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A Randomized, Double-Blind, Non-Inferiority Trial Comparing Microbial and Porcine Pancreatic Enzyme Replacement Therapy in Chronic Pancreatitis (Np-Pert Trial) - Protocol

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A RANDOMIZED, DOUBLE-BLIND, NON-INFERIORITY TRIAL COMPARING MICROBIAL AND PORCINE PANCREATIC ENZYME REPLACEMENT THERAPY IN CHRONIC PANCREATITIS (NP-PERT TRIAL) - PROTOCOL

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Abstract:

Background: Chronic pancreatitis (CP) is a progressive inflammatory disorder causing irreversible pancreatic damage, eventually resulting in pancreatic exocrine insufficiency (PEI). This may lead to malabsorption, malnutrition, weight loss, and impaired quality of life. Pancreatic enzyme replacement therapy (PERT) is the standard treatment for PEI and is predominantly derived from porcine sources. However, religious, ethical, dietary, and supply-related concerns highlight the need for effective non-porcine alternatives. Microbial based pancreatic enzymes have shown promising safety and efficacy in preliminary studies, but evidence in CP remains limited.

Objective: To compare the efficacy and safety of non-porcine microbial -based pancreatin with standard porcine-based pancreatin in patients with PEI secondary to CP.

Methods: This investigator-initiated, randomized, double-blind, single-center, non-inferiority trial will enroll 134 adults with CP-associated PEI (defined as having a faecal elastase <100 µg/g) and a Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q) score of >1.4. After a two-week washout period, participants will be randomized 1:1 to receive either microbial-based or porcine-based pancreatin for 12 weeks. The primary outcome is the change from baseline in the PEI-Q score at 12 weeks. Secondary outcomes include nutritional status, anthropometric measures, gastrointestinal symptoms, pain scores, stool consistency, glycemic parameters, laboratory markers, and quality of life.

Discussion: This study aims to evaluate whether microbial-based pancreatin is non-inferior to porcine-based therapy and may provide a culturally acceptable and sustainable alternative for managing CP-related PEI.

Keywords: chronic pancreatitis; pancreatic exocrine insufficiency; porcine enzyme preparation; microbial based enzyme preparation; non-inferiority randomized controlled trial.

Trial Registration:

NCT number with URL: **NCT07697352**; www.clinicaltrials.gov. Registered on 5th July, 2026.
Protocol date and version number: 22nd October, 2026; Version 4.

Author contributions:

AMD, SSO, and RT designed the study. KS drafted the manuscript. RT conceived the study and drafted the manuscript. All other authors participated in the design of the study, reviewed and edited the manuscript, and approved the final manuscript. No professional writers were involved.

INTRODUCTION AND RATIONALE:

Chronic pancreatitis (CP) is a complex inflammatory disorder of the pancreas. It is characterized by persistent inflammation that progressively damages the pancreatic tissue, leading to irreversible fibrotic changes. The dominant clinical manifestation of is **abdominal pain** and ongoing parenchymal injury leads to a gradual decline in both **exocrine** and **endocrine** function. However, the onset of pancreatic exocrine insufficiency (PEI) and diabetes is not universal, as a subset of individuals with CP retains sufficient exocrine reserve to avoid clinically significant malabsorption. When functional decline advances, however, patients may ultimately develop PEI and diabetes.[1] In the absence of disease-modifying treatments, the current primary goal of management is early recognition and management of these complications. Treatment includes pain management, digestive support with pancreatic enzyme supplementation and nutrition, and endocrine management with oral antidiabetic medications and/or insulin. [2]

In PEI, insufficient secretion of pancreatic enzymes leads to inadequate digestion and absorption of nutrients, resulting in weight loss, malnutrition, metabolic bone disease, and deficiencies of fat-soluble vitamins and minerals.[3] PEI develops frequently in patients with CP, with a prevalence ranging from 30%–85% within 10–15 years after diagnosis.[4]

Large cohort studies report an overall PEI prevalence of 50%–75%, particularly in patients with alcohol-related CP and longer disease duration.[5] Management of PEI secondary to CP is important to improve nutritional status and quality of life. Pancreatic enzyme replacement therapy (PERT) is the mainstay of treatment for PEI. According to two meta-analyses [6,7] supportive treatment with pancreatic enzyme replacement showed significant improvement in the symptoms and consequences of PEI in patients with CP.

Currently available PERT preparations are primarily derived from porcine pancreas. Although clinically effective, porcine-derived PERT has certain limitations, including concerns related to its animal origin. Additionally, some patients may avoid such supplements due to lifestyle or ethical choices, such as vegetarians and vegans, while others, particularly followers of Islam and Judaism, may refrain from porcine-derived products due to religious dietary restrictions. Importantly, there is an increased lack of supplies due to the increasing prevalence of CP and other diseases associated with PEI.[8]

Therefore, new formulations of PERT are an unmet need.

Advances in biotechnology have led to the development of non-porcine microbial based pancreatic enzymes that have been shown to have a good safety profile and efficacy in several conditions. Animal studies and human pilot studies have also shown benefit in CP.[9] While the use of porcine PERT is well established in CP, the utilization of non-porcine microbial-based PERT

and its efficacy in CP is unclear. We hypothesize that non-porcine PERT will be as efficacious as the porcine based pancreatic enzymes in nutrient digestion. Hence, the aim of this study is to evaluate the clinical efficacy of non-porcine, microbial-based pancreatic enzymes compared with the current standard of care porcine enzymes, as a supportive therapy for patients with PEI secondary to CP.

Methods

The study protocol is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2025 guidelines.[10]

Study Design and duration

This is a multi-center, randomized, double-blind, parallel-group (1:1), placebo-controlled, non-inferior trial. The trial duration is 3 months (including enrolment and follow-up period). The study will be conducted in three independent branches of AIG hospitals, at Gachibowli, Somajiguda, and Banjara Hills, Hyderabad, India. The main branch at Gachibowli will be the coordinating center. Ethical approval has already been procured in the coordinating center (Asian Institute of Gastroenterology, Gachibowli). **Figures 1** and **2** depicts the study design and timelines respectively.

Inclusion criteria:

- CP fulfilling the M-ANNHEIM criteria[11] with documented PEI (defined as fecal elastase <100 µg/g stool on the background of morphological changes of CP).
- PEI-Q score of >1.4
- Willingness to undergo a 2-week wash-out period without pancreatic enzyme therapy before enrolment.
- Age ≥18 years.
- Willing and able to provide written informed consent.

Exclusion criteria

- Major psychiatric illness impairing study participation.
- Systemic illness affecting digestion or study outcomes.
- Any condition deemed unsuitable for study participation by the investigator.
- Concurrent acute exacerbation of the CP at the time of screening.

Study medication

The study medications will consist of non-porcine microbial -based pancreatin and standard-of-care porcine-based pancreatin. Both preparations will be packaged identically to maintain blinding of participants, investigators, study staff, and outcome assessors throughout the study period. The non-porcine microbial enzyme preparation will contain amylase (6650 DU), lipase (13000 FIP), and protease (7120 HUT, 15 SAPU, 3000 PC) derived from a source (AORA Health, Parque Científico de Madrid, Spain). These medications will be taken TID with major meals of the day for a duration of three months. The quality and concentration of the individual components of the enzyme preparations will be verified by an independent third party prior to initiation of the study. The standard of care porcine-based enzyme preparation will contain amylase (8000 U), lipase (25000 U), and protease (1000 U).[13] The porcine-based pancreatin has been designed to closely resemble the non-porcine microbial pancreatin study medication in appearance, including capsule colour (red), size ('00'), shape (oval), and packaging (bottle), to maintain blinding.

The enzyme preparations will be procured from Aora Health, Madrid and imported to India by Mascot Health Services Pvt. Ltd. These companies will have no role in study design, randomization, allocation concealment, patient management, follow-up, data analysis, interpretation of results, or manuscript preparation.

Concomitant medications

Patients will be instructed to continue their regular medications during the study period. All concomitant medications will be recorded twice: once at the screening visit and again at the final study visit. Any changes to the medication regimen during the study period will be documented.

Dietary advice

All enrolled patients will be provided with a need-based nutrition regimen following the ESPEN guidelines.[14] This will be done at each study center by a dedicated registered dietitian. The patients will be required to record any deviation from the dietary protocols in a daily diary that will be provided. Dietary compliance will be monitored during the telephone interviews.

Follow-up plan

The patients will be provided with a structured diary wherein they will record their body weight every week using the same weighing machine for all measurements to ensure consistency. They will also record their medication intake, need for hospital visits, and any deviation in their diet regimen. A research coordinator will make a telephone call to each patient after weeks 4, 6, and

8 to collect any data that the patient recorded over the weeks. At the same time, the coordinator will also ensure and encourage compliance with the treatment. At the end of the study, the patient will visit the study centers where all the baseline measurements will be repeated. The patients will be directed to bring the study medicine containers, and a pill count will be done.

Outcome measures

The outcome measures for this study are designed to evaluate the clinical effectiveness of the non-porcine-based microbial enzyme preparation compared to the standard of care porcine preparation in improving various clinical, nutritional, and functional parameters in patients.

Primary outcome

Change in Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q) score

The primary outcome is the change in PEI-Q score from baseline to week 12. The PEI-Q will be administered at baseline and again at week 12, and the between-group difference in the change in PEI-Q scores over this interval will serve as the primary endpoint.

Secondary outcomes

1. **Change in body composition**- Bioimpedance analysis (BIA) will be used to evaluate the body composition of the patients and the between-group difference of change from baseline to 12 weeks will be calculated.
2. **Change in nutritional status**-Nutritional status will be assessed using the semi-quantitive tool Subjective Global Assessment (SGA)[15] and quantitatively using anthropometric measures and biochemical markers (for details, see later). Between-group difference of changes in these parameters from baseline to 12 weeks will be compared.
3. **Change in SARC-F questionnaire-** The SARC-F questionnaire,[16] which evaluates strength, assistance with walking, rising from a chair, climbing stairs, and falls, will be administered at baseline and again at 12 weeks to identify individuals at risk of sarcopenia. The between-group difference of changes in the score from baseline to 12 weeks will be compared to assess the effect of the intervention on sarcopenia risk.
4. **Change in Patient Global Impression of Change (PGIC)**- The PGIC status[17] will be assessed at the end of 12 weeks to determine the patient's perception of overall health and improvement at the end of the study. This subjective measure will provide additional insight into the impact of the intervention on patient’s well-being and perceived improvement in health.

5. **Change in Stool consistency-** Stool consistency will be assessed using the Bristol Stool Scale,[18] while gastrointestinal symptom severity will be evaluated using the Patient Assessment of Upper Gastrointestinal Disorders – Symptom Severity Index (PAGI-SYM) questionnaire.[19] Both the validated questionnaires will be administered at baseline and after 12 weeks. The between-group difference of changes in these parameters from baseline to 12 weeks will be compared.
6. **Change in quality of life**- Quality of life will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[20] along with the EORTC QLQ-PAN28[21] at baseline and at the end of the intervention period. The between-group difference of changes in these parameters from baseline to 12 weeks will be compared.
7. **Change in pain severity**- Pain intensity will be recorded using a daily pain diary with the Visual Analog Scale (VAS) of 0-10, while pain-related symptoms and characteristics will be assessed using the Short-form Comprehensive Pain Assessment Tool (SF-COMPAT)[22] in participants experiencing pain in accordance with recommendations.[23] These assessments will be conducted at study initiation and upon completion of the intervention. The mean of the VAS over the week preceding enrolment will be considered as the baseline pain intensity score. The SF-COMPAT displays different dimensions of pain, and gives a more comprehensive assessment that can be used to phenotype pain characteristics.[24] Changes in scores across the two assessment points will be analyzed to determine the effect of the intervention on pain burden and related symptoms.
8. **Readmissions during the study period**- The number of hospital readmissions during the 12 weeks study period will be tracked for both treatment and placebo groups.
9. **Change in functional mobility during the study period**- Functional mobility will be assessed using the Timed Up and Go (TUG)[25] test at baseline and at the end of the intervention period. Between-group difference of changes in the TUG parameters from baseline to 12 weeks will be compared to evaluate the effect of the intervention on mobility and physical function.
10. **Change in Endocrine Status**- Endocrine function will be evaluated through measurements of fasting blood sugar (FBS), HbA1c, and C-peptide levels. The changes in these parameters after 12 weeks will help assess the effect of the intervention on endocrine function.

Randomization, blinding, and PERT allocation

After obtaining written informed consent by the designated research coordinator, eligible participants who satisfy the inclusion criteria and complete the 2-week wash-out period will be randomized in a 1:1 ratio to either the non-porcine microbial-based pancreatin group or the porcine-based standard-of-care pancreatin group. Each patients will receive 6 capsules (2 each per meal) daily to achieve the proposed dosage. A block randomization method with a block size of 8 will be used to ensure equal allocation between the two groups. Randomization will be performed using a sealed envelope randomization software (https://www.sealedenvelope.com/power/continuous-noninferior/) by a statistician who is not involved in patient interaction, study interventions, or data analysis. Treatment allocation and blinding will be managed by an independent research coordinator not involved in the conduct of the study or patient care.

The principal investigator (PI), co-investigators, study staff, outcome assessors, and participants will remain blinded to treatment allocation throughout the study to ensure unbiased treatment administration and outcome assessment.

Unblinding will be permitted only in the event of a medical emergency or serious adverse event where knowledge of the assigned intervention is essential for clinical management. The PI will authorize unblinding and access the allocation code for the specific participant through the secure randomization system. The reason and date of unblinding will be documented, and the Institutional Ethics Committee will be notified as per regulatory requirements. Unblinding will be restricted to the affected participant and will not compromise the overall blinding of the trial.

Study and assessment methods

Once the initial screening is completed by the PI and participant allocation is performed by an independent research coordinator, the designated co-investigators and research team from each center will systematically assess and record clinical, radiological, biochemical, and previous treatment-related details at baseline. The following tools and methods will be employed for assessment of the study outcomes:

1. **Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q) Assessment:**

The pancreatic exocrine insufficiency related symptoms will be assessed using the Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q).[26,27]

The PEI-Q is a validated multilingual (English, Hindi, Turkish) patient-reported outcome questionnaire designed to assess the severity and impact of symptoms related to pancreatic exocrine insufficiency (PEI) on patients' daily life and overall well-being.

The questionnaire evaluates multiple symptom domains commonly associated with PEI, including gastrointestinal symptoms, dietary difficulties, fatigue, emotional well-being, and limitations in daily activities.

Each item in the questionnaire is scored using a standardized Likert-scale (0-5 based on the severity of symptoms) response system. The means of the Abdominal symptoms domain (7 questions), Bowel movements domain (6 questions) and Impacts domain (5 questions) scores provides the sum scores for the individual domains. The average of individual sum scores for the three domains gives the total summary score. Higher scores indicate greater symptom burden and poorer PEI-related quality of life.

The questionnaire will be administered and interpreted according to standardized scoring guidelines to ensure consistency and reliability of assessment across all study participants.

2. **Stool Consistency and Gastrointestinal Symptom Assessment**

Changes in stool consistency and gastrointestinal symptom severity will be assessed using the following parameters:

Bristol Stool Scale

The Bristol Stool Scale is a validated visual assessment tool used to classify stool form and consistency into seven categories ranging from Type 1 (separate hard lumps, indicating constipation) to Type 7 (watery stool, indicating diarrhoea). Participants will be asked to report their usual stool consistency based on the scale at baseline (week 0) and again at 12 weeks. Changes in stool type over the study period will be used to evaluate the effect of the intervention on bowel habits and stool consistency.

Patient Assessment of Upper Gastrointestinal Disorders – Symptom Severity Index

The Patient Assessment of Upper Gastrointestinal Disorders – Symptom Severity (PAGI-SYM) is a validated questionnaire-based tool used to assess the severity of upper gastrointestinal symptoms experienced by patients. The questionnaire evaluates multiple symptom domains,

including nausea/vomiting, postprandial fullness, bloating, upper abdominal pain, heartburn, and early satiety. Each item is scored on a Likert scale based on symptom severity, with higher scores indicating greater gastrointestinal symptom burden.

3. **Sarcopenia Assessment**

Changes in sarcopenia risk will be assessed using the SARC-F Questionnaire. This is a validated screening questionnaire used to identify individuals at risk of sarcopenia and impaired muscle function. The questionnaire assesses five components: Strength, assistance with walking, rise from a chair, climb stairs, and falls. Each component is scored from 0 to 2 based on the degree of difficulty experienced by the participant, with total scores ranging from 0 to 10. Higher scores indicate a greater risk of sarcopenia and poorer functional status. A total SARC-F score of ≥4 will be considered suggestive of sarcopenia risk.

4. **Nutritional Assessment**

The nutritional status of participants will be assessed using the following parameters:

- **Clinical Parameters:**
    - **Percent change in body weight:** Assessment of weight gain or loss relative to baseline values.
    - Subjective Global Assessment (SGA)
        - The SGA is a validated questionnaire-based tool that assesses a patient's overall nutritional status using structured clinical parameters based on clinical history and physical examination. Nutritional status will be graded as normal (SGA A), mild/moderate malnutrition (SGA B), and severe malnutrition (SGA C).
    - **Anthropometric Measurements:**
        - Mid-arm circumference (MAC)
        - Triceps skinfold thickness (TSF)
        - Mid-upper arm muscle circumference (MAMC)
        - Mid-arm muscle area (MAMA)
- **Biochemical Parameters:**
    - Prealbumin
    - Haemoglobin (Hb)

- Vitamin D

  Vitamin B12

5. **Quality of Life Assessment**

The Short Form-36 (SF-36) questionnaire will be used to evaluate participants' quality of life. This tool provides a comprehensive assessment of physical and mental health domains, including physical functioning, general health perception, emotional well-being, and social functioning.

6. Faecal elastase-1 test

The Faecal elastase-1 (FE-1) test will be performed to determine and quantify pancreatic exocrine insufficiency (PEI). Results will be categorized as follows:

- **<100 µg/g:** Severe exocrine pancreatic insufficiency
- **100–200 µg/g:** Moderate to mild exocrine pancreatic insufficiency
- **>200 µg/g:** Normal pancreatic exocrine function

7. ^{13}C Mixed triglyceride breath test:

Pancreatic exocrine function will be assessed in a subgroup of patients using a ^{13}C mixed triglyceride test[28]. Patients will be provided 300mg of mixed ^{13}C triglyceride orally with a solid test meal containing 15 gm wheat bread and 10 gm butter (14 gm fat, 19 gm carbohydrate, 3 gm protein and 705 kJ energy) along with 100ml water. Metoclopramide (10mg) will be given orally 30mins before the breath test to avoid gastric emptying related issues. Breath samples will be collected before the test meal and thereafter every 30 mins until 6 hrs. Breath samples will be collected in duplicates in customised breath bags and then be transferred to 10 mL glass exetainers (Becton Dickinson). Breath samples will be analysed for 13CO2 enrichments using isotopic ratio mass spectrometer (IRMS, Delta V Advantage, Thermo Fisher Scientific Inc.

8. **Endocrine function assessment**

Endocrine status will be evaluated using the following parameters:

- **Fasting blood sugar:** To assess baseline glucose levels.
- **HbA1c:** To determine long-term glycemic control.
- **Plasma C-Peptide:** To evaluate pancreatic beta-cell function and insulin secretion.

9. **Body composition:**
    - Bioimpedance analysis (BIA) (SECA company) will be used to evaluate the body composition of the patients and the difference between baseline and 3-months follow-up will be calculated.

Study monitoring and safety

A Data Safety Monitoring Board (DSMB) has been constituted to oversee the safety and integrity of the study. The DSMB consists of three independent members with expertise relevant to the study, including a statistician, a gastroenterologist, and a nutritionist. These individuals will not be directly involved in the design, implementation, or day-to-day conduct of the study, ensuring an unbiased review process.

The DSMB will be responsible for:

1. **Monitoring study conduct:** The DSMB will periodically review the progress of the study, ensuring adherence to the protocol and compliance with ethical and regulatory standards.
2. **Safety oversight:** The DSMB will evaluate participant safety by reviewing adverse events, serious adverse events, and any potential risks associated with the study interventions.
3. **Interim analyses:** The DSMB will oversee an interim analysis after completion of follow-up of one-third patients to assess the efficacy and safety of the interventions. This will include evaluating data for any early signs of harm, benefit, or futility.
4. **Recommendations on study continuation:** Based on their findings, the DSMB will provide recommendations on whether the study should continue as planned, be modified, or be discontinued for reasons such as safety concerns, lack of efficacy, or ethical considerations.

We do not anticipate any significant harm from the study interventions because both study arms consist of routinely used pancreatic enzyme preparations with established safety profiles. However, rarely, some patients may experience mild gastrointestinal adverse effects such as bloating, abdominal discomfort, nausea, or constipation. These adverse effects are generally mild and self-limiting.

Adverse event reporting:

Based on previous experience, both the study and comparator enzymes are expected to cause any major adverse event. Nevertheless, any serious adverse event/reaction will be reported to the DSMB, the ethics committee and Aura within 24 hours. Fatal or life threatening unexpected serious

adverse event/reaction will be reported to the Eudravigilance database as soon as possible and no later than 7 days.

Sample size calculation

The study is designed as a non-inferiority trial comparing non-porcine microbial based with porcine-based standard of care pancreatin on the primary continuous outcome measured by the PEI-Q total score (range 0–72). Non-inferiority will be concluded if the upper bound of the one-sided 97.5% confidence interval for the mean difference does not exceed a pre-specified non-inferiority margin of 10 units, which is considered the minimal clinically important difference for the PEI-Q based on expert consensus. Sample size and power calculations for a range of non-inferiority margins (Δ= 5, 7.5, 10, 12.5, and 15 units), assuming a common standard deviation of 15 units and n = 60 participants per group, indicate that the study has approximately 94% power to demonstrate non-inferiority for a margin of 10 units, with higher power for larger margins and lower power for smaller margins (Table 1). To adjust for 10% drop outs, we will increase to sample size to 67 patients in each group adding up to a total of 134 patients.

Non-Inferiority Margin (Δ, units)	SD (units)	Standardized Margin (Δ/SD)	Sample Size per Group for 80% Power	Power with n = 60 per Group
5	15	0.33	142	≈35%
7.5	15	0.5	63	≈69%
10	15	0.67	36	≈94%
12.5	15	0.83	23	≈99%
15	15	1.0	17	>99%

Statistical Analysis

A centralized database will be developed in REDCap. Data will be uploaded from the three study centers and curated by Rasmus Bach Nedergaard from the monitoring center in Aalborg, Denmark. All analyses will be conducted at the University of Aalborg by Soren S Olesen, who will be blinded to treatment allocation and randomization.

Continuous variables will be expressed as mean with standard deviation (SD) or median with interquartile range (IQR), as appropriate. Categorical variables will be presented as frequencies and proportions.

A linear mixed-effects model will be used to assess changes in PEI-Q scores across all assessment time points. Summary statistics with corresponding 95% confidence intervals (CI) will be reported with the between group-difference at 12 weeks being the primary endpoint.

Continuous secondary outcomes, including changes in nutritional parameters, SARC-F score, stool consistency, gastrointestinal symptom severity, quality of life, endocrine function, faecal elastase-1 levels, and body composition, will be analysed using mixed-effects regression models for normally distributed variables and quantile regression models for non-normally distributed variables. Categorical outcomes will be analysed using risk differences between groups with corresponding 95% confidence intervals.

Missing data will be handled using multiple imputation techniques. A two-tailed p-value of <0.05 will be considered statistically significant.

Discussion

PEI remains a major contributor to malnutrition, gastrointestinal symptoms, sarcopenia, and impaired quality of life in patients with CP. Although porcine-derived PERT is the current standard of care, concerns regarding animal origin, cultural and religious acceptability, and accessibility highlight the need for effective non-porcine alternatives. Emerging microbial -based enzyme preparations offer a promising option; however, comparative clinical evidence in patients with CP is limited. Therefore, a randomized double-blind non-inferiority trial is warranted to determine whether microbial-based pancreatin provides symptom control and nutritional benefits comparable to standard porcine-based therapy. As CP is a chronic and irreversible disease, long-term supportive management aimed at improving nutritional and functional outcomes remains a cornerstone of therapy.

Recent advances in biotechnology have enabled the development of non-porcine microbial -based pancreatic enzyme preparations. Preliminary animal studies and limited human data suggest that microbial-based enzymes may provide effective digestive support with a favourable safety profile[29-31]. However, evidence comparing microbial-based PERT with standard porcine-based therapy in patients with CP remains scarce.

This randomized double-blind non-inferiority trial has therefore been designed to evaluate whether non-porcine microbial -based pancreatin is comparable to standard porcine-based pancreatin in improving pancreatic exocrine insufficiency-related symptoms in patients with CP. In addition to assessing changes in PEI-Q scores, this study will comprehensively evaluate nutritional parameters, sarcopenia risk, stool consistency, gastrointestinal symptom burden, endocrine status, pain scores, body composition, and quality of life outcomes following 12 weeks of intervention.

In conclusion, this study addresses an important and underexplored area in the management of CP-associated PEI. The findings of this trial will help clarify the clinical role of non-porcine microbial-based pancreatic enzyme therapy and its potential as an alternative to conventional porcine-derived preparations. The results of this study are expected to provide valuable evidence regarding its effectiveness, safety, and applicability in improving nutritional and patient-reported outcomes in chronic pancreatitis.

Name and contact of trial sponsor: Asian Institute of Gastroenterology, Gachibowli, Hyderabad.

Telephone: +91 40 42322334

Funding: The NP-PERT trial is an investigator-initiated trial. Financial support is sought from relevant funding bodies. Sponsors will have no influence on the design of the study, data collection, results, or publication.

Trial status:

The trial has been approved by the Institutional Ethics Committee (AIG/IEC-BH&R 82/04.2026/09) and has been registered with clinicaltrials.gov (NCT **NCT07697352**). The first patient was to be randomized on 10th October 2026 (5 patients recruited so far) and we expect the trial to be completed by October 2027.

Availability of data and materials: Participants will be assigned a unique study identification number to ensure anonymization. The linkage between participant identifiers and study codes will be accessible only to the principal investigator and his authorized representative. Source documents will be securely stored by the project leader at the Asian Institute of Gastroenterology for a period of five years in accordance with institutional policy.

All data generated or analysed during this study will be reported in the published results. De-identified datasets supporting the findings of this study, along with relevant documentation, will be available from the corresponding author upon reasonable academic request. Data requests will

be reviewed by the principal investigator and Institutional Ethics Committee to ensure compliance with ethical standards and data protection regulations. A data-sharing agreement may be required prior to data release.

Dissemination policy: The results of this trial will be disseminated through publication in peer-reviewed scientific journals and presentation at national and international scientific conferences. Summary results will be updated in the trial registry in accordance with registry requirements.

A plain language summary of the study findings will be prepared after study completion and will be made available to participants upon request. Findings may also be shared with healthcare professionals through academic meetings and institutional forums to support evidence-based clinical practice.

Patient and Public Involvement: Patients and members of the public were not involved in the design, conduct, reporting, or dissemination plans of this trial.

Conflicts of Interest: None

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Legends to figures:

Figure 1: Schematic representation of the study design.

Figure 2: Schedule of enrolment, interventions, and assessments.

Footnote to Figure 2-

[a & b] Arrows indicates continuous delivery.
[c] **Baseline variables:** age; sex; height; weight; etiology;, cross-sectional imaging results; medications, including concomitant; disease severity & interventions; nutritional and laboratory assessment.
[d] **Primary outcome:** Change in Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q) score.
[e] **Secondary outcomes:** Change in nutritional status, Bristo Stool Scale, PAGI SYMquality of life (European Organization for Research and Treatment of Cancer Quality of Life questionnaire), , endocrine status, and change in Patient Global Impression of Change (PGIC).
[f] **Patient diary & compliance:** daily symptoms, deviations in treatment, adverse reactions, hospital visits, dietary recall, and weekly weight.

Figure 1: Schematic representation of the study design.

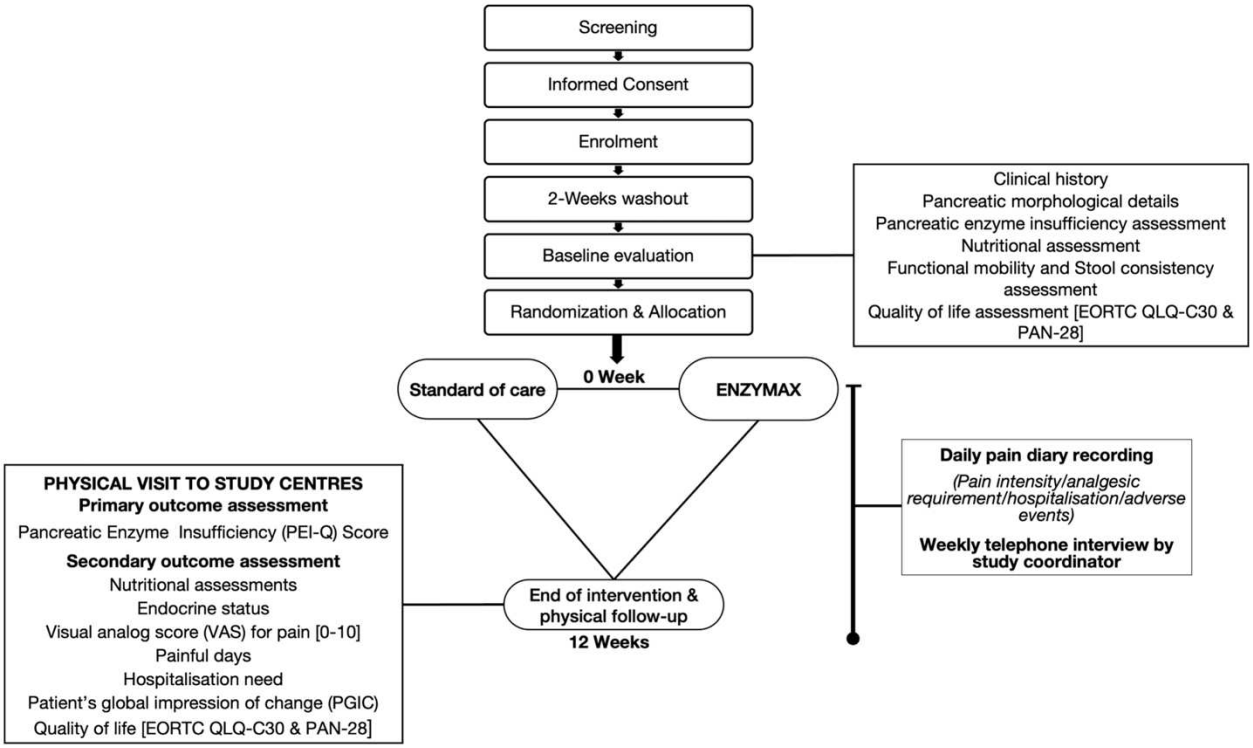


Figure 2: Schedule of enrolment, interventions, and assessments.

	TRIAL PERIOD				
	Screening	Baseline	Post-randomization		Post-randomization (End visit)
TIME POINT[b]	*Week -2*	Day 0	*Week 1 (±2 days)*	*Week 11 (77±2 days)*	*Week 12 (84 ±7 days)*
ENROLLMENT:					
Eligibility screen	X				
Informed consent	X				
2-Week enzyme washout	X				
Allocation/Randomization		X			
INTERVENTION/ COMPARATOR:					
Non-porcine microbial PERT [a]			X →	→	X
Porcine standard of care PERT [b]			X →	→	X
ASSESSMENTS:					
Baseline variables [c]		X			
Primary outcome [d]	X				X
Secondary outcomes [e]		X			X
Patient diary & medication compliance [f]			X (weekly telephonic/ WhatsApp)	X (weekly telephonic/ WhatsApp)	X (physical assessment & pill count)

Footnote to Figure 2-

[a & b] Arrows indicates continuous delivery.

[c] **Baseline variables:** age; sex; height; weight; etiology;, cross-sectional imaging results; medications, including concomitant; disease severity & interventions; nutritional and laboratory assessment.

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[f] **Patient diary & compliance:** daily symptoms, deviations in treatment, adverse reactions, hospital visits, dietary recall, and weekly weight.

SPIRIT 2025 checklist of items to address in a randomized trial protocol*

Section / Topic	No	SPIRIT 2025 checklist item description	Reported on page no.
Administrative information			
Title and structured summary	1a	Title stating the trial design, population, and interventions, with identification as a protocol	1
	1b	Structured summary of trial design and methods, including items from the World Health Organization Trial Registration Data Set	1
Protocol version	2	Version date and identifier	2
Roles and responsibilities	3a	Names, affiliations, and roles of protocol contributors	1,3
	3b	Name and contact information for the trial sponsor	16
	3c	Role of trial sponsor and funders in design, conduct, analysis, and reporting of trial; including any authority over these activities	16
	3d	Composition, roles, and responsibilities of the coordinating site, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable	12,13
Open science			
Trial registration	4	Name of trial registry, identifying number (with URL), and date of registration. If not yet registered, name of intended registry	2
Protocol and statistical analysis plan	5	Where the trial protocol and statistical analysis plan can be accessed	16
Data sharing	6	Where and how the individual de-identified participant data (including data dictionary), statistical code, and any other materials will be accessible	16
Funding and conflicts of interest	7a	Sources of funding and other support (e.g., supply of drugs)	6,16
	7b	Financial and other conflicts of interest for principal investigators and steering committee members	17
Dissemination policy	8	Plans to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., reporting in trial registry, plain language summary, publication)	16
Introduction			
Background and rationale	9a	Scientific background and rationale, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	9b	Explanation for choice of comparator	4,5
Objectives	10	Specific objectives related to benefits and harms	5
Methods: Patient and public involvement, trial design			
Patient and public involvement	11	Details of, or plans for, patient or public involvement in the design, conduct, and reporting of the trial	5,6,7
Trial design	12	Description of trial design including type of trial (e.g., parallel group, crossover), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Trial setting	13	Settings (e.g., community, hospital) and locations (e.g., countries, sites) where the trial will be conducted	5
	14a	Eligibility criteria for participants	5

Eligibility criteria	14b	If applicable, eligibility criteria for sites and for individuals who will deliver the interventions (e.g., surgeons, physiotherapists)	NA
Intervention and comparator	15a	Intervention and comparator with sufficient details to allow replication including how, when, and by whom they will be administered. If relevant, where additional materials describing the intervention and comparator (e.g., intervention manual) can be accessed	6
	15b	Criteria for discontinuing or modifying allocated intervention/comparator for a trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	9,13
	15c	Strategies to improve adherence to intervention/comparator protocols, if applicable, and any procedures for monitoring adherence (e.g., drug tablet return, sessions attended)	7
	15d	Concomitant care that is permitted or prohibited during the trial	7
Outcomes	16	Primary and secondary outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome	7,8
Harms	17	How harms are defined and will be assessed (e.g., systematically, non-systematically)	13
Participant timeline	18	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig pg
Sample size	19	How sample size was determined, including all assumptions supporting the sample size calculation	13,14
Recruitment	20	Strategies for achieving adequate participant enrollment to reach target sample size	14
Methods: Assignment of interventions			
Randomization:			
Sequence generation	21a	Who will generate the random allocation sequence and the method used	9
	21b	Type of randomization (simple or restricted) and details of any factors for stratification. To reduce predictability of a random sequence, other details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	9
Allocation concealment mechanism	22	Mechanism used to implement the random allocation sequence (e.g., central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	23	Whether the personnel who will enroll and those who will assign participants to the interventions will have access to the random allocation sequence	9
Blinding	24a	Who will be blinded after assignment to interventions (e.g., participants, care providers, outcome assessors, data analysts)	9
	24b	If blinded, how blinding will be achieved and description of the similarity of interventions	9
	24c	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			

Data collection methods	25a	Plans for assessment and collection of trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of trial instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be accessed, if not in the protocol	10,11,12
	25b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6,7
Data management	26	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be accessed, if not in the protocol	9,14
Statistical methods	27a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	14
	27b	Definition of who will be included in each analysis (e.g., all randomized participants), and in which group	14
	27c	How missing data will be handled in the analysis	15
	27d	Methods for any additional analyses (e.g., subgroup and sensitivity analyses)	14
Methods: Monitoring			
Data monitoring committee	28a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and funder; conflicts of interest and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12,13
	28b	Explanation of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Trial monitoring	29	Frequency and procedures for monitoring trial conduct. If there is no monitoring, give explanation	13
Ethics			
Research ethics approval	30	Plans for seeking research ethics committee/institutional review board approval	16
Protocol amendments	31	Plans for communicating important protocol modifications to relevant parties	NA
Consent or assent	32a	Who will obtain informed consent or assent from potential trial participants or authorized proxies, and how	9
	32b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	33	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Ancillary and post-trial care	34	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA