Fractyl Health Demonstrated Significant Improvement in Weight Loss in Head-to-Head Preclinical Obesity Studies of its Rejuva® GLP-1- Based Pancreatic Gene Therapy Candidate (GLP-1 PGTx) Compared to Chronic Semaglutide at EASD's Annual Meeting

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Single administration GLP-1 PGTx resulted in 24.8% lower total body weight at Day 15 compared to 18.4% for chronic semaglutide 10 nmol/kg/day in the Diet-Induced Obesity (DIO) rodent model
New data in DIO model builds upon proprietary Fractyl delivery technology combined with proprietary AAV-based GLP-1 PGTx data presented earlier this year in Yucatan pigs and db/db rodent model of T2D
Results provide further evidence for a single administration pancreatic gene therapy with GLP-1-based transgenes to overcome known challenges with the existing class of GLP-1-based therapies in T2D and obesity

LEXINGTON, Mass.–(BUSINESS WIRE)– 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 European Association for the Study of Diabetes (EASD) 2023 Annual Meeting. The oral presentation, titled "Pancreatic Gene Therapy Durably Improves Glycemia and Delays Disease Progression in a Murine Model of Type 2 Diabetes," highlighted the promising implications of the Rejuva platform in potentially reshaping the treatment landscape for T2D and 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 late-breaking results from an additional, second efficacy model of metabolic disease, the well-validated DIO rodent model of obesity. 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 15, with 24.8% weight loss for GLP-1 PGTx vs. 18.4% weight loss for semaglutide ($p<0.01$ for the difference between a GLP-1 PGTx and semaglutide, n=10 in each arm). Weight loss had not yet plateaued in either arm by day 15 of the study. Both semaglutide and GLP-1 PGTx treatment arms saw reduced food intake compared to vehicles that persisted through day 15, providing a mechanistic explanation for the weight loss in these animals. The data presented corroborates the fundamental hypothesis that local delivery of a GLP-1 PGTx, driven by the insulin promoter, can potentially provide sustained weight loss after a single administration in obese subjects.

"The success of gene therapies in a number of rare diseases may now open the door to sustained benefit from gene therapy for more common diseases, like obesity and T2D," said Mark Kay MD PhD, Professor of Pediatrics and Genetics at Stanford University Medical School and Fractyl Health's Scientific Advisor. "Results now in two efficacy models for GLP1 PGTx and toxicology studies accumulating thus far suggest that local administration of gene therapy to the pancreas may now be feasible for society's most vexing chronic diseases."

"We aim to design a better GLP-1 therapy which has the potential for more potency, better tolerability, and more durability," said Timothy Kieffer, PhD, Chief Scientific Officer of Fractyl Health. "Our GLP-1 PGTx has the potential to offer these benefits because it targets the pancreas, is designed to mimic human physiology, and may provide durable benefits that persist after the treatment itself."

"The power of the GLP-1 mechanism in obesity and T2D is obvious, but we also know we need treatments for T2D and obesity that work even after patients stop taking them," said Dr. Harith Rajagopalan, CEO of Fractyl Health. "Our goal with our Rejuva platform is to develop gene therapy candidates that can durably change the trajectory of both obesity and T2D, and today's results further consolidate preclinical proof-of-concept data for the viability of this approach."

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.

Contacts

Corporate Contact
Lisa Davidson, Chief Financial Officer
Lisa@fractyl.com, 781.902.8800

Media Contact
Beth Brett, Corporate Communications
Bbrett@fractyl.com, 720.656.6544