Fractyl Health Presents New Preclinical Data on Sustained Weight Maintenance and Improved Body Composition from its Rejuva® Single-Administration GLP-1 Pancreatic Gene Therapy in President's Select Oral Presentation at the American Diabetes Association's 84th Scientific Sessions

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Single administration of Rejuva reduced fat mass and improved glycemia in the well-validated diet-induced obesity (DIO) mouse model

Rejuva also prevented weight and glycemic rebound after semaglutide withdrawal

Data provide first demonstration that Rejuva treatment has potential to mimic natural release of GLP-1 from pancreas

BURLINGTON, Mass., June 23, 2024 (GLOBE NEWSWIRE) -- Fractyl Health, Inc. (Nasdaq: GUTS) (the "Company"), a metabolic therapeutics company focused on pioneering new approaches for the treatment of obesity and type 2 diabetes (T2D), today presented new data from its preclinical Rejuva pancreatic gene therapy program in an oral presentation at the American Diabetes Association (ADA)'s 84 th Scientific Sessions in Orlando, FL. The presentation titled "Single-Dose GLP-1-Based Pancreatic Gene Therapy Durably Maintains Body Composition and Glycemia After Semaglutide Withdrawal in a Murine Model of Obesity," and was chosen as noteworthy and one of eight President's Select Abstracts at ADA this year.

Rejuva is the Company's adeno-associated virus (AAV)-based GLP-1 pancreatic gene therapy program (PGTx), designed to enable durable production of GLP-1 in the pancreas for the treatment of obesity and T2D. The study presented at ADA compared the effects of a single dose of Rejuva and daily semaglutide treatment on body composition and glycemic parameters in the well-validated mouse model of diet-induced obesity (DIO). It also examined the effects of single-dose Rejuva in the DIO mice after semaglutide was discontinued.

"These data demonstrate that Rejuva can durably improve body composition and fasting glucose, compared to or better than semaglutide, by restoring GLP-1 production in a 'one-and-done' treatment," said Harith Rajagopalan, M.D., Ph.D., co-founder and Chief Executive Officer of Fractyl. "These data also show Rejuva could help maintain improvements after semaglutide is withdrawn, highlighting our therapy's potential to fill an emerging and critical need in the management of obesity and T2D: a reliable, 'off ramp' from chronic GLP-1 drugs that allows people to maintain the weight loss and blood sugar benefits, even as they stop taking these medicines."

In the study presented at ADA, obese (DIO) mice were randomized 1:1:1 to one of the following and followed for 4 weeks:

- Arm 1: single administration of a Rejuva GLP-1-based gene therapy candidate,
- Arm 2: daily semaglutide injections, or
- Arm 3: placebo

At the end of 4 weeks, semaglutide was discontinued for mice in Arm 2 and those animals were further randomized 1:1 to receive either a single administration of the Rejuva gene therapy candidate or placebo, and all animals were followed for an additional 4 weeks, leading to the following assessment arms at 8 weeks:

- Arm 1: continued follow-up of a single administration of a Rejuva GLP-1-based gene therapy candidate
- Arm 2a: semaglutide withdrawal at week 4
- Arm 2b: semaglutide withdrawal with crossover to single administration Rejuva at week 4
- Arm 3: continued follow up of placebo

At the end of 8 weeks, the pancreatic islets were then isolated to study the effect of glucose exposure on GLP-1-based transgene release from genetically modified islets.

At week 4, the Rejuva arm experienced reduced fat mass of 21% versus 16% of body weight with semaglutide (both $p<0.0001$ versus placebo, $p<0.05$ Rejuva versus semaglutide) while both Rejuva and semaglutide preserved lean mass with a loss of only 5% of body weight (both, $p<0.0001$ versus placebo).

At week 8, fat mass rebounded to 1% below baseline (n.s.) in the semaglutide withdrawal group (Arm 2a), whereas semaglutide-withdrawn mice treated with Rejuva (Arm 2b) maintained fat reduction of 17% ($p<0.01$) and weight loss of 22% ($p<0.0001$) at

week 8.

Glucose and insulin levels in all intervention groups corresponded to changes observed in fat mass, with statistically significant improvements in fasting glucose and fasting insulin in semaglutide-treated and Rejuva treated mice at 4 and 8 weeks, but no improvement in glucose or insulin in semaglutide-withdrawn mice that did not crossover to Rejuva at week 8.

"In addition to the compelling durability of weight loss, body composition, and glucose improvements seen in this model, we are pleased that isolated, genetically modified islets from Rejuva-treated mice show this release of GLP-1 in response to nutrients," said Timothy Kieffer, Ph.D., Chief Scientific Officer of Fractyl. "We believe this clearly demonstrates that Rejuva can mimic the physiologic release of GLP-1 that occurs naturally in the human body."

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.

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 trials or readouts, the content, information used for, timing or results of any IND-enabling studies or IND applications, the potential launch or commercialization of any of our product candidates or products, the sufficiency of our cash, cash equivalents, and investments to fund our operating activities for any specific period of time, 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. 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 May 13, 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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