1.2. Primary Objective

To assess the effect of pancreatic enzyme replacement (Zenpep) therapy on the completion rate of standard of care adjuvant therapy among participants with resected pancreatic adenocarcinoma (PDAC).

1.3. Secondary Objectives

- To assess the effect of pancreatic enzyme replacement (Zenpep) therapy on the initiation rate of standard of care adjuvant therapy
- To assess subject adherence to pancreatic enzyme replacement therapy
- To evaluate the frequency of study-drug related dose modifications and severity of drug related adverse events during stage 1
- To evaluate the incidence and severity of postoperative complications during stage 1
- To evaluate the effect of pancreatic enzyme replacement therapy on nutrition status during postoperative recovery and adjuvant treatment
- To assess quality of life as measured by the EQ-5D-5L during postoperative recovery and adjuvant treatment
- To evaluate grip strength, nutritional status and ECOG performance during postoperative recovery and adjuvant treatment

2. BACKGROUND

2.1. Study Disease(s)

In 2015, the estimated number of new cases of pancreatic cancer in the US was 48,960 with nearly the same number of deaths[1]. Multimodal treatment of early stage pancreatic cancer, including surgical resection followed by adjuvant therapy, remains standard of care as the only potential treatment offering long-term survival. Supporting patients through surgery and subsequent adjuvant therapy remains a significant clinical challenge. Rapid early progression from undetected distant disease metastases is common, and delayed recovery from surgical resection frequently precludes adjuvant therapy. Given these factors, median survival is limited to 23 months following surgical resection and adjuvant treatment in most published studies.[1,2]

3.2. Stage 1 Enrollment Criteria prior to surgery

3.2.1. Participant must be a candidate for standard of care surgical resection of a mass suspected or proven to be pancreatic adenocarcinoma (PDAC) and its WHO variants

3.2.1.1. A signed surgical consent to perform elective pancreatic resection is sufficient documentation of eligibility for standard of care surgical resection

3.2.1.2. All standard of care pancreatic resections are eligible, including potential concurrent vascular resection and reconstruction with or without vein grafting.

3.2.1.3. Suspicious masses may be located anywhere within the pancreas.

3.2.2. Pathological confirmation of pancreatic adenocarcinoma (PDAC) is NOT required prior to enrollment if the resection specimen is the planned source tissue for confirmatory pathology.

3.2.2.1. Participants with prior biopsy or cytology confirmation of pancreatic adenocarcinoma are eligible.

3.2.3. Participant must be a candidate for standard of care adjuvant treatment according to their treating oncologist.

3.2.3.1. The anticipated treatment regimen and duration will be confirmed and recorded by study staff during the enrollment process.

3.2.3.2. Participants receiving preoperative/neoadjuvant chemotherapy and/or radiation therapy for pancreatic cancer are eligible if additional chemotherapy and/or radiotherapy is planned in the adjuvant setting.

3.2.3.2.1.Participants must not have completed more than half of the planned chemotherapy in the neoadjuant setting.

3.2.3.3. Study staff shall confirm that potential participants are willing to consider adjuvant treatment after surgery. Participants who absolutely refuse to consider adjuvant treatment during the enrollment process are ineligible.

3.2.4. ECOG performance status ≤2.

3.2.5. Participant must tolerate oral intake as their sole source of nutrition.

3.2.6. Age ≥18 years. Participants <18 years old are excluded from this study because subsequent adjuvant therapy is based on therapy guidelines in the adult population.

3.2.7. Pre-operative laboratory values adequate to undergo resection of pancreatic cancer, as defined below:

- Hemoglobin > 7.0 g/dL;
- Platelets ≥ 40,000/mL;
- Creatinine < 2.5 mg/dL or; Creatinine clearance ≥ 20 mL/min/1.73m^2 for participants with creatinine levels above institutional normal.

3.2.8. Ability to understand and willingness to provide written informed consent.

3.2. Stage 1 Exclusion Criteria

- Nausea – due to delayed gastric emptying and pancreatic leak
- Early Satiety- due to delayed gastric emptying and pancreatic leak
- Weight loss due to anorexia, prolonged delayed gastric emptying, untreated EPI, untreated diabetes resulting from pancreatic resection
- Surgical site infections (deep and superficial)

Resumption of Adverse Event Reporting During Stage 1
Adverse event reporting will resume on the date that study drug is restarted and shall continue through completion of stage 1, which ends on the start date of adjuvant therapy or postoperative week 12, whichever comes first.

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the (CAEPR), appears in a separate column and is identified with bold and italicized text. This subset of AEs (CAEPR) is a list of events that are protocol specific exception to expedited reporting.

If an AE meets the reporting requirements of the protocol, and it is listed on the CAEPR, it should only be reported if the grade being reported exceeds the grade listed in the parentheses next to the event in the CAEPR.

7.2. Adverse Events List

7.2.1.1. Comprehensive Adverse Events and Potential Risks (CAEPR) List for Zenpep (pancrelipase)

Table 7.1.1 Expected adverse effects	**Comprehensive Adverse Events and Potential Risks (CAEPR)**
Gastrointestinal Disorders*	
Abdominal Pain	Abdominal Pain (Grade 2)
Flatulence	Flatulence (Grade 2)
Diarrhea	Diarrhea (Grade 2)
Abdominal Distension	Abdominal Distension (Grade 2)
Nausea	Nausea (Grade 2)
Early Satiety	Early Satiety (Grade 2)
Weight loss	Weight loss (Grade 2)
Surgical site infection (deep and superficial)	Infection (grade 3)

postoperative week 12. Among participants who received neoadjuvant treatment, completion of fewer than 6 intended cycles of chemotherapy, or not completing all 6 cycles of adjuvant chemotherapy by week 28 after surgery, or not completing all intended fractions of radiation therapy will be considered failure to complete adjuvant treatment.

The calculation of week 28 follows: adjuvant treatment must start by week 12; if 3 cycles of treatment are planned after surgery (4 weeks each) plus a four week delay requires adjuvant therapy to conclude by week 28.

10.2. Methods for Evaluation of Objective Response

Evaluation of objective response will take place during Stage 2 of this trial:

1. Monthly visits to the primary medical oncologist as part of standard of care during adjuvant therapy.
2. Standard of care adjuvant chemotherapy may be administered by a community medical oncologist. In such cases, participants will be evaluated at BIDMC by research team every 4 weeks (+/- 7 days), either in person or by telephone according to the Stage 2 study calendar in section 10.2.
3. If a DFHCC medical oncologist is the treating provider, participant will undergo standard of care visits in person, after which study interventions will be conducted strictly for research purposes (see Study Calendar).
4. Research nurse will contact treating medical oncologist to establish intended treatment plan, set intended goals/cycles, and monitor progress with monthly contacts and medical record retrieval.

2.2. Effect of Exocrine Pancreatic Insufficiency (EEPI) on Surgical Outcomes

Although pancreatic enzyme replacement therapy (PERT) has been shown to improve quality of life (QOL) among participants with chronic pancreatitis[9], there are no similar studies of pancreatic enzyme replacement among patients with PDAC that evaluate postoperative nutrition status and reductions in complication rates after surgical resection .

The onset of exocrine pancreatic insufficiency (EPI) after resection of localized PDAC corresponds to the period of maximal nutritional and metabolic stress during surgical recovery (0-3 months) and subsequent adjuvant treatment (3-10 months). EPI causes malabsorption, steatorrhea, and weight loss and adversely impacts quality of life and survival, particularly among surgical patients with extremely low levels of fecal pancreatic elastase.[6,7] EPI affects up to 68% of PDAC patients following potentially curative resection regardless of the type of surgical procedure, with 42% of those being severely affected.[8] Poor post-operative nutrition is associated with increased risk of complications after surgery, and 40% of surgical patients with poor nutrition develop severe complications, including pancreatic fistula.[10]

2.3. Completion of Adjuvant Therapy

Data from the prospective randomized ESPAC3 trial of 985 participants with resected PDAC shows a significant survival advantage among participants who completed adjuvant therapy regardless of the selected chemotherapy regimen, which in this trial was gemcitabine vs. 5-fluorouracyl plus folinic acid.[5] These data have recently been amplified by results of the as-yet-unpublished PRODIGE trial comparing adjuvant FOLFIRINOX with gemcitabine-based regimens with postoperative median survival as long as 54 months among resected participants able to tolerate FOLFIRINOX and its significantly higher frequency of treatment-associated adverse events.

Although level I evidence demonstrates the efficacy of adjuvant chemotherapy for resected PDAC, completion rates among these studies average approximately 50% when analyzed by intention to treat.[1,2] Rates of initiating adjuvant therapy in current clinical practice remain low, with SEER data indicating standard adjuvant therapy rates below 50%.[4] The observed rate at our Institution was 40% during a recent audit.[4]

Causes for low rates of adjuvant therapy are multifactorial. Studies report delayed recovery from surgery and poor participant acceptance of adjuvant therapy as significant barriers to adherence with recommendations for adjuvant therapy [3].

Despite ongoing development of new agents and chemotherapy combinations in the adjuvant setting, strategies are clearly needed to improve initiation and completion rates of adjuvant therapy to improve patient outcomes. This trial is designed to achieve that endpoint using a low risk adjunct to nutritional therapy.

2.4. Pancrelipase (Zenpep)

3.2.1. Any prior surgical resection, or attempted resection, of the pancreas for PDAC
3.2.1.1. surgical biopsies of the pancreas are permitted
3.2.2. Any prior treatment for local recurrence or metastasis due to pancreatic adenocarcinoma (i.e. salvage chemo- or radiotherapy or re-resection for recurrence are not permitted)
3.2.3. Participant unable to tolerate oral nutrition as the sole source of caloric intake at the time of enrollment (i.e. no supplemental tube feeding or total parenteral nutrition)

3.2.4. History of prior or concurrent malignancy requiring treatment ≤3 years prior to enrollment.
3 Exceptions: Curatively treated non-melanoma skin cancer, cervical cancer in situ, or prostatic intraepithelial neoplasia, or prostate cancer that do not require ongoing treatment
3.2.5. History of allergic reactions or hypersensitivity attributed to compounds of similar chemical or biologic composition to pancrelipase
3.2.6. Pregnant women are excluded because adjuvant therapy required by this study to assess the primary endpoint is teratogenic. Pancrelipase is category C. Animal reproduction studies have not been conducted on pancrelipase, and minimal data is available.
3.2.7. Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
3.2.8. Participants receiving any other investigational agents.

Skin Disorders	
Pruritus	Pruritis (Grade 2)
Urticaria	Urticaria (Grade 2)
Rash	Rash (Grade 2)
Nervous System	
Headache	Headache (Grade 2)
Respiratory System	
Cough	Cough (Grade 2)

* Grade 3 or higher gastrointestinal expected adverse events will be reported after Standard of Care causes are excluded with algorithm.

7.1.2 Unexpected adverse effects

10.3. Evaluation for progressive disease while on adjuvant therapy

Management of Imaging Performed at DFHCC and non-DFHCC Sites

Imaging studies will be performed per standard of care and ordered at the discretion of the treating physician. Study staff shall retrieve all imaging studies performed per SOC regardless of facility participation in DFHCC.

Provision of adjuvant therapy is a standard of care decision. If the treating medical oncologist cancels treatment as no longer in the participant's interest for whatever reason prior to completion, the participant shall be taken off study and undergo an End of Treatment visit. If an imaging study performed per SOC indicates disease progression during adjuvant treatment, the participant shall be taken off study and undergo an End of Treatment visit provided that the TIMC central reading concurs with the treating radiologist. If there is discordance between the TIMC read and the official SOC radiology report, the research RN shall contact the treating physician within 48 hours of the central TIMC reading to report these findings to the treating MD. The TIMC report shall be entered into the participant research file and communicated orally to the treating MD.

All final decisions regarding the advisability, or not, of continued SOC adjuvant treatment shall be made solely by the treating physician without interference by the study team. Decisions of the treating physician are final. TIMC readings shall not be entered into the participant's medical record or communicated to the participant by the study team.

Progressive Disease (PD):

TIMC shall evaluate imaging studies from all facilities according to the following RECIST criteria for disease progression (CT or MRI):

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm since the adjuvant treatment started;

OR:

The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. Disease progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) and analyzed by Tumor Imaging Metrics Core (TIMC). Changes in the