Feasibility and Safety of Endoscopic Ultrasound-Guided Delivery of Human GLP-1 Pancreatic Gene Therapy in a Porcine Model

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Introduction

- Glucagon-like peptide 1 (GLP-1) therapy is now the cornerstone of metabolic disease treatment. Although efficacious, discontinuation is frequent and results in near-complete glycemic and weight rebound
- We have developed a single-dose, pancreatic gene therapy (PGTx) that enables durable, nutrient-responsive, islet-driven GLP-1 production (Smart GLP-1™) (**Figure 1.**)
- In murine models, we have previously shown that GLP-1 PGTx can improve glucose control, induce weight loss, and durably maintain weight loss after semaglutide withdrawal

Here, we evaluate the feasibility and safety of delivering human GLP-1 PGTx (RJVA-001) with an endoscopic ultrasound (EUS)-guided delivery system into porcine pancreas (Figure 2.)

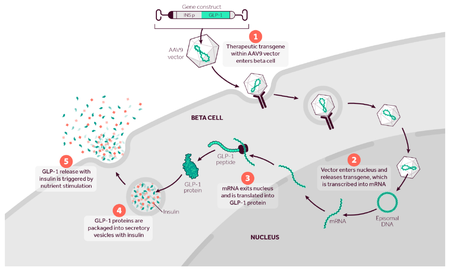

Figure 1. Human GLP-1 PGTx (RJVA-001) Therapeutic Mechanism of Action. **1**) The RJVA-001 transgene construct, consisting of human insulin promoter and GLP-1 sequences, is packaged into adeno-associated virus (AAV)-9 vectors which are taken up by the beta cell. **2**) Vectors enter the nucleus and release the transgene, which is transcribed into GLP-1 mRNA. **3**) GLP-1 mRNA exits the nucleus and is translated into protein. **4**) GLP-1 proteins are packaged into secretory vesicles with insulin. **5**) GLP-1 with insulin release is triggered by nutrient stimulation.

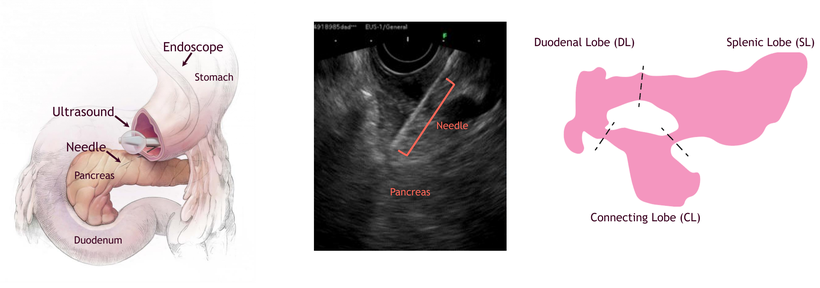

Figure 2. EUS-Guided Delivery System and Pancreatic Infusion Procedure. An echoendoscope with a custom needle integrated with a proprietary fluid delivery system is tracked into the porcine stomach. Utilizing ultrasound, anatomic landmarks (splenic artery, spleen, and liver) guide transgastric infusions of RJVA-001 into the parenchymal tissue (**A** and **B**) of the targeted splenic lobe of the porcine pancreas (**C**, equivalent to the human body and tail of the pancreas).

Methods and Results

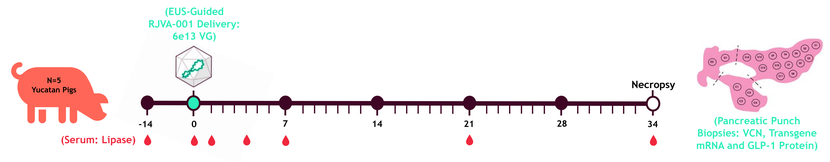

Figure 3. Porcine Study Design and Analyses. RJVA-001 [6e13 vector genome (VG)] EUS-guided delivery was evaluated in five non-diseased Yucatan pigs. Serum lipase, as a surrogate marker of pancreatitis, was assessed on days -14, 0, 1, 4, 7, 21, and 34 to establish early and longer-term procedural safety. Animals were necropsied at day 34 post-procedure and punch biopsies were taken from 20 locations across the pancreas to establish vector copy number (VCN), transgene ribonucleic acid (RNA) and protein expression as indicators of vector transduction efficiency and RJVA-001-driven GLP-1 production.

Figure 4. EUS-Guided RJVA-001 Delivery Led to Robust AAV9 Transduction, GLP-1 Transcription, and a Five-Fold Increase in Active Pancreatic GLP-1 Protein. Transgastric delivery of RJVA-001 resulted in increased adeno-associated virus (AAV)-9 transduction (**A**, shown as vector genome per diploid genome(VG/DG)], GLP-1 transgene transcription (**B**), and subsequent active GLP-1 protein expression (**C**) within the targeted splenic lobe of the pancreas. Active GLP-1 protein was five-fold greater in RJVA-001 treated animals compared to untreated controls (**D**, p<0.02). Pancreatic vector copy number (VCN), and RJVA-001 transgene RNA levels were positively correlated (**E**, r=0.85, p<0.0001). Likewise, RNA levels correlated with RJVA-001 islet-driven GLP-1 protein levels (**F**, r=0.85, p<0.0001). Data shown as mean ± standard error of the mean (A-D), mean lobe values (E and F). CL=connecting lobe, DL=duodenal lobe, SL=splenic lobe.

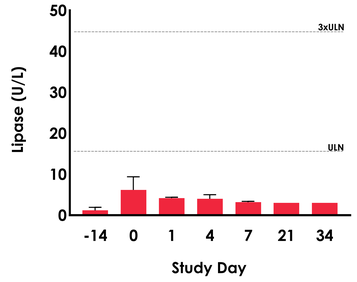

Figure 5. EUS-Guided RJVA-001 Delivery Was Well-Tolerated. All 5 animals tolerated the transgastric delivery procedure well with serum lipase levels remaining within the upper limit of normal (ULN) at all timepoints evaluated from day -14 pre-procedure to day 34 post-procedure. Data shown as mean ± standard error of the mean.

Conclusions and Next Steps

These data demonstrate that RJVA-001 can be safely delivered endoscopically in a large animal model allowing for direct pancreatic targeting

RJVA-001-driven human pancreatic GLP-1 production demonstrates the feasibility of single-dose local gene therapy as a durable strategy for the treatment of metabolic diseases

Anticipate submitting the first clinical trial application module for RJVA-001 in type 2 diabetes in the first half of 2025

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Disclaimer: Pancreatic gene therapy (PGTx) is a preclinical development program that has yet to be assessed by regulatory bodies for investigational or commercial use.
Disclosures: CCT is a consultant and serves on advisory boards for Fractyl Health, Inc. He is also a shareholder of Fractyl Health, Inc. LSL is a consultant for Fractyl Health, Inc TK, JW, MB, LS, NP, RR, AF, EC, SS, JC & HR are employees and share or option holders of Fractyl Health, Inc. HR is also a board member of Fractyl Health, Inc. EM is a former employee of Fractyl Health, Inc.
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