Fractyl Health Advances Rejuva® Gene Therapy Platform with Submission of First Clinical Trial Application Module in Europe for RJVA-001 in Type 2 Diabetes

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First-in-human study will evaluate safety, tolerability, and early efficacy of a one-time, pancreas-targeted smart GLP-1™ gene therapy for patients with inadequately controlled T2D and obesity

Expect to dose first patients and report preliminary data in 2026, pending CTA authorization

BURLINGTON, Mass., May 19, 2025 (GLOBE NEWSWIRE) -- Fractyl Health, Inc. (Nasdaq: GUTS) (the Company), a metabolic therapeutics company pioneering pattern-breaking treatments for obesity and type 2 diabetes (T2D), today announced that it has submitted the first module of its Clinical Trial Application (CTA) in Europe for RJVA-001, the Company's gene therapy candidate from its Rejuva platform. RJVA-001 is designed to express glucagon-like peptide-1 (GLP-1) locally in pancreatic beta cells using nutrient-responsive control, potentially enabling physiologic hormone secretion without the high circulating levels that contribute to side effects seen with systemic GLP-1 drug therapy. Pending regulatory clearance, Fractyl anticipates initiating first-in-human dosing and reporting preliminary data in 2026.

RJVA-001 is delivered via a one-time, minimally invasive endoscopic ultrasound-guided infusion directly into the pancreas. The gene therapy construct is designed to harness a proprietary, engineered version of the human insulin promoter and trafficking signals that allow for nutrient-triggered secretion of GLP-1 from transduced pancreatic beta cells—offering a "smart," physiologic alternative to chronic pharmacotherapy. RJVA-001 is designed to enable the physiologic hormone signaling of GLP-1 through native metabolic circuits in the gut and portal vein rather than relying on high systemic drug levels. This difference from GLP-1 drug pharmacology opens the door to efficacy that matches or exceeds drugs with potentially superior tolerability profiles due to low circulating levels of drug. The Company recently presented data at the American Society of Cell and Gene Therapy (ASGCT) 2025 meeting, demonstrating safety, dose-dependent potency, and adaptive nutrient-responsive secretion of RJVA-001 with low circulating GLP-1 levels in preclinical animal models.

"Completing our first CTA module submission for RJVA-001 marks a major step forward in our mission to reimagine treatment for metabolic disease with what we believe can be best-in-class incretin therapies," said Harith Rajagopalan, M.D., Ph.D., Co-Founder and Chief Executive Officer of Fractyl Health. "Our goal is to develop a platform of therapies that offer superior durability, potency, tolerability, and convenience to conventional GLP-1 based drugs. We believe Rejuva can unlock a one-time, durable gene therapy approach to normalize blood glucose and body weight while reducing the burden, side effects, and limitations of lifelong injectable drugs. We believe that our work on developing a potentially superior therapeutic profile with RJVA-001 and our efforts to drive manufacturing scalability and efficiency open the door to a commercially viable path to durable disease remission in T2D and obesity."

About the RJVA-001 First-in-Human Study

The upcoming Phase 1/2 study is designed to be an open-label, multicenter, single ascending dose study evaluating the safety, tolerability, and preliminary efficacy of RJVA-001 in adults with inadequately controlled T2D despite use of multiple glucose-lowering agents, including GLP-1 receptor agonists (GLP-1RAs).

"We've spent decades managing T2D as a chronic, progressive disease, and this upcoming first-in-human study of RJVA-001 represents the first real attempt to reverse it at the source by targeting the beta cell directly," said Professor Jacques J.G.H.M. Bergman, Professor of Gastrointestinal Endoscopy, Deputy Chair, Department of Gastroenterology & Hepatology at Amsterdam UMC. "If successful, RJVA-001 could transform how we think about diabetes from something you manage daily to something you potentially treat once. That's a fundamentally different future for patients."

Participants will undergo a standardized medication run-in and GLP-1 washout before receiving RJVA-001 delivered via endoscopic ultrasound-guided intrapancreatic injection. Three escalating dose cohorts (up to 3 participants each) will be followed by an optional expansion cohort of up to 10 additional participants treated at the selected optimal dose. Participants will be monitored for 12 months for safety, glucose control, immune response, and GLP-1 expression, and enrolled in a long-term follow-up study for up to 5 years.

Key inclusion criteria:

- Adults aged 35–70 with T2D
- HbA1c between 7.0–10.0%
- BMI 30–40 kg/m²
- On stable background therapy with GLP-1RA and up to 3 non-insulin oral agents
- Demonstrated tolerance and benefit from prior GLP-1RA use

Primary endpoints include safety and tolerability. Secondary endpoints include change in HbA1c, fasting plasma glucose, and time-in-range (by CGM). Exploratory endpoints assess beta-cell function, metabolic biomarkers, cardiovascular risk markers, and transgene expression.

About Fractyl Health
Fractyl Health is a metabolic therapeutics company pioneering pattern-breaking treatments for 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 .

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 has submitted the first Clinical Trial Application (CTA) module for RJVA-001 in T2D to regulators, and if the CTA is authorized, the Company expects to dose the first patients with RJVA-001 and report preliminary data in 2026.

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, primary and secondary endpoints, and results of clinical enrollment and any clinical studies or readouts, the content, information used for, timing or results of any investigational new drug (IND)-enabling studies, IND applications or Clinical Trial Applications, communications with regulators, 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, redefining the future of metabolic disease treatment, positioning our Company at the forefront of the global opportunity for metabolic care, 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 May 13, 2025 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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