Fractyl Health Unveils New Rejuva® Smart GLP-1™ Pancreatic Gene Therapy Preclinical Data Highlighting Durable Potency and Safety with Limited Systemic GLP-1 Exposure at ASGCT 2025

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Data suggests that single dose of RJVA-001 leads to durable metabolic improvements with low systemic GLP-1 exposure in db/db mouse model of T2D —potentially simultaneously addressing durability, adherence, and tolerability challenges seen with current GLP-1 drugs

Endoscopic ultrasound-guided delivery achieves targeted pancreatic expression in a large animal model with no toxicity observed to date

Data show nutrient-responsive GLP-1 secretion in human beta cells and human islets, demonstrating that Rejuva mimics natural hormone regulation rather than constant drug-driven stimulation

Rejuva advancing toward first-in-human studies; first CTA module submission for RJVA-001 expected by June 2025

BURLINGTON, Mass., May 17, 2025 (GLOBE NEWSWIRE) -- Fractyl Health, Inc. (Nasdaq: GUTS) (the Company), a metabolic therapeutics company focused on pattern-breaking approaches that treat root causes of obesity and type 2 diabetes (T2D), today announced an oral presentation of new preclinical data from its Rejuva smart GLP-1 gene therapy platform at the American Society of Gene and Cell Therapy (ASGCT) 2025 Annual Meeting. The data highlight RJVA-001's potential to deliver durable, nutrient-responsive GLP-1 secretion from pancreatic beta cells—mimicking natural hormone regulation with low circulating levels of GLP-1, offering a potentially profound mechanistic advantage over pharmacologic GLP-1 drugs. RJVA-001 also showed strong efficacy, targeted delivery, and a favorable safety profile, reinforcing its readiness for first-in-human studies.

The data were featured in an oral presentation at ASGCT titled "Endoscopic Ultrasound-Guided Delivery of Human Glucagon-like Peptide-1 Pancreatic Gene Therapy: Safety and Feasibility in a Porcine Model."

"RJVA-001 represents a fundamentally different approach to treating metabolic disease - one that delivers the power of GLP-1 in a more natural manner," said Professor Randy Seeley, Ph.D., Henry King Ransom Professor of Surgery and Director of Michigan Nutrition Obesity Research Center at Michigan School of Medicine. "The ability to drive durable metabolic effects with physiologic hormone levels, from a one-time treatment, would be a scientific breakthrough with huge potential implications for patients. This has the potential to reshape how we think about treating T2D and obesity at scale."

Key Data Presented at ASGCT 2025:

- **Single-dose RJVA-001 led to durable, dose-dependent metabolic improvements in a well-established diabetic model:** In *db/db* mice, treatment with RJVA-001 led to sustained reductions in blood sugar, improved fasting insulin levels, and improvements in body weight over six weeks— supporting Rejuva's potential for sustained disease modification on both blood sugar and body weight control. Treatment with RJVA-001 resulted in a >200 mg/dL reduction in fasting blood sugar, a >2-fold increase in fasting insulin levels, and prevention of weight gain, compared to a ~20% increase seen in vehicle-treated controls. These results demonstrate broad-based metabolic improvement in insulin secretion, weight gain, and blood sugar control in this gold-standard model of T2D.
- **RJVA-001 achieved glycemic control and prevented weight gain with significantly lower systemic GLP-1 exposure than required by GLP-1 drugs to achieve similar effects:** Circulating GLP-1 levels were more than 5-fold lower than those seen with pharmacologic GLP-1 drugs and were comparable to levels observed after gastric bypass surgery —suggesting a substantially lower risk of GLP-1-related side effects such as nausea and vomiting. In*db/db* mice, circulating levels of active GLP-1 were 10-20 pM with RJVA-001, compared to 50-150 pM typically reported with pharmacologic GLP-1 drugs[1].
- **Data show nutrient- and dose-responsive GLP-1 secretion in transduced human beta cells and islets, demonstrating that Rejuva mimics native hormone regulation rather than constant drug-driven stimulation:** RJVA-001 activated glucose-dependent expression of GLP-1 in both *in vitro* and *ex vivo* models, consistent with physiologic endocrine function. In transduced human beta cells, GLP-1 secretion more than doubled— and GLP-1 bioactivity increased >3-fold — when shifting from low glucose to high glucose conditions. These results demonstrate tight nutrient gating and dose-responsive control of RJVA-001 drug action.
- **Adaptive expression based on disease state**: In *db/db* mice, RJVA-001 drove higher GLP-1 expression in diabetic animals than in healthy controls at the same dose, demonstrating the platform's ability to adapt to metabolic need.

RJVA-001-treated healthy mice maintained normal weight and blood sugar, reinforcing the potential safety of this nutrient-responsive smart GLP-1. At equal dosing, *db/db* mice had more than twice the circulating GLP-1 levels of healthy mice, with no effect on weight or blood sugar in the healthy group. These results support the physiologic, selective, and adaptive action of RJVA-001 based on the body's metabolic state.

- **Endoscopic ultrasound–guided delivery of RJVA-001 in large animals showed targeted pancreatic expression with no observed toxicity:** In Yucatan pigs, device deployment was completed in an average procedure time of <20 minutes using a standard clinical endoscopic ultrasound technique. RJVA-001 localized to the pancreas with minimal systemic distribution and no adverse safety findings, even at doses exceeding projected clinical levels. Biodistribution studies showed vector copy number of 7 vector genomes/nucleus in the targeted splenic lobe of the pancreas (equivalent to the body and tail of the human pancreas) versus <0.2 vector genomes/nucleus in the liver. These results indicate profound de-targeting of the liver with local administration with the Rejuva catheter and ultrasound-guided route of administration. No acute or longer-term serum or histopathological evidence of toxicity was observed post-procedure. Serum lipase, neurofilament-light, troponin I, and ALT all remained below the upper limit of normal or below detection, indicating the absence of pancreatic, neuronal, cardiac, and liver toxicity, respectively. No on-target or off-target organ inflammation or other histopathological findings were observed in the study.

"We believe RJVA-001 represents a transformative advance in metabolic medicine," said Dr. Harith Rajagopalan, Co-Founder and Chief Executive Officer of Fractyl Health. "These data suggest that a one-time, smart GLP-1 can restore physiologic signaling in the pancreas and achieve durable disease modification in diabetes and obesity - without the high levels of systemic drug exposure that causes side effects with current GLP-1 therapies. RJVA-001 has demonstrated superior potency, durability, and convenience in preclinical models, along with a potentially improved tolerability profile than GLP-1 drugs. We believe the Rejuva platform has the potential to usher in a category-closing modality for T2D and obesity. We look forward to our upcoming CTA submission for RJVA-001 and, pending regulatory authorization, preliminary human data in 2026."

The full ASGCT presentation is available on the Fractyl Health website in the Presentations & Publications section.

About Fractyl Health
Fractyl Health is a metabolic therapeutics company focused on pattern-breaking approaches that treat root causes of 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 plans to submit the first Clinical Trial Application (CTA) module for RJVA-001 in type 2 diabetes to regulators by June 2025, 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 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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[1] Smits MM, Holst JJ. Endogenous glucagon-like peptide (GLP)-1 as alternative for GLP-1 receptor agonists: Could this work and how? Diabetes Metab Res Rev. 2023 Nov;39(8):e3699. doi: 10.1002/dmrr.3699. Epub 2023 Jul 24. PMID: 37485788.