

Pancrelipase Treatment of Exocrine Pancreatic Insufficiency Due to Chronic Pancreatitis: Rationale and Methodology of a Real-World, Prospective, Observational Study

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Key Words: chronic pancreatitis, exocrine pancreatic insufficiency, pancrelipase, pancreatic exocrine insufficiency questionnaire, quality of life

(*Pancreas* 2025;54:e728–e730)

Chronic pancreatitis (CP) is a fibro-inflammatory syndrome with genetic, environmental, and/or other risk factors and a prevalence of 41.8 to 91.9 per 100,000 person-

years in the United States.^{1,2} Individuals with CP are at increased risk of developing exocrine pancreatic insufficiency (EPI), a condition resulting from insufficient production, delivery, or activity of pancreatic enzymes.³ The probability of developing EPI increases substantially over time in patients with CP.^{4,5} Left untreated, EPI results in maldigestion, steatorrhea, fat-soluble vitamin deficiencies, malnutrition, an increase in bone fractures,⁶ and impaired health-related quality of life (HRQoL).^{3,7} Diagnosis is challenging due to nonspecific clinical symptoms and being secondary to underlying primary diseases. Measurement of fecal elastase (FE-1) in stool samples is the most common diagnostic test, but limitations include poor sensitivity in mild to moderate EPI, and inaccuracies when used on liquid stool samples.^{8,9} The established cutoff of stool FE-1 levels for the assessment of EPI severity (abnormal, <200 µg/g; mild to moderate, 100–200 µg/g; and severe, <100 µg/g) is still debated due to these limitations.^{8,9} Consequently, EPI is often diagnosed based on clinical presentation including abnormalities on pancreatic imaging, abnormal serum nutritional markers, presence of risk factors, unintentional weight loss, and abdominal and bowel symptoms which are nonspecific or become overt only as severity worsens. The cornerstone of treatment for EPI is pancreatic enzyme replacement therapy (PERT), a combination of porcine-derived lipases, proteases, and amylases that help mitigate maldigestion, malnutrition, and other adverse health outcomes.³ Our current understanding of PERT effects on clinical symptoms of EPI is limited.¹⁰ Short-term pancrelipase treatment in patients with CP and EPI has been shown to improve HRQoL¹¹; however, real-world data informed by validated patient-reported outcome assessments are lacking for US patients.

To inform clinical practice, a real-world study [CREON® Impact of EPI Symptoms in Chronic Pancreatitis (CisCP)] of US patients with EPI due to CP is examining the effects of pancrelipase on patient-reported EPI symptoms and its impact on HRQoL by utilizing the validated Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q). The aim of this study is to describe the methodology to expand similar research in other settings and report current patient enrollment and characteristics.

This is an ongoing prospective, real-world, observational, cohort study (NCT04949828) conducted at 7 US academic pancreatology centers. Enrollment started in May 2021, and follow-up is planned to end in 2024. The study design is provided in Figure 1 and detailed in the supplement. The study is conducted in accordance with the protocol, International Council for Harmonisation of

Received for publication February 27, 2024; accepted April 15, 2025.

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AbbVie Inc. funded this study and participated in the study design, research, analysis, data collection, interpretation of data, and writing, reviewing, and approving the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. M.O.O. serves as consultant for AbbVie, Apollo, Boston Scientific Corporation, ConMed, Creo Medical, Lumendi, and Olympus and has received grant/research support from AbbVie, Boston Scientific Corporation, ConMed, and Lucid Diagnostics. L.F.L. serves as a consultant and on a speakers bureau for AbbVie. G.T. serves as a consultant for Boston Scientific Corporation. W.P. is a consultant and advisory committee/board member for AbbVie, Ariel Medicine, Pfizer, Ionis, Horizon Therapeutics, and Nestle, and is a consultant for Acumen, Olympus, Arctx Medical, and Capsovision. J.J.K., M.L., and D.H. are full-time employees of AbbVie Inc. and may hold AbbVie stock and/or stock options. The remaining authors declare no conflict of interest.

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Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.pancreasjournal.com.

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DOI: 10.1097/MPA.0000000000002506

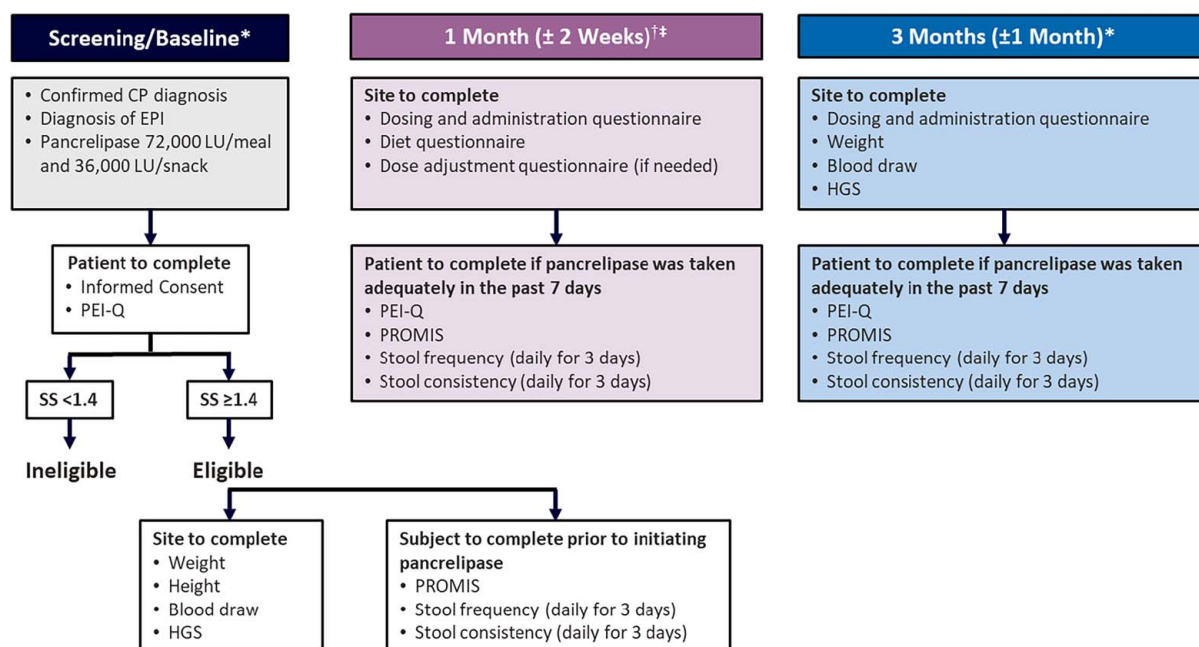


FIGURE 1. Study flowchart. *In person at the clinical research site or virtual study visit. †Virtual study visit. ‡Dose adjustments were performed at the discretion of the physician if needed based on the dose adjustment questionnaire. CP indicates chronic pancreatitis; EPI, exocrine pancreatic insufficiency; HGS, hand-grip strength; LU, lipase unit; PEI-Q, Pancreatic Exocrine Insufficiency Questionnaire; PROMIS, Patient-Reported Outcomes Measurement Information System; SS, PEI-Q Total Symptom Score.

Technical Requirements for Pharmaceuticals for Human Use guidelines, applicable regulations, and guidelines governing study conduct and ethical principles that have their origin in the Declaration of Helsinki.

Eligible patients include adults aged ≥ 18 years with a medical history of probable or definite CP and moderate to severe EPI [PEI-Q Total Symptom Score (PEI-Q SS) ≥ 1.4], who were recommended to initiate pancrelipase (CREON®)¹² treatment at 72,000 lipase units (LU)/meal and 36,000 LU/snack by their treating physician. Patients are PERT-naïve or PERT-experienced (ie, no PERT within the past 3 months, or 7 days if dose is $< 40,000$ LU/meal). Key exclusion criteria are non-EPI-related gastrointestinal symptoms/conditions, recent systemic antibiotic therapy, and upcoming pancreatic endotherapy or surgery.

The primary endpoint is change from baseline to 1-month visit in the PEI-Q SS comprised of 13 questions from the abdominal and bowel symptoms domains^{13–15} (Fig. 1). Secondary endpoints include the proportion of patients at 1 month achieving improvement in EPI symptoms by ≥ 1 grade (PEI-Q SS severity scale: none, mild, moderate, severe) and change from baseline to 1-month visit in the following outcomes: stool frequency and stool consistency (using Bristol Stool Form Scale¹⁶) assessed based on patient recall; HRQoL evaluated using the PEI-Q Impact Score and Total Summary Score; and comorbidities including anxiety, depression, and fatigue obtained using the corresponding short forms of the Patient-Reported Outcomes Measurement Information System (PROMIS; ie, Anxiety-4a, Depression-4a, and Fatigue-6a).¹⁷ Additional endpoints include change from baseline to 3-month visit in all secondary and nutritional status outcomes. Nutritional status is assessed based on body weight and blood levels of nutritional markers (vitamins A, E, and D; magnesium; retinol-binding protein; and prealbumin).^{10,18}

Safety assessments include treatment-emergent and treatment-related adverse events (AEs), serious AEs, and AEs leading to premature study discontinuation.

A sample size of 35 evaluable patients is needed to achieve 90% power at a 2-sided P value of 0.05 in a 1-sample t test. This is based on the SD of the PEI-Q SS of 0.7 for patients with EPI with moderate to severe symptoms¹⁴ and assuming the true mean of the primary endpoint of 0.4. Additional statistical methods are provided in the Supplement, Supplemental Digital Content 1, <http://links.lww.com/MPA/B381>.

As of May 2024, 49 patients have enrolled with a median age of 59 years, 53% female, 62% white, and 97% non-Hispanic (Supplementary Table 1, Supplemental Digital Content 2, <http://links.lww.com/MPA/B382>). Steatorrhea was present in 62% of patients and the mean FE-1 concentration was 65 $\mu\text{g/g}$ stool. Median body weight was 158 lbs, 49% of patients had diabetes, and 30% were current alcohol users.

The clinical efficacy of pancrelipase (CREON®) and pancreatin (KREON®) for EPI secondary to CP has been demonstrated in 2 randomized, double-blind, placebo-controlled studies.^{19,20} One study showed significant improvements in stool frequency, stool consistency, and flatulence but not in abdominal pain.²⁰ In contrast, no differences between pancrelipase versus placebo were observed for stool consistency, flatulence, or abdominal pain during the double-blind period of the other study.¹⁹ In addition, these studies had methodological limitations that may affect the applicability of the results to real-world clinical practice, including a lack of statistical power, limited clinical assessment of only 4 symptoms, and the utilization of nonvalidated patient-reported outcome tools to assess EPI symptom. This study is evaluating the effect of pancrelipase on EPI symptom burden, HRQoL, and state

of nutrition in the real-world setting among patients with EPI secondary to CP utilizing the validated PEI-Q for the first time. Results are expected to address key research gaps, inform clinical practice, and aid the management of patients with EPI due to CP.

DATA SHARING

AbbVie is committed to responsible data sharing regarding the clinical studies we sponsor. This includes access to anonymized, individual, and study-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the studies are not part of an ongoing or planned regulatory submission. This includes requests for clinical study data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: <https://vivli.org/ourmember/abbvie/>, then select “Home.”

ACKNOWLEDGMENTS

AbbVie and the authors thank the participants, study sites, and investigators participating in this study. The PEI-Q was developed and validated by Adelphi Value, UK and Abbott and is owned by Abbott. The authors gratefully acknowledge Gwendolin Janssen-van Solingen from Abbott for making the PEI-Q available to them. Medical writing support was provided by Paul Wisniewski, PhD, of The Curry Rockefeller Group, LLC (Tarrytown, NY) and Catherine Barone, PhD, of AbbVie, and was funded by AbbVie (North Chicago, IL).

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