Fractyl Health Demonstrated That a Single Dose of a GLP-1-Based Pancreatic Gene Therapy Candidate (GLP-1 PGTx) Durably Maintained Weight Loss After Semaglutide Withdrawal in a Murine Model of Obesity at WCIRDC 2023 Annual Meeting

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Single administration GLP-1 PGTx resulted in 27% total body weight loss at Day 28 compared to 21% for chronic semaglutide 10 nmol/kg/day in the Diet-Induced Obesity (DIO) rodent model

Animals subsequently withdrawn from semaglutide who received single-dose GLP-1 PGTx maintained initial body weight loss, while animals who did not crossover to PGTx regained 19% body weight by Day 57

Results provide evidence that a single administration of pancreatic gene therapy encoding nutrient-stimulated hormones like GLP-1 has the potential to offer clinically meaningful and sustained weight loss without the need for ongoing pharmacotherapy

LEXINGTON, Mass., Dec. 11, 2023 (GLOBE NEWSWIRE) — Fractyl Health, a metabolic therapeutics company focused on pioneering new approaches for the treatment of type 2 diabetes (T2D) and obesity, presented preclinical findings from its Rejuva® gene therapy platform at the World Congress Insulin Resistance Diabetes and Cardiovascular Disease 2023 Annual Meeting. The oral presentation, titled “Singledose GLP-1-based Pancreatic Gene Therapy Maintains Weight Loss After Semaglutide Withdrawal in a Murine Model of Obesity,” highlighted the promising implications of the Rejuva platform in providing a durable therapeutic solution for obesity with a GLP-1- based pancreatic gene therapy candidate (GLP-1 PGTx) designed to target the pancreas to provide long-term metabolic benefits from a single administration.

During the oral presentation today, the company presented results from the well-validated DIO rodent model of obesity. In the first phase of the study, a single dose of a GLP-1 PGTx was compared to chronic semaglutide 10 nmol/kg/day in a head-to-head study. GLP-1 PGTx demonstrated improved weight loss compared to semaglutide at day 28, with 27% weight loss for GLP-1 PGTx vs. 21% weight loss for semaglutide ($p<0.05$ for the difference between a GLP-1 PGTx and semaglutide, n=10 in each arm). The data demonstrated that local delivery of a GLP-1 PGTx, driven by the insulin promoter, can potentially lead to sustained and plateaued weight loss after a single administration in obesity.

In the second phase of the study, semaglutide was withdrawn on day 29, and animals were randomized to receive vehicle control (n=5) or single dose GLP-1 PGTx (n=5) for an additional 4 weeks. By Day 57, the semaglutide-withdrawn vehicle arm had regained 19% body weight to a total body weight loss of 2% from baseline, nearly eliminating all semaglutide-induced weight loss. The animals who crossed over from semaglutide to single-dose GLP-1 PGTx, however, lost additional body weight to a total body weight loss of 26% from vehicle, thereby maintaining semaglutide-induced weight loss. Animals who were originally randomized to GLP-1 PGTx continued to maintain weight loss through day 57 with sustained activity throughout the study duration.

“Today’s results imply that the pancreas can be used to produce hormones like GLP-1 that have therapeutic benefit over extended periods,” said Dr. David D’Alessio, the James B. Wyngaarden Distinguished Professor of Medicine and Chief, Division of Endocrinology and Metabolism, Duke University School of Medicine. “Perhaps the single biggest barrier to successful treatment of metabolic diseases has been maintenance of effective therapy over time, and these data with the Rejuva platform support a novel and feasible remedy to that problem.”

“With up to 2/3 of patients discontinuing even weekly GLP-1 therapies within one year of prescription, and with near total loss of metabolic benefit after treatment discontinuation, there is a need for therapies that can offer durable benefit even after treatment withdrawal,” said Dr. Harith Rajagopalan, CEO of Fractyl Health. “Our goal with our Rejuva platform is to change the trajectory of both obesity and T2D to help navigate a path to a post-obesity society, and we view the Rejuva platform as a potentially highly scalable ‘vaccination’ strategy against metabolic disease.”

Fractyl Health anticipates progressing its GLP-1 PGTx through lead optimization and IND-enabling toxicity studies in 2024.

About Fractyl

Fractyl Health is a metabolic therapeutics company focused on pioneering new approaches to the treatment of metabolic diseases, including T2D and obesity. Despite advances in treatment over the last 50 years, T2D and obesity continue to be rapidly growing drivers of morbidity and mortality in the 21st century. Fractyl Health’s goal is to transform metabolic disease treatment

from chronic symptomatic management to durable disease-modifying therapies that target the organ-level root causes of disease. Fractyl Health is based in Lexington, MA. For more information, visit www.fractyl.com or www.twitter.com/FractylHealth.

About Rejuva®

Fractyl Health's Rejuva ® platform focuses on developing next generation adeno-associated virus (AAV)-based, locally delivered gene therapies for the treatment of T2D and obesity. The Rejuva platform is in preclinical development and has not yet been evaluated by regulatory agencies for investigational or commercial use. Rejuva leverages advanced delivery systems and proprietary screening methods to identify and develop metabolically active gene therapy candidates targeting the pancreas. The program aims to transform the management of metabolic diseases by offering novel, disease-modifying therapies that address the underlying root causes of disease.

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