A high potency protein that normalizes body weight in DIO mice through triple agonism at the FGF21, Glp-1 and GIP receptors

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Obesity is endemic throughout much of the world and obesity-related morbidities include heart disease, stroke, non-alcoholic steatohepatitis (NASH) and type 2 diabetes (T2D). Glucagon-Like Peptide 1 (GLP-1) agonists have emerged as highly effective treatment for T2D and more recently for management of obesity. Glucose-dependent Insulinotropic Polypeptide (GIP) agonists when combined with GLP-1 agonism strengthen the pharmacology and yield further decreases in hyperglycemia, body weight and adiposity. The unimolecular GLP-1/GIP coagonist peptide named Tirzepatide recently received regulatory approval for the treatment of T2D, with significant associated loss of body weight. Fibroblast Growth Factor 21 (FGF21) is also an endocrine hormone that has received appreciable attention for treatment of the metabolic syndrome. It has demonstrated profound reductions in serum lipids including triglycerides, LDL, total cholesterol, and hepatic fat fraction, but less impressive relative to incretin-based drugs in control of hyperglycemia. Efruxifermin, an Fc-FGF21 agonist is being studied in the clinic for NASH. It has shown regression in hepatic fibrosis and normalization of liver fat in 12 weeks of treatment. Collectively the clinical studies with incretin and FGF-21 analogs have demonstrated the complimentary nature of these mechanisms to address the full spectrum of diseases associated with the metabolic syndrome. As such we designed, synthesized, and biologically characterized a long-acting protein that is highly potent and balanced in activity at the GLP-1, GIP and FGF21 receptors. This first-in-class triple agonist showed exquisite efficacy at reversing diet-induced obesity in mice and simultaneously provides the precedent-setting glycemic and weight benefits of GLP-1 and GIP coagonism with the enhanced lipid lowering properties of FGF21 agonism.

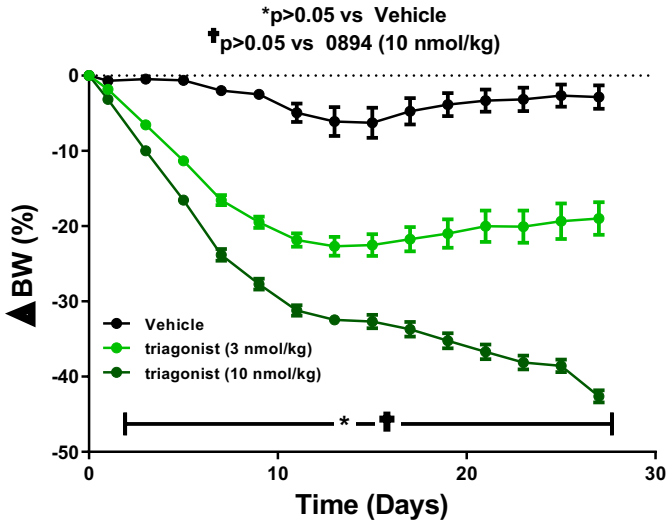

Figure 1. Treatment DIO mice with a novel incretin/FGF21 triagonist to provide near-normalization of body weight.