Pancreatic enzyme replacement and glucose regulation in Type 1 diabetes

NCT05266963

Statistical Analysis Plan

12/4/2023

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NCT05266963 - Pancreatic Enzyme Replacement and Glucose Regulation in Type 1 Diabetes (CREON)

Background

In T1D, there is significant reduction in pancreas volume. The biological impact of this is not known. Because islet cells make up a small fraction of pancreas size, the major reduction in volume is due to loss of exocrine tissue. Since patient with T1D have substantial loss of exocrine tissue and pancreatic enzymes support glucoe regulation and pancreas function, this study tests the hypothesis that pancreatic enzyme replacement will improve C-peptide secretion to regulate glucose excursions and/or will improve symptoms of pancreatic exocrine insufficiency. This document provides additional description of the analysis plan and complements the protocol document where study details are provided.

Primary objective

Aim 1: To assess impact of pancreas enzyme replacement on C-peptide auc in subjects with T1D and reduced pancreas volume

Aim 2: To assess the impact of pancreas enzyme replacement on symptoms of pancreatic exocrine insufficiency (PEI) in T1D.

Secondary Objectives

Secondary assessments will be made to explore mechanisms of effect if the primary outcome is met. These could include analysis of CGM data, measure of circulating hormones and cytokines, assessment of dietary intake.

Trial Design

The study is a single center, double-blinded randomized cross over design in which subjects receive Creon or placebo each for 1 week with a 1 week washout period between.

Eligibility

Inclusion Criteria	Exclusion Criteria
• Diagnosed with T1DM for at least 12 months • Age over 18 • Total daily dose of insulin greater than 0.6u/kg/day	• History of celiac disease or inflammatory bowel disease • Unwilling to temporarily discontinue use of medication or supplements

• Current use of a CGM • Current use of smart phone • Able to read and speak English • Willingness and ability to download and provide CGM and pump (if applicable) data • Reduction of pancreas volume (<0.6mL/kg BW)	other than insulin to control blood glucose • Pregnant or breast feeding • Following a restrictive diet (such as very low carb diet) • History of major bowel or bariatric surgery

Treatment

Participants will continue their standard care for diabetes with calculation and adjustment of doses per their primary endocrinologists.

Participants will receive a range of 50,000-100,000 lipase units per meal (approx. 2 Creon 36,000 capsules) and 25,000-50,000 per snack (1 capsule). The participant will be instructed to take same number of capsules of placebo. Participant and provider will be blinded to capsule assignment.

Assessment of Outcomes

Outcomes will be assessed at baseline and at completion of each treatment week.

Hypothesis

The null hypothesis to be tested is that there will be no difference between the treatment groups.

Blinding

Subjects and investigators will be blinded to treatment assignment. Blinded drug or placebo is provided by the VUMC Investigational Pharmacy.

Analysis

Only subjects completing both arms will be included in the final analysis.

Data collection

Demographics: Participants age, sex, weight will be obtained.

Diabetes Management: Participants estimated or actual insulin dosing, CGM download, diet history, pancreas volume index will be obtained.

Study results: Participants will complete MMTT and PEI questionnaires.

Adherence

Pill counts will be obtained. Participants with significant discrepancy between pill count and diet history may be excluded from analysis.

Primary Outcome Analysis

C-peptide AUC will be calculated from MMTT data. Data from creon and placebo intervals will be compared for each individual in a matched analysis. Comparison will be made by Wilcoxon matched-pairs assessment.

Severity score will be calculatd from the PEI-Q survey. Data from creon and placebo intervals will be compared for each individual in a matched analysis. Comparison will be made by t-test

Statistical Software

Analysis will be performed on Prism Ver 10 or on current version of Microsoft excel.

Exploratory Analysis

Additional analyses may be performed if primary endpoint is met to provide mechanistic insight or if requested by journal or editorial review.