Fractyl Health Announces New Results From Its Rejuva® Platform Demonstrating Potent and Durable Effects of a Single Dose of a Human GLP-1 Pancreatic Gene Therapy Transgene Compared to Semaglutide in the db/db Mouse Model of Diabetes and Obesity

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Data provides first demonstration of glucose lowering and weight loss potency from pancreas-produced native human GLP-1, highlighting the capacity of pancreatic GLP-1 to provide metabolic control.

The human GLP-1 transgene sequence used in RJVA-001 was administered to eight-week-old db/db mice with established disease and resulted in up to 50% blood sugar lowering and 11% weight loss vs vehicle at four weeks after a single administration, compared to 32% glucose lowering and 2% weight loss vs vehicle with chronic semaglutide.

These results with a native, short half-life human GLP-1 sequence to be used in RJVA-001 build upon earlier results with a prototype transgene GLP-1 analogue.

BURLINGTON, Mass., March 12, 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 announced promising new preclinical findings for the first clinical candidate in its Rejuva® pancreatic gene therapy platform. RJVA-001 is the Company's first GLP-1 gene therapy candidate to emerge from the platform, setting the stage for a potentially transformative approach to treating metabolic diseases, including obesity and T2D.

"As we advance our Rejuva program through preclinical development, we now observe that a single-dose administration of a human GLP-1 transgene (as in RJVA-001) can achieve durable lowering of blood sugar and body weight compared to vehicle or chronic semaglutide administration in the well-validated *db/db* mouse model of diabetes," said Dr. Timothy Kieffer, Fractyl Health Chief Scientific Officer. "With these data, we are one step closer to IND enablement for RJVA-001 as part of our broader preclinical development package."

These results show that the human GLP-1 coding sequence of RJVA-001 demonstrates potency on both glucose lowering and weight loss in *db/db* mice, the standard rodent T2D efficacy model used for clinical development. The Company has reached alignment with European regulators on the use of this efficacy model to support the submission of a Clinical Trial Application (CTA) in Europe.

"While there are clear benefits of GLP-1 for weight loss, glucose control, and metabolic health in general, there remains a need for advances in care that can offer a major step forward in GLP-1 therapy," said Dr. Harith Rajagopalan, CEO of Fractyl Health. "Our goal with RJVA-001 is to change the trajectory of both obesity and T2D with a single administration therapy that offers the potential for the durable remission of metabolic disease."

Fractyl Health anticipates progressing RJVA-001 through IND-enabling toxicity studies in 2024 and initiating First-in-Human clinical studies in the first half of 2025.

About Fractyl Health
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 Burlington, 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.

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. 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; changes in methods of the Company's Rejuva gene therapy candidate manufacturing or formulation; and any contamination or interruption in the Company's Rejuva gene therapy candidates' manufacturing process, shortages of raw materials or failure of the Company's suppliers of plasmids and viruses to deliver necessary components could result in delays in the Company's Rejuva gene therapy candidates' preclinical and clinical development or marketing schedules. These and other important factors discussed under the caption "Risk Factors" in the Company's prospectus filed with the Securities and Exchange Commission (the "SEC") on February 2, 2024, and its other filings with the SEC, could cause actual results to differ materially from those indicated by the forward-looking statements made in this press release. Any such forward-

looking statements represent management's estimates as of the date of this press release. 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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