Fractyl Health Unveils Promising Preclinical Data Demonstrating Safety and Feasibility of Local Delivery of RJVA-001 Rejuva® Smart GLP-1™ Pancreatic Gene Therapy at the World Congress Insulin Resistance, Diabetes and Cardiovascular Disease (WCIRDC)

December 12, 2024

RJVA-001 was successfully delivered in large animal Yucatan pig models at low total viral dose

Results confirm ability to directly target pancreas with novel delivery catheter and route of administration

Local delivery of RJVA-001 achieved therapeutically relevant GLP-1 expression within pancreatic beta cells with no adverse safety effects observed

Company plans to initiate first-in-human studies with RJVA-001 in first half of 2025

BURLINGTON, Mass., Dec. 12, 2024 (GLOBE NEWSWIRE) -- Fractyl Health, Inc. (Nasdaq: GUTS) (the "Company"), a metabolic therapeutics company focused on pioneering pattern breaking approaches for the treatment of obesity and type 2 diabetes (T2D), will present new data from its preclinical Rejuva Smart GLP-1 pancreatic gene therapy program in a poster titled "Feasibility and Safety of Novel Endoscopic Ultrasound-Guided Delivery of Human GLP-1 Pancreatic Gene Therapy in Pigs" at the 22nd World Congress Insulin Resistance, Diabetes & Cardiovascular Disease (WCIRDC).

Rejuva is the Company's adeno-associated virus (AAV)-based pancreatic gene therapy program, designed to enable durable production of therapeutic proteins by the pancreas for the treatment of obesity and T2D. The data that will be presented at WCIRDC evaluated the safety and feasibility of infusing RJVA-001, the Company's GLP-1 development candidate for T2D, with an endoscopic ultrasound-guided delivery system into the pancreas of a large animal.

An endoscope with custom delivery needle was used to deliver RJVA-001 into the pancreas of Yucatan pigs. This procedure closely mimics the intended route of administration for the first-in-human studies the Company plans to initiate in 2025. An AAV9 vector genome dose of 6e13 vg per pig was administered, approximating a potential human dose of 6e11 vg/kg (for a 100 kg adult with T2D). This dose is more than two orders of magnitude lower than other approved systemic AAV9 therapies, demonstrating the potential of RJVA-001 to be safe and effective at a low total viral dose.

At Day 34 post-procedure pancreatic biopsies showed that active GLP-1 protein expression capacity within pancreatic islets was greatly enhanced. RJVA-001 achieved therapeutically relevant GLP-1 expression levels based on observations in disease models and were five times higher in treated than untreated animals ($p < 0.02$). Pancreatic lipase, a marker of pancreatitis, remained in the normal range in all animals. These results demonstrate the potential of RJVA-001 to dramatically enhance GLP-1 production capacity to therapeutically relevant levels without any observed adverse safety signals.

These data also show that RJVA-001 can be safely delivered endoscopically in a large animal model, allowing for direct pancreatic targeting with a gene therapy, giving the Company confidence in the potential for safe and effective delivery of RJVA-001 in humans.

"RJVA-001 has the potential to be a game changer in the field of obesity and T2D," said Harith Rajagopalan, M.D., Ph.D., Co-Founder and CEO, Fractyl Health. "We have previously shown in mice models that a single dose of Rejuva can help maintain improvements in both weight and blood glucose levels after withdrawing semaglutide - which is a critical unmet need in the management of obesity and T2D. These data presented at WCIRDC help to establish safety and feasibility of targeted delivery in a large animal model - which is one of the last pieces of data we need to have confidence in the successful delivery to the pancreas in humans, as well as to understand the correct dose for our first-in-human studies with our Smart GLP-1 gene therapy, which will be initiated in the first half of 2025. We look forward to reporting additional data from Rejuva Clinical Trial Application (CTA)-enabling studies at upcoming scientific meetings."

About Fractyl Health
Fractyl Health is a metabolic therapeutics company focused on pioneering new approaches to the treatment of metabolic diseases, including obesity and T2D. Despite advances in treatment over the last 50 years, obesity and T2D 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 Burlington, MA. For more information, visit www.fractyl.com or https://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 obesity and T2D. 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. The Company intends to initiate its first-in-human study for RJVA-001, the Company's first nominated GLP-1 pancreatic gene therapy candidate designed for the treatment of T2D, in the first half of 2025.

Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including, without limitation, statements regarding the promise and potential impact of our preclinical or clinical trial data, the design, initiation, timing and results of clinical enrollment and any clinical studies or readouts, the content, information used for, timing or results of any IND-enabling studies, IND applications or Clinical Trial Applications, the potential launch or commercialization of any of our product candidates or products, the potential treatment population or benefits for any of our product candidates or products, and our strategic and product development objectives and goals, including with respect to enabling long-term control over obesity and type 2 diabetes without the burden of chronic therapies, and the timing of any of the foregoing. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors

that may cause the Company's actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: the Company's limited operating history; the incurrence of significant net losses and the fact that the Company expects to continue to incur significant net losses for the foreseeable future; the Company's need for substantial additional financing; the Company's ability to continue as a going concern; the restrictive and financial covenants in the Company's credit agreement; the lengthy and unpredictable regulatory approval process for the Company's product candidates; uncertainty regarding its clinical studies; the fact that the Company's product candidates may cause serious adverse events or undesirable side effects or have other properties that may cause it to suspend or discontinue clinical studies, delay or prevent regulatory development, prevent their regulatory approval, limit the commercial profile, or result in significant negative consequences; additional time may be required to develop and obtain regulatory approval or certification for the Company's Rejuva gene therapy candidates; the Company's reliance on third parties to conduct certain aspects of the Company's preclinical studies and clinical studies; the Company's reliance on third parties for the manufacture of the materials for its Rejuva gene therapy platform for preclinical studies and its ongoing clinical studies; the regulatory approval process of the FDA, comparable foreign regulatory authorities and lengthy, time-consuming and inherently unpredictable, and even if we complete the necessary clinical studies, we cannot predict when, or if, we will obtain regulatory approval or certification for any of our product candidates, and any such regulatory approval or certification may be for a more narrow indication than we seek; and the potential launch or commercialization of any of Company's product candidates or products and our strategic and product development objectives and goals, and the other factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (the "SEC") on November 12, 2024 and in our other filings with the SEC. These forward-looking statements are based on management's current estimates and expectations. While the Company may elect to update such forward-looking statements at some point in the future, the Company disclaims any obligation to do so, even if subsequent events cause its views to change.

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