlando demonstrate the long-term efficacy and tolerability of ZGN-201 in both rodent and canine models. ZGN-201, also known as fumagillin, is a prototype MetAP2 inhibitor. The first study (abstract #1803-P) evaluated the effects of treatment for nine months with ZGN-201 on body weight and metabolic parameters in obese male mice. Treatment reduced food intake and normalized body weight and fat pad size. Significant changes in liver functions were observed, including: reduced liver weights and fat content, suppressed fatty acid biosynthetic pathway gene expression, and increased ketone body levels. Fasting glycemia was improved and insulin concentrations were normalized, indicating treatment improved insulin sensitivity. These findings demonstrate that MetAP2 inhibitor treatment appears to be well tolerated and shows promise as a strategy to reverse obesity-associated metabolic abnormalities while driving rapid weight loss.

The second study (abstract # 24-LB) evaluated the effects of treatment for two months with ZGN-201 on body weight and metabolic parameters in overweight canines. In animals fed a high fat, high fructose (HFF) diet, daily oral treatment with ZGN-201 promoted loss of 81 percent of excess body weight and reduced food intake by 29 percent. Glycerol and ketone body levels increased, reflecting enhanced lipolysis and fat oxidation. ZGN-201 treatment reversed 75 percent of the abnormality in the plasma glucose excursion during the oral glucose tolerance tests, despite a reduction in insulin secretion. Study author Alan Cherrington, Ph.D., professor of medicine and molecular physiology and biophysics at Vanderbilt University and former American Diabetes Association president, said, "These results suggest that, in addition to reducing body weight in obese animals, MetAP2 inhibitor treatment appears to overcome the defect in hepatic glucose uptake caused by a high fat, high fructose diet. These findings uncover a potentially important regulatory principle controlling blood glucose and highlight the potential for use of MetAP2 inhibitors in the treatment of type 2 diabetes."

"While our understanding of the biology of obesity continues to evolve, more and more research points to the role of adipose tissue itself as an important component of the disease," said Randy J. Seeley, Ph.D., professor of medicine and director of the Center of Excellence in Obesity and Diabetes at the University of Cincinnati College of Medicine, and a member of Zafgen's scientific advisory board. "Zafgen's approach using MetAP2 inhibitors aims to target the underlying differences between obese and lean individuals by impacting how the body metabolizes fat in those who are obese. ZGN-201 works by restoring control of adipose tissue lipolysis (breakdown of fat stored in fat cells), ketogenesis, food intake and fat synthesis, to release fat that is then used by the body as fuel – as opposed to being stored – driving weight loss."

About Obesity and Fat Metabolism
Obesity continues to be one of the world's most costly and underserved health issues. As such, there exists a tremendous unmet medical need for effective drug therapies to treat obesity, which has reached epidemic proportions and is growing at an alarming rate. Obesity currently affects approximately 400 million people worldwide, with 72 million Americans – over 30 percent

of the U.S. adult population – considered obese. Obesity plays a major role in other diseases, such as type 2 diabetes, hypertension, coronary heart disease, stroke and cancer, compounding the urgency for new and effective treatment options. Currently available weight loss treatments function by blocking fat absorption or signalling feelings of fullness or diminished appetite in the brain, and frequently suffer from undesirable side effects and limited efficacy that fails to provide sustainable weight loss in many patients.

Research has shown that fat metabolism differs between obese and lean individuals. Recent studies seem to indicate that once a person becomes obese, the body undergoes certain changes and is “programmed” to make and store more fat. These metabolic adaptations that take place in obese people impair the normal release of fatty acids from adipose tissue and restrict the ability to stimulate formation of ketone bodies (a byproduct of the breakdown of fatty acids). Simultaneously, the body becomes much more efficient in diverting calories from food and storing them as fat.

About Zafgen, Inc.
Zafgen is pioneering novel obesity therapeutics that directly target fat metabolism to help the body regain and sustain a lean, healthy state. The company’s approach focuses on restoring control of key metabolic processes, releasing stored fat which then is used by the body as fuel. Zafgen’s first generation product, named ZGN-433, is being studied in a Phase 1b clinical trial for its use as a pharmacological alternative to bariatric surgery in the treatment of severe obesity. Zafgen's leadership and scientific advisors include leading experts in obesity, metabolic disorders and medicinal chemistry. Founded in 2005, the company is located in Cambridge, Massachusetts. For more information, visit www.zafgen.com.