DF/HCC Protocol #: 17-450

TITLE: A Phase II Study of Pancreatic Enzyme Replacement (Zenpep) on Completion Rates of Adjuvant Treatment among Subjects with Resected Pancreatic adenocarcinoma.

Coordinating Center: *Beth Israel Deaconess Medical Center*

***Principal Investigator (PI):** *A. James Moser, MD*
Department of Surgery
Beth Israel Deaconess Medical Center
330 Brookline Ave.
Boston, MA 02215
Tel: (617) 667-2792
Email: ajmoser@bidmc.harvard.edu

Co-Principal Investigator: *Bruno Bomfim da Silva Bockorny, MD*
Division of Hematology-Oncology
Beth Israel Deaconess Medical Center
330 Brookline Ave.
Boston, MA 02215
Tel: (617) 667-2100
Fax: (617)667-4809
Email: bbockorn@bidmc.harvard.edu

Statistician: *Hui Zheng, PhD*
Massachusetts General Hospital
450 Brookline Ave, BP332A
Tel: (617)726-0687
Fax: (617) 632-4452
E-mail: hzheng1@partners.org

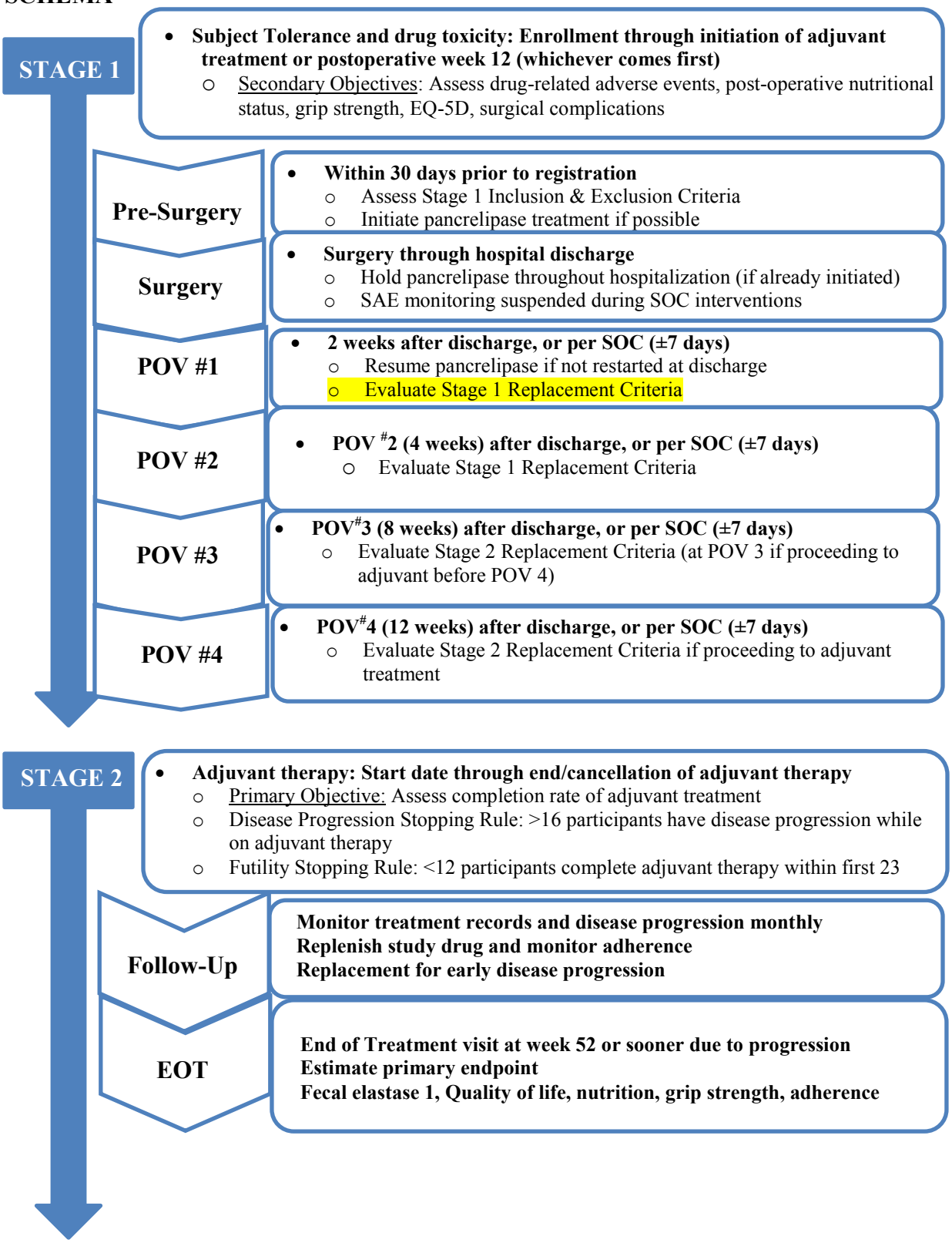
Agents: Zenpep, supplied by Allergan PLC

Study Exempt from IND Requirements per 21 CFR 312.2(b).

Protocol Type / Version # / Version Date: *Amendment 3 / March 4, 2019*

TABLE OF CONTENTS

SCHEMA


STAGE 1
Subject Tolerance and drug toxicity: Enrollment through initiation of adjuvant treatment or postoperative week 12 (whichever comes first)
Secondary Objectives: Assess drug-related adverse events, post-operative nutritional status, grip strength, EQ-5D, surgical complications
Pre-Surgery
Within 30 days prior to registration
Assess Stage 1 Inclusion & Exclusion Criteria
Initiate pancrelipase treatment if possible
Surgery
Surgery through hospital discharge
Hold pancrelipase throughout hospitalization (if already initiated)
SAE monitoring suspended during SOC interventions
POV #1
2 weeks after discharge, or per SOC (±7 days)
Resume pancrelipase if not restarted at discharge
Evaluate Stage 1 Replacement Criteria
POV #2
POV #2 (4 weeks) after discharge, or per SOC (±7 days)
Evaluate Stage 1 Replacement Criteria
POV #3
POV#3 (8 weeks) after discharge, or per SOC (±7 days)
Evaluate Stage 2 Replacement Criteria (at POV 3 if proceeding to adjuvant before POV 4)
POV #4
POV#4 (12 weeks) after discharge, or per SOC (±7 days)
Evaluate Stage 2 Replacement Criteria if proceeding to adjuvant treatment
STAGE 2
Adjuvant therapy: Start date through end/cancellation of adjuvant therapy
Primary Objective: Assess completion rate of adjuvant treatment
Disease Progression Stopping Rule: >16 participants have disease progression while on adjuvant therapy
Futility Stopping Rule: <12 participants complete adjuvant therapy within first 23
Follow-Up
Monitor treatment records and disease progression monthly
Replenish study drug and monitor adherence
Replacement for early disease progression
EOT
End of Treatment visit at week 52 or sooner due to progression
Estimate primary endpoint
Fecal elastase 1, Quality of life, nutrition, grip strength, adherence

OBJECTIVES

1.1. Study Design

This is a single institution, single arm, open label, phase II clinical trial of pancrelipase (ZENPEP) among subjects undergoing standard of care pancreatic resection for early stage pancreatic adenocarcinoma. The study will have a 2 stage design.

Stage 1: Tolerance to study drug during post-operative recovery following standard of care pancreatic resection
Stage 1 takes place during the postoperative recovery following standard of care pancreatic resection among subjects with suspected pancreatic adenocarcinoma. Stage 1 will monitor the following secondary objectives between the date of hospital discharge and the start date of adjuvant treatment through postoperative week 12 (whichever comes first):

- frequency of adverse events related to study drug
- frequency of study-drug related dose modifications
- study drug adherence
- complications after pancreatic surgery (Calvien Dindo)
- post-operative nutritional status (weight and albumin)
- grip strength
- ECOG status
- quality of life (EQ-5D-5L)
- Fecal pancreatic elastase

Stage 2: Completion of adjuvant treatment and monitoring of disease progression in response to study drug.
Stage 2 consists of evaluable subjects with resected, pathologically-confirmed pancreatic adenocarcinoma and initiate adjuvant therapy by week 12 after surgery. Stage 2 begins with the start date of adjuvant treatment and ends 52 weeks after surgery.

Stage 2 will estimate:

- the primary objective (the completion rate of adjuvant treatment),
- rate of early disease progression, defined as local recurrence or distant metastases during adjuvant treatment (a monitored toxicity).
- Secondary outcomes
    - the initiation rate of adjuvant treatment
    - nutritional status (weight and albumin)
    - grip strength
    - ECOG status
    - quality of life (EQ-5D-5L)
    - Fecal pancreatic elastase
    - One year progression-free and one year overall survival

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]

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)

Zenpep (pancrelipase) is an FDA approved drug for the treatment of exocrine pancreatic insufficiency. Post-marketing data has been available on pancrelipase since 2009. Pancrelipase is orally administered and excreted through the gastrointestinal (GI) tract. The pancreatic enzymes in pancrelipase catalyze the hydrolysis of fats to monoglycerides, glycerol, and free fatty acids, protein into peptides and amino acids, and starch into dextrins and short chain sugars such as maltose and maltriose in the duodenum and proximal small intestine, thereby mimicking digestive enzymes physiologically secreted by the pancreas. There have been two clinical trials confirming pancrelipase's efficacy and safety in the treatment of pancreatic enzyme insufficiency[11,12]. Initial dosing is 75,000 IU with every meal, based on dosage for a 75 kg individual derived from clinical trial data and the package insert.

- The most common side effects are:
  - abdominal pain (18%),
  - flatulence (6%),
  - headache (15%),
  - confusion (6%),
  - weight loss (6%),
  - cough (6%),
  - and early satiety (6%).
- Pancrelipase was generally safe and well-tolerated in both studies.
- There were no deaths during either study and no serious adverse events (SAEs) related to pancrelipase[11].
- No drug interactions have been identified.

2.5. Rationale

The frequency and clinical severity of EPI among patients with pancreatic carcinoma is much higher than widely recognized. Up to sixty-eight (68%) percent of patients have EPI prior to surgical resection, with even higher rates are observed by one year after resection[13].

EPI causes significant physiological impact and nutritional stress during recovery from surgery and receipt of adjuvant treatment. EPI is associated with reduced survival, diminished QOL, and poor nutrition among PDAC patients[14].

Because PERT may improve nutrition status and QOL in the post-operative period, we hypothesize that PERT may increase rates of adjuvant therapy initiation and completion.

3. TWO STAGE DESIGN

3.1. PARTICIPANT SELECTION FOR STAGE 1

Definition of stage 1: Stage 1 begins on the date that study drug is started and ends either at postoperative week 12 (± 5days) or the date that adjuvant treatment is started (whichever comes first).

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

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.

3.3. Stage 1 Re-screening Procedures after Surgery

All study procedures will be suspended during hospitalization for standard of care surgical treatment. As a result, no adverse events resulting from standard of care surgical procedures will be attributed to study drug. The frequency and severity of adverse events occurring in the SOC setting will be recorded as secondary measures of the morbidity of surgery and correlated to nutritional and performance measures (i.e. grip strength and ECOG status) in the secondary analysis.

Consequently, all study calendar references to postoperative visits during stage 1 will be timed according to the date of hospital discharge, rather than anchored to the date of surgery or enrollment, to simplify study calendar management for the following reasons:

- Standard of care events may prolong hospitalization and delay or completely preclude interventions planned according to an absolute study calendar.
- The intent of a flexible postoperative study calendar is to prevent unavoidable deviations related to the study calendar that have no effect on study safety or outcomes because study interventions are completely suspended during unplanned delays caused by prolonged hospitalization.

Participants will be re-screened twice in the postoperative period to confirm continued eligibility:

3.3.1. During postoperative visit #1 (POV#1; 2 weeks after hospital discharge ± 7 days), participants who did not undergo pancreatic resection for any reason shall be replaced.

3.3.2. By POV#2 (4 weeks after hospital discharge ± 7 days), all participants must meet the following eligibility criteria:

3.3.2.1. Pancreatic resection performed

3.3.2.2. ECOG performance status ≤ 2

3.3.2.3. Able to tolerate oral intake as their sole source of nutrition;

3.3.2.4. Able to self-administer study drug.

**Note: Subjects who reside in Skilled Nursing Facilities or rehabilitation centers after surgery are not barred from participation so long as they are tolerating oral nutrition and can self-administer study drug provided to them by the SNF/rehab staff.

3.3.3. Stage 1 End of Treatment Visit

The end of treatment (EOT) visit for ineligible participants will be conducted during POV#2; study drug will be retrieved at that time with no further issuance. If the EOT must be delayed so that study procedures do not interfere with SOC treatment (as late as postoperative week 12), no further study drug will be issued, and ineligible participants will be instructed by study staff to stop taking study drug during/after POV#2 ± 7 days..

3.4. Transition to Stage 2

Stage 2 eligibility criteria shall be applied prior to initiation of adjuvant treatment at POV #3 or POV#4 depending on participant recovery, but not later than postoperative week 12. Participants who do not meet eligibility criteria prior to initiation of stage 2 shall be replaced.

The purpose of stage 2 eligibility criteria is to maximize accrual of a uniform population of resected PDAC patients for estimation of the primary endpoint and its competing risk of early disease progression.

Stage 2 Eligibility Criteria

Final pathology must be pancreatic adenocarcinoma or WHO variants of PDAC or mixed histology if the predominant histology is adenocarcinoma.
Participant unwilling to take study drug or receive adjuvant therapy following surgical resection of disease, which equates to withdrawal of study consent for stage 2.

Monitoring of Disease Progression during Stage 2
Disease progression will be monitored by imaging studies. Imaging studies will be ordered by the treating physician may be performed in the community or at DFHCC locations.

All imaging studies will be retrieved by study staff and reviewed by TIMC. Radiographic findings will be recorded using RECIST criteria.

Participants experiencing radiologic disease progression according to RECIST 1.1 during adjuvant treatment will be replaced but shall count toward the monitored safety metric of early disease progression in response to study drug.
Participants must be replaced to maintain a strict definition of adjuvant treatment for evaluable subjects. Disease progression signifies local recurrence (stage 3) or distant metastases (stage IV) and defines failure of the current adjuvant regimen. Progression therefore makes participants unevaluable for the primary endpoint regarding completion of adjuvant treatment, as adjuvant treatment is cancelled by early recurrence.

3.5. Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1. General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol treatment. Any subject in screening that does not meet Stage 1 eligibility criteria will be logged as a screen fail in OnCore.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI).

4.2. Registration Process for DF/HCC Institutions.

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3. Study Procedures

4.3.1. Study Procedures Performed at BIDMC:

Research staff will register eligible participants at BIDMC. All research related procedures will take place at BIDMC by research personnel.

4.3.2. Administration of Standard of Care Adjuvant Treatment and related Imaging studies at non-DF/HCC Community Sites:

Participants may receive standard of care adjuvant treatment and related imaging provided by a community medical oncologist per SOC at non-DFHCC sites.

Participants receiving SOC adjuvant therapy in the community will be contacted by BIDMC research staff every 4 weeks (+/- 7 days) as detailed in Section 10.

5. TREATMENT PLAN

5.1. Treatment Regimen

Pancrelipase (Zenpep) will be administered with every meal (breakfast, lunch, dinner) and snack(s), continuously. There is no limit to the number of snacks a participant can have per day. Treatment will be administered on an outpatient basis. The maximum number of capsules to be taken per day will be based on body weight and tolerance.

Participants will be reassessed according to the Study Calendar (section 10). Adverse event reporting during Stage 1 and description of potential risks are described in Section 7. Appropriate dose modifications for Pancrelipase (Zenpep) are described in Section 6.

No investigational, commercial agents or therapies intended to treat the participant's pancreatic enzyme insufficiency may be administered other than Zenpep. Study participants should not be enrolled on any other therapeutic clinical trials.

5.1.1. Initiation of Study Drug

Participants may begin pancrelipase at any time after registration. Whenever possible, study drug should be initiated prior to surgery.

If a given subject cannot begin pancrealipase prior to surgery for any reason, study drug will be started upon hospital discharge or during POV #1.

5.1.2. Management of Study Drug during Standard of Care Surgery

Study procedures and reporting will be suspended on the day of surgery and throughout the hospital stay after surgery. Pancrelipase will also be held.

If the subject is tolerating oral intake as their sole source of nutrition and can take their medications orally, pancrelipase will resume on the day of hospital discharge (±7 days). If not, pancrelipase administration will be held and re-assessed during POV #1.

5.1.3. Reconfirmation of eligibility at POV#1
Stage 1 eligibility/inclusion and exclusion criteria shall be reconfirmed for all study participants per section 3. Subjects meeting Stage 1 eligibility criteria will receive up to 12 weeks of pancrelipase treatment regardless of stage 2 eligibility criteria.

5.1.4. Stage 2 Eligiblity Criteria
Subjects who complete stage 1 will be assessed for Stage 2 eligibility during POV 4 or prior to starting adjuvant therapy, whichever comes first.

Study medication shall be retrieved from participants who do not meet stage 2 eligibility criteria at their EOT visit.

5.2. Agent Administration

Participants must maintain a medication diary of each dose of study medication. The medication diary will be reviewed by study staff according to the study calendar until completion of adjuvant treatment.

If study subjects are receiving adjuvant treatment at non-DFHCC sites during stage 2, study staff will retrieve the relevant medication diaries monthly using a pre-printed and stamped mailer and review those entries by telephone before refilling study drug. Subjects receiving adjuvant treatment at non-DFHCC sites shall return for in person study visits not less frequently than q 3 months, at which time medication diaries shall be reviewed in person with study staff.

Participants must be able to swallow pancrelipase (Zenpep). If participant is not able to swallow Zenpep capsule whole, content may be sprinkled on small amounts of soft acidic food (e.g. applesauce or other commercially available preparations of bananas, or pears). The Zenpep-soft food mixture should be swallowed immediately without crushing or chewing, and followed with water or juice to ensure complete ingestion. Care should be taken to ensure that no drug is retained in the mouth. The initial Zenpep dose will be 75,000 lipase units per meal

(3 pills) and 25,000 lipase units per snack (1 pill) orally as per package insert. Zenpep must be swallowed whole and taken with water or other liquid. Part of the dose of Zenpep should be taken in the middle of the meal and the remainder of the dose should be taken at the end of the meal. The maximum daily dose is 10,000 lipase units per kilogram of weight. If a dose is missed or vomited, it should not be made up. The next dose will be taken regularly with the next snack or meal. Storage of Zenpep must be in the same container, closed tightly between doses and stored at room temperature (i.e. subjects should not store Zenpep in a daily pill container with other medications).

5.3. General Concomitant Medication and Supportive Care Guidelines

No drug interactions have been identified. No formal interaction studies have been conducted.

5.4. Criteria for Taking a Participant Off Protocol Therapy

The duration of treatment with study drug will depend on individual tolerance and evidence of disease progression to a maximum of 52 weeks after surgery.

Participants meeting the following criteria will be removed from the study:

- Unacceptable adverse event(s) defined as: unexpected grade 3 events or higher during Stage 1 that are unresponsive to dose modifications and deemed possibly, probably or definitely related to study treatment.
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements.
- Participant decides to withdraw.
- Continuation not in the best interest of participant, or as otherwise determined by investigator.
- Participant is replaced according to criteria (Section 3)

When participants are removed from protocol therapy, the reason and date of removal from protocol therapy will be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, treating investigator must immediately notify the overall PI, A. James Moser at (617)-632-1032.

5.6. Duration of Follow Up

If no criteria from Section 5.4 are met, study participants will be followed for 52 weeks unless:

- Participants removed from the study due to unacceptable adverse events attributed to study drug. Participants will be followed for 6-months or until resolution, stabilization or death even if this follow up would extend beyond 52 weeks after surgery.

- Subjects who are replaced for any reason during stages 1 or 2 will complete an end of treatment (EOT) visit per section 10. Participants who are replaced shall be followed solely to determine their vital status one year after surgery (± 4 weeks).

5.7. Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up defined as lack of subject response to three attempted contacts by the study team after the first missed visit specified in the study calendar
- Withdrawal of consent for data submission
- Death

Participant will be replaced or removed from study according to criteria listed in Section 3 and section 5.7.

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSE MODIFICATIONS

Rationale for Dose Modifications
The objective of Stage 1 is to distinguish adverse events associated with pancrelipase from toxicity caused by standard of care surgery or untreated pancreatic exocrine insufficiency. As a result, adverse events and toxicity will be assessed only during Stage 1. Dose modifications will only be made during Stage 1.

Dose modifications may be made during Stage 2 only after discussion with a treating clinician delegated to do so by the principal investigator on the delegation of authority log. When adjuvant treatment is held, study drug may also be withheld at the discretion of the treating physician. The maximum permissible delay in completing adjuvant treatment is 30 days. In parallel, the maximum duration of time that pancrelipase can be held during stage 2 is 30 cumulative days.

Adverse event toxicity during study drug administration may be indistinguishable from the symptoms of undertreated exocrine pancreatic insufficiency. For example, the side effects of weight loss, abdominal distension, diarrhea, flatulence, early satiety, and nausea may indicate undertreated EPI. Because there is no standard efficacious dose of Zenpep (pancrelipase), and

because no standard tests allow Zenpep (pancrelipase) therapy to be monitored/tailored, we have developed a dose modification algorithm to adapt Zenpep (pancrelipase) dosing to symptoms of EPI while minimizing the risks of study-drug related toxicity.

Dose Modification Algorithm
The lowest dose permissible to stay on study is 25,000U of pancrelipase per meal or snack.

Treatment modifications are based on specific safety criteria. Participants will delay or discontinue pancrelipase if they experience a Grade 3 adverse event, specified below, determined to be probably or definitely related to pancrelipase. We encourage early evaluation to identify if a dose reduction or a dose increase should be performed, as indicated in the following management tables and event specific guidelines. After a dose reduction, pancrelipase cannot be escalated.

Please use these participant management tables and algorithms to determine dosing delay, restarting doses, dose increase or discontinuation:

In the event that a participant experiences several adverse events, and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.

Table 1. Dose Modifications for Zenpep (pancrelipase)

<u>Gastrointestinal Disorders</u>	
Flatulence	
Grade 1	Maintain dose level
Grade 2	See Appendix C for algorithm
Diarrhea	
Grade 1	Maintain dose level
Grade 2	See Appendix C for algorithm
Grade 3	See Appendix C for algorithm
Grade 4	See Appendix C for algorithm
<u>Neurologic Disorders</u>	
Headache	
Grade 1	Maintain dose level

Grade 2	Decrease every meal dose by 25,000 unit [#]
Grade 3 or higher	Discontinue drug

Respiratory Disorders

Cough

Grade 1	Maintain dose level
Grade 2	Decrease every meal dose by 25,000 units [#]
Grade 3	Discontinue drug

Skin Disorders

Pruritus

Grade 1	Maintain dose level
Grade 2	Decrease every meal dose by 25,000 units [#]
Grade 3	Discontinue Drug

Urticaria

Grade 1	Maintain dose level
Grade 2	Hold until Grade 1 or resolved
Grade 3	Discontinue Drug

General System Disorder

Weight loss

Grade 1	Maintain dose level
Grade 2	Assessment by study staff*. If EPI, increase dose to 150,000 IU per meal[◊]. If AE, hold until < Grade 2
Grade 3	Hold Drug*

* Recommended management: see General System Disorder AE management algorithm (Appendix C)
# The snack dose will remain 25,000 units when the meal doses drop by 25,000 units

◊ In the case of the dose increase to 150,000 units per meal, the snack dose should always be one third of the prescribed meal dose.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

These AE (adverse event) management guidelines are intended to ensure the safety of each participant while attempting to characterize the safety and tolerability of Zenpep (pancrelipase) after surgery. In agreeing to the provisions of this protocol, the Investigators of this investigator-initiated trial accept all responsibilities for prompt notification of serious adverse events (SAEs) listed below to Allergan and the appropriate regulatory authorities as described below.

Definitions:

> **Adverse event**: Any untoward medical occurrence associated with the use of the study drug.
>
> **Unexpected**: the adverse event is not listed or the specificity or severity that has been observed is not listed.

7.1. Expected Toxicities

Suspension of Adverse Event Reporting after Standard of Care Surgery
Adverse event reporting shall be suspended from the date of surgery until the date that study drug is restarted. All adverse events occurring between those dates shall be attributed to standard of care adverse events caused by surgery.

Participants are observed during stage 1 to monitor their recovery until POV#2, at which time participants must either restart study drug or be replaced due to delayed postoperative recovery. Post-operative morbidity in this group of patients is frequent, reaching a rate as high as 40%. Some of the most frequent complications can be found below:

Post Pancreatectomy Complications Overlapping with Possible Adverse Events

- Abdominal Pain – Post Operative Pain
- Flatulence –surgery-induced changes in gastrointestinal function or Clostridium difficile infection
- Diarrhea –surgery-induced changes in gastrointestinal function or Clostridium difficile infection
- Abdominal Distension - delayed gastric emptying and pancreatic leak

- 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)

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

Fibrosing Colonopathy
Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products. Fibrosing colonopathy is a rare serious adverse reaction initially described in association with high-dose pancreatic enzyme use, usually with use over a prolonged period of time and most commonly reported in pediatric patients with cystic fibrosis. The underlying mechanism of fibrosing colonopathy remains unknown. Patients with fibrosing colonopathy should be closely monitored because some patients may be at risk of progressing to stricture formation. It is uncertain whether regression of fibrosing colonopathy occurs.

Potential for Irritation to Oral Mucosa
Care should be taken to ensure that no drug is retained in the mouth. Zenpep should not be crushed or chewed or mixed in foods having a pH greater than 4.5. These actions can disrupt the protective enteric coating resulting in early release of enzymes, irritation of oral mucosa, and/or loss or enzyme activity. Recommendations about administration of Zenpep are detailed in Section 5.2.

Potential for Risk of Hyperuricemia
Caution should be exercised when prescribing Zenpep to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels.

Allergic Reactions
Caution should be exercised when administering pancrelipase to a patient with a known allergy to proteins of porcine origin. Rarely, severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported with other pancreatic enzyme products with different formulations of the same active ingredient (pancrelipase). The risks and benefits of continued Zenpep treatment in patients with severe allergy should be taken into consideration with the overall clinical needs of the patient.

7.3. Grading and Attribution of Adverse Events

Adverse event reporting begins on the date that study drug is resumed during stage 1.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

- Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

Algorithm for Assigning Causality of Adverse Events during Stage 1

- All AEs ≥Grade 3 will be reviewed with the surgeon/co-investigator to assess clinical significance and determine if the event is an expected toxicity from surgery. AE and SAE grading, attribution and reporting will be performed by the Investigators and discussed with the treating surgeon as this time period overlaps with the participant's postoperative recovery process. SAEs occurring as a result of planned admissions for surgical resection and related standard of care interventions will not be considered or reported as an SAE. SAEs occurring in the process of readmissions after surgical resection and related standard of care interventions will not be considered or reported as an SAE unless attributed to study drug.

- If the AE is not determined to be a standard surgical toxicity, surgeon/co-investigator will assess whether the AE is "possibly", "probably" or "definitely" related to exocrine pancreatic insufficiency. If the AE is determined to be "possibly", "probably" or "definitely" related to pancreatic insufficiency, the dose may be modified per table 1. If after two dose modifications, the AE does not resolve, it will be assumed that the AE is attributed to Zenpep, not pancreatic insufficiency.

- If AE is not "possibly", "probably" or "definitely" related to pancreatic insufficiency, the AE will be attributed to Zenpep therapy and will be reported as per DF/HCC SAE reporting requirements.

Adverse Event Monitoring during Stage 2

Study drug toxicity and dose modifications are completed during stage 1. Adjuvant treatment is prescribed according to standard of care guidelines in stage 2. As a result, no AEs or SAEs will be collected or reported during adjuvant treatment. Early disease recurrence is the only monitored toxicity.

Participants will be evaluated monthly during stage 2 to monitor early disease progression. All participants will return to BIDMC every three months for re-evaluation and routine oncological care including re-staging imaging as delineated in the study calendar.

For participants receiving their adjuvant treatment at BIDMC, monthly study visits to assess the progress of treatment and adherence/dispensing of study drug will occur in conjunction with routine SOC treatment. The study team will consult with the treating physician(s) and

Electronic Medical Records to perform study-related activities and ascertain completion of adjuvant chemotherapy.

For participants receiving adjuvant treatment outside of BIDMC, the study team will contact participants monthly to complete study calendar activities over the telephone. Monthly, participants will receive by mail a new drug diary, one month's supply of study drug, and

7.4. Reporting of an adverse event or serious adverse event:

Zenpep (pancrelipase) is approved by the FDA for pancreatic enzyme insufficiency and its side effects are known. Only the following AEs will be reported:

- known expected AEs that do not qualify as standard of care complications, and
- unexpected grade 3 or higher AEs (section 7.3).
  Reporting of these AE/SAEs will be done per DF/HCC Adverse Event reporting policy. SAEs have to be reported up to 30 days post last dose of study medication.

The Investigator should evaluate all expected and unexpected AEs (section 7.3) and make an immediate effort to determine their etiology. Participants continuing to experience toxicity at the end of stage 1 (start of adjuvant therapy or postoperative week 12, whichever comes first) may be contacted for additional assessment until the toxicity has resolved or is deemed irreversible.

Adverse events and serious adverse event reporting is limited to stage 1 prior to participant initiation of adjuvant treatment.

Study medications may be interrupted for an AE at the discretion of the Investigator. Participants requiring toxicity management should be assessed and evaluated at least monthly as indicated by the severity of the event

7.3. Expedited Adverse Event Reporting

7.3.1. Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form. An exception to this are AEs reported on the CAEPR list. SAEs will be reported per DF/HCC reporting policy.

7.3.2. DF/HCC Expedited Reporting Guidelines

BIDMC Investigators will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.4. Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

Non-serious (Grade 1-2) AEs will not be reported routinely. All unexpected Grade 3 or higher AEs that are classified as Possible, Probable or Definite will be reported. All unexpected Grade 4 AEs will be reported. All Grade 5 AEs will be reported. An exception to this are AEs reported on the CAEPR list or those occurring during or as a result of standard of care hospitalizations. However, AEs that are determined to be unlikely or unrelated to study drug, Zenpep (pancrelipase), will not be reported and do not require further evaluation.

7.5. Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with Zenpep (pancrelipase) can be found in Section 7.1. Pancrelipase is provided as investigational drug Zenpep by Allergan PLC.

8.1. Zenpep

8.1.1. Description

Zenpep (pancrelipase) is a combination of porcine-derived lipases, proteases, and amylases. The pancreatic enzymes in Zenpep (pancrelipase) catalyze the hydrolysis of fats to monoglycerides, glycerol, and free fatty acids, protein into peptides and amino acids, and starch into dextrins and short chain sugars such as maltose and maltriose in the duodenum and proximal small intestine, thereby acting like digestive enzymes physiologically secreted by the pancreas.

The pancreatic enzymes in Zenpep (pancrelipase) are enteric-coated to minimize destruction or inactivation in gastric acid. Zenpep (pancrelipase) is designed to release most of the enzymes in vivo at pH greater than 5.5. Pancreatic enzymes are not absorbed from the gastrointestinal tract in any appreciable amount.

Zenpep (pancrelipase) will be provided in 25,000 units of lipase/pill capsules. Participants will use 3 capsules (75,000 units total) per meal and 1 capsule (25,000 units) per snack initially. Dosing will be adjusted per symptoms as described in section 6. Participants will be supplied with a sufficient supply on the initial visit to last through the second post op visit. Subjects will be supplied in one month increments on subsequent visits.

8.1.2. Form

Zenpep (pancrelipase) will be provided in 25,000 units of lipase/pill capsules. Each Zenpep (pancrelipase) capsule is available as a two piece hypromellose capsule with blue opaque cap and white body with a blue radial print.

Zenpep is manufactured and will be provided by Allergan Inc.

8.1.3. **Storage and Stability**

Avoid excessive heat. Store at room temperature (68-77°F; 20-25°C), brief excursions permitted to 15-40°C (59-104°F). Protect from moisture. After opening, keep bottle tightly closed between uses to protect from moisture.

8.1.4. **Compatibility**

Zenpep (pancrelipase) should be taken with meals or snacks, with sufficient fluid (8oz). Pancrelipase capsules and capsule contents should not be crushed or chewed. Capsules should be swallowed whole. For participants who are unable to swallow intact capsules, the capsules may be carefully opened and the contents sprinkled on small amounts of acidic soft food of pH 4.5 or less (e.g., commercially available preparations of bananas, pears and applesauce).

The pancrelipase-soft food mixture should be swallowed immediately without crushing or chewing, and followed with water or juice to ensure complete ingestion. Care should be taken to ensure that no drug is retained in the mouth.

8.1.5. **Handling**

Keep out of reach of children. Do not crush Zenpep (pancrelipase) delayed release capsules.

8.1.6. **Availability**

Zenpep will be distributed by Allergan Inc and provided free of charge for this study. Zenpep is commercially available.

8.1.7. **Preparation**

Zenpep (pancrelipase) comes in capsules and should be swallowed whole with water or other liquid with a meal (breakfast, lunch, dinner and snack). For participants who are unable to swallow intact capsules, the capsules may be carefully opened and the contents sprinkled on small amounts of acidic soft food of pH 4.5 or less (e.g., commercially available preparations of bananas, pears and applesauce).

8.1.8. **Administration**

Zenpep (pancrelipase) dose will initially be 75,000 lipase units/meal (3 pills) and 25,000 lipase units/snack (1 pill). Pancrelipase must be swallowed whole and taken with water or any liquid; if participant is not able to swallow pancrelipase content may be sprinkled on small amounts of

soft acidic food (e.g. applesauce). If a participant misses a dose, the next dose should be taken on schedule with the next snack or meal. In case of a vomited dose, participant should take next scheduled dose with next snack or meal. Recommendations about administration of Zenpep are detailed in Section 5.2.

8.1.9. **Ordering**

Zenpep will be ordered by qualified personnel at BIDMC directly from Allergan Inc.

8.1.10. **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

8.1.11. **Destruction and Return**

Unused or expired pancrelipase will be destroyed on site per pharmacy regulations. Investigators must maintain proper drug accountability records in the site master file.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

No correlative studies will be performed.

STUDY CALENDAR

Table 10.1. Schedule of Assessments during Stage 1

POV 3[D]	**POV 4[D]**
Week 8[B]	Week 12[B,D]
± 7 Days[C]	± 7 Days[C]

X	X													
X	X													

	X	X	X
	X	X	X
	X	X	X
		X[I]	

		X^D													
		X^D													

ss2 Rubydrugmentcriteria Suspe nd		X X	X	X				Suspend						X^D	
	X	X	X												
	X^E														

A. Screening assessments must be completed within 30 days prior to registration. Ca19-9 and fecal elastase specimens will be obtained before pancrelipase is initiated. None of these results need to be available prior to registration or initiation of pancrelipase as the decision to perform surgery is made per SOC and the study drug is FDA approved.

B. Timing of post-operative visit 1during stage 1 should occur 2 weeks after date of hospital discharge. If subject was not sufficiently recovered at two weeks post-surgery to be discharged, POV 2, which is to

occur 4 weeks post-surgery may be omitted and the next study visit a subject will complete is POV 3 (8 weeks ±7days post date of surgery).

C. The postoperative visit schedule is determined per SOC. If a planned POV falls outside the scheduled study visit window by more than 7 days, study staff shall contact the surgeon and negotiate a follow-up visit within the prescribed visit window. However, it will not be considered a protocol deviation if the visit cannot be scheduled in the ±7 day window.

D. Assessments prior to the initiation of adjuvant treatment may be performed at POV #3 or POV #4 (±7 days) depending on the patient's rate of recovery. If adjuvant treatment starts before POV#4, POV#4 may be skipped from the stage 1 study calendar.

E. EOT (End of Treatment) during stage 1 applies to subjects meeting replacement criteria in Section 3.3.4. In addition to planned POV assessments, EOT requires collecting the study drug and drug diary.

F. Study drug will be dispensed to subjects in person or by mail at any time after registration. Study drug will be held from the day of surgery until reassessment upon discharge (±7 days from discharge) or POV#1 if patient's are not fit to restart pandrelipase at hospital discharge (Section 5).

G. Imaging and Ca19-9 are ordered per SOC prior to surgery; visit windows do not apply.

H. Pre-Operative Labs include: CBC, glucose, blood urea nitrogen (BUN), total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), sodium, potassium, chloride, bicarbonate, creatinine.

I. These tests must be performed once during stage 1 but may be done at any POV; POV#1 is preferred.

Table 10.2 Stage 2 Study Calendar**Visit**[a]	**Week 16**[c]	**Week 20**[c]	**Week 24**[b]	**Week 28**[c]	**Week 32**[c]	**Week 36**[b]	**Week 40**[c]	**Week 44**[c]	**Week 48**[c]	**Week 52**[b] **or EOT**[D]	**Follow Up**[d]
Visit Window	±7 days										
Pancrelipase Therapy	X	X	X	X	X	X	X	X	X	Stop	
Dispense Pancrelipase	X	X	X	X	X	X	X	X	X	Retrieve Drug	
Interval History	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X
ECOG Status	X	X	X	X	X	X	X	X	X	X	X
Grip Strength			X			X				X	
EQ-5D-5L			X			X				X	
Imaging[e]			X			X				X	
Ca19-9			X			X				X	
Uric Acid										X	
Albumin			X			X				X	
HbA1c			X			X				X	
Fecal elastase 1										X	
Review medication diary	X	X	X	X	X	X	X	X	X	X	
Monitor disease progression[f]	X	X	X	X	X	X	X	X	X	X	
Contact Treating Oncologist[g]	X	X	X	X	X	X	X	X	X	X	X

a. Visit dates in Stage 2 are counted from the date of surgery.

b. Study visit must occur at BIDMC regardless of the location at which SOC adjuvant therapy is being provided.

c. Study visit conducted by telephone for participants receiving adjuvant treatment at non-DFHCC locations. The study team will retrieve medical records from the treating physician to determine symptoms, physical findings, weight data, treatment records, laboratory studies, and interval imaging which may indicate disease progression or alterations/delays/or cancellations of adjuvant therapy. Participants will receive a new medication diary and study drug via mail every month. A stamped, self-addressed envelope will be provided for returning unused study drug and the medication diary for review by study staff.

d. EOT visit will be completed for all subjects completing the study or meeting stopping criteria in Section 5.4. EOT assessments will be done instead of scheduled assessments. EOT will be performed for all subjects completing treatment at week 52.

e. Imaging prescribed per SOC; visit windows are not applicable to imaging. Available imaging studies will be reviewed by TIMC.

f. Disease progression assessed per section 3

g. The intended adjuvant therapy regimen, including duration and number of cycles, will be ascertained from the treating medical oncologist and recorded prior to the start of adjuvant therapy. Intended fractions of radiation therapy will also be obtained from the treating radiation oncologist prior to initiating radiation therapy.

10. MEASUREMENT OF EFFECT

10.1. Initiation and Completion of Adjuvant Therapy

The primary endpoint is completion of adjuvant therapy (a discrete binary variable).

Completion of Adjuvant Treatment

Definition of Evaluable
In order to be evaluable for the primary endpoint, participants must begin adjuvant treatment by postoperative week 12. After receiving a single dose of adjuvant therapy, subjects are considered evaluable for the primary endpoint and will be assessed for completion of adjuvant therapy at each study visit.

Definition of Completion of Adjuvant Treatment (Treatment Naïve)
The completion rate is defined as the percentage of subjects who initiate adjuvant therapy by postoperative week 12 and complete all predefined adjuvant therapy course without radiographic evidence of disease progression satisfying RECIST 1.1 criteria. Tumor markers and clinical evidence of disease progression must be confirmed by imaging studies reviewed by TIMC. Disease progression cancels adjuvant treatment by definition and makes participants unevaluable for the primary endpoint.

Participants must receive all intended cycles of standard of care chemotherapy as well as all intended fractions of radiation to satisfy the primary endpoint. Four weeks of treatment delays is permitted. When treatment is held, Zenpep may also be held. Treatment delays and omissions ordered by the treating physician are permissible as long as participant completes adjuvant treatment by the end of week 40 after surgery and delays do not exceed four weeks.

Therefore: completion of fewer than 6 intended cycles of chemotherapy, or not completing 6 cycles of adjuvant chemotherapy by week 40 after surgery, or not completing all intended fractions of radiation therapy will be considered failure to complete adjuvant treatment.

Definition of Completion of Adjuvant Treatment (after Preoperative Treatment)
Neoadjuvant patients are eligible so long as additional adjuvant treatment is planned before surgery is performed. Participants who have received all intended multimodality therapy in the preoperative setting shall be ineligible.

The completion rate shall be defined as the percentage of subjects who initiate adjuvant therapy by postoperative week 12 and complete all predefined adjuvant therapy course without radiographic evidence of disease progression satisfying RECIST 1.1 criteria. Tumor markers and clinical evidence of disease progression must be confirmed by imaging studies reviewed by TIMC. Disease progression cancels adjuvant treatment by definition and makes participants unevaluable for the primary endpoint.

The required completion date for adjuvant treatment among neoadjuvant participants shall not exceed the duration of intended cycles plus a 4 week delay. Adjuvant treatment must begin by

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.

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

largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progressive disease (PD) based on a new lesion.
(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at

follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.
Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm progressive disease when biopsies are obtained or to determine recurrence following surgical resection.

Tumor markers. Tumor markers alone cannot be used to assess recurrence of disease.

10.4. Initiation of adjuvant therapy

Participants will be assessed by their treating oncologist prior to initiating adjuvant therapy. The selection of the specific standard of care adjuvant therapy regimen will be at the discretion of the treating oncologist and may include systemic chemotherapy as well as radiation. Initiation of adjuvant treatment will be defined as date participant receives the first dose of standard of care adjuvant therapy. This will be determined by chart review of participant's oncologic records and phone call by research nurse to treating medical oncologist. The intended adjuvant therapy regimen, which must begin by the end of week 12, will be specified in the CRF and will specify the intended chemotherapy regimen and number of intended cycles as well as the number of intended fractions of radiotherapy, if any.

Patients who do not start adjuvant treatment by the end of week 12 will be considered as failure to initiate chemotherapy.

10.5. Evaluable for toxicity.

All participants are evaluable for toxicity from the time of their first treatment with pancrelipase until end of Stage 1. No toxicities of SOC adjuvant treatment will be

monitored. The only monitored outcome is early disease progression, defined as radiographic evidence of progressive disease defined by RECIST 1.1 prior to completion of adjuvant treatment.

10.6. Assessment of pancreatic enzyme insufficiency

Fecal elastase 1 specimens will be obtained for analysis before initiation of pancrelipase at time of enrollment as well as at weeks 12 and 52. Note: the results of the fecal elastase testing do not need to be available prior to enrollment.

10.7. Assessment of nutrition status

This will be assessed via preoperative albumin and then with postoperative levels drawn once again as specified in the study calendars (10.1 and 10.2). Weight will also be documented as specified in the study calendar (10.1 and 10.2).

10.8. Quality of Life Assessments

Quality of life assessments will be done utilizing the EORTC EQ-5D-5L as specified in the time periods dictated in the study calendar (10.1 and 10.2).
EORTC EQ-5D-5L Questionnaire: Please see Appendix A

10.9. Functional assessments

Grip Strength: Evaluation of grip strength using a handgrip dynamometer will take place per the study calendar (10.1 and 10.2) and will be correlated with quality of life and functional assessments.

ECOG performance scale: Please see Appendix B

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

11.1. Data Reporting

11.1.1. Method

Data will be collected, stored and managed using the secure electronic data capture application InForm supported by the Clinical Trials Research Informatics Office (CTRIO) at DFHCC and employing secure BIDMC network.

11.2. Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

11.3. Multicenter Guidelines

N/A

12. STATISTICAL CONSIDERATIONS

12.1. Study Design/Endpoints

This is a single institution, single arm, open label, phase II clinical trial of pancrelipase (Zenpep) on subjects with resectable pancreatic cancer. Sixty-seven subjects will be enrolled prior to pancreatic resection in order to have 39 evaluable subjects to assess the primary endpoint.

The primary endpoint is completion of adjuvant therapy (a discrete binary variable).

The study will have a 2-stage design:

Stage 1: Post-operative recovery and initiation of adjuvant therapy
Starting at screening and lasting until POV 4 or initiation of adjuvant therapy, whichever comes first. This will encompass surgery and recovery time. This stage will evaluate the frequency of adverse events in response to study drug and the rate of initiation of adjuvant therapy.

Stage 2: Progression monitoring and completion rate of adjuvant therapy
Starting after POV 4 or start of adjuvant therapy, whichever comes first, and lasting until last follow up visit in week 52 after surgery. This stage will encompass completion of adjuvant therapy and monitoring for disease progression.

Participants who meet stage 1 eligibility criteria (section 3) will be started on pancrelipase (Zenpep) as defined in section 5. Pancrelipase will start at the standard dose of 75,000 units/meal and 25,000/snack. Participants will receive therapy for a maximum of 52 weeks

after surgery, or until meeting criteria for discontinuation (section 5). Pancrelipase treatment will be held on the day of surgery and resumed during postoperative follow-up (POV #1). Stage 1 replacement criteria will be assessed at POV #1 and POV#2. Subjects meeting stage 1 replacement criteria shall discontinue study medication and will be replaced.

Participants will be allowed to pursue adjuvant therapy at non-DFHCC sites.Subject stage 2 replacement criteria will be assessed prior to initiating adjuvant treatment or at POV 4, whichever comes first. Subjects who meet develop early disease progression will be replaced.

Adherence with study medication will be assessed by participant diary and pill counts by the study staff, conducted either in person for BIDMC or remotely via telephone for non-BIDMC patients to maximize participant convenience.

Stopping Rule
A Simon 2 stage design futility analysis will be conducted within the first 23 evaluable participants that have begun adjuvant therapy. If 12 participants complete adjuvant therapy, the study will continue. If only 11 complete adjuvant therapy, the trial will be stopped. If the study is not stopped for futility an additional 16 participants will be enrolled and evaluated. At the end of the trial if 24 or more participants have completed adjuvant therapy the trial will be declared having met its primary endpoint objective.
There is also a disease progression rule while on adjuvant therapy because theoretically improved nutrition can cause cancer cells to grow. If greater than 16 participants experience disease progression based on RECIST criteria while on adjuvant therapy, the trial will be stopped. This is based on a 40% historical rate of disease progression while on adjuvant therapy.[5]

12.2. Sample Size, Accrual Rate and Study Duration

The sample size is 39. This is based on detecting a 40% relative improvement in adjuvant therapy completion rate using a Simon's minimax two-stage design. Proportion response under the null is 50%. Proportion response under the alternative is 70% (or greater). Power is set to 90% and alpha is 10% (one-sided). Having a target completion rate of 70%.

Approximately 67 participants must be enrolled to meet the final needed 39 participants. This discrepancy is created by the need to have surgical pathology define tumor histology and allow subjects with inoperable tumors or prolonged surgical recovery to be replaced as they will be ineligible for the primary endpoint. Additionally, tolerance of an oral diet requires some time period following surgical resection. We anticipate accruing 3-4 participants/month. The anticipated time of accrual is approximately 2 years.

12.3. Interim Monitoring Plan

Interim monitoring plan specified above in Section 13.1.

12.4. Analysis of Primary Endpoints

Primary Endpoint: Completion rate of adjuvant therapy.

Completion of adjuvant therapy: Completion rate is defined as percentage of subjects who initiate adjuvant therapy by postoperative week 12 and complete all predefined adjuvant therapy course within the intended time frame allowing one month for treatment delays/holds.

For example, subjects receiving 6 months' adjuvant treatment are expected to complete all intended adjuvant treatment by week 40 (12 weeks during stage 1; 24 weeks for adjuvant treatment, with 4 weeks total treatment delay.

For participants receiving neoadjuvant treatment lasting three months, the intended time frame for adjuvant treatment is shortened by 12 weeks and must be complete by week 28 (12 weeks stage 1; 12 weeks stage 2 plus 4 weeks total treatment delay).

Subjects who experience disease progression during treatment are excluded from this assessment as disease progression cancels adjuvant treatment by definition and makes participants unevaluable for the primary endpoint.

12.5. Analysis of Secondary Endpoints

This study has several secondary endpoints:

(1) **Initiation rates of adjuvant therapy:** Initiation of standard of care adjuvant treatment will be defined as subject receiving the first planned dose of adjuvant therapy by post-operative week 12. This rate will be estimated with a 95% confidence interval. A one-sample binomial test will be performed to compare the initiation rates to historical control values of initiation rates of adjuvant therapy.
(2) **Measurement of subject adherence to pancreatic enzyme replacement therapy**: This assessment will be conducted through participant diaries and pill counts. This will be conducted starting at the first post-operative visit (POV) and then every 28 days ±7 days following that point. The rate of adherence to pancreatic enzyme replacement will be estimated and a 95% confidence interval provided.
(3) **Investigate whether pancreatic enzyme replacement therapy improves postoperative nutrition status:** This will be assessed via pre-treatment albumin and albumin at 12, 24,36, and 52 weeks, weight gain/loss at monthly visits. Measurements of albumin and weight will be analyzed with descriptive statistics such as means (or medians) and 95% confidence intervals (or interquartile ranges) depending on the distribution of the measure.
(4) **Evaluate quality of life, measured via EQ-5D-5L Questionnaire (Appendix A) at weeks 2, 4, 8, 12, 24, 36 and 52 week following surgery**. Questionnaire will be analyzed and descriptive statistics, means and 95% confidence intervals will be presented overall and by adjuvant therapy completion status. Participants who complete adjuvant therapy versus those who do not complete adjuvant therapy will be compared using two-sample t-tests.

(5) **Monitor the incidence and severity of postoperative complications:** Postoperative complications will be graded via the Clavien-Dindo surgical complications grading system on day 90 after the date of surgery (Appendix E) and analyzed with descriptive statistics.
(5) **Grip strength measurement during initial visit to perform correlation with post-operative nutrition and quality of life status**.
(6) **For participants receiving neoadjuvant therapy, survival measures will commence on the day of their first dose of neoadjuvant treatment.**
(7) **For patients undergoing surgery as their first cancer-directed therapy, survival measures begin on the day of surgery.**

12.6. Reporting and Exclusions

12.6.1. Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment with pancrelipase through Stage 1 of the study.

15. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-review journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcome should be made public no later than three (3) years after the end of the study.

REFERENCES

1. Neoptolemos JP, Moore MJ, Cox TF, et al: Effect of Adjuvant Chemotherapy with Fluorouracil Plus Folinic Acid or Gemcitabine vs. Observation on Survival in Patient with Resected Periampullary Adenocarcinoma: The ESPAC-3 Periampullaru Cancer Randomized Trial. JAMA 308:147-156, 2012

2. Oettle H NP, Hochhaus A, Thomas-Hartmann J, Gellert K, Ridwelski K, NiedergethmannNm, Zulke C, Fahlke J, Arning MB, Sinn M, Hinke A, Riess H: Adjuvant Chemotherapy with Gemcitabine and Long-term Outcomes Among Patients with Resectable Pancreatic Cancer: The CONKO-001 Randomized Trial. JAMA 310:1473-81, 2013

3. Davila JA CE, Hasche JC, Peterson NJ, McGlynn KA, Shaib YH: Utilization and determinants of adjuvant therapy among older patients who receive curative surgery for pancreatic cancer. Pancreas 38:e18-25, 2009

4. McDade TP HJ, Simons JP, Piperdi B, Ng SC, Zhou Z, Kadish SP, Fitzgerald TJ, Tseng JF: A national propensity-adjusted analysis of adjuvant radiotherapy in the treatment of resected pancreatic adenocarcinoma Cancer 1:3256-66, 2010

5. Valle JW, Palmer D, Jackson R, et al: Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. J Clin Oncol 32:504-12, 2014

6. Partelli S, Frulloni L MC, Bassi C, Barugola G, D'Onofrio M, Crippa S, Falconi M: Fecal elastase-1 is an independent predictor of survival in advanced pancreatic cancer. Dig Liver Dis 44:945-51, 2012

7. Gooden HM, White KJ: Pancreatic cancer and supportive care—pancreatic exocrine insufficiency negatively impacts on quality of life. Supportive Care in Cancer 21:1835-1841, 2013

8. Matsumoto J, Traverso L: Exocrine function following the whipple operation as assessed by stool elastase. J Gastrointest Surg 10:1225-9, 2006

9. de la Iglesia-García D, Huang W, Szatmary P, et al: Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis. Gut, 2016

10. Kanda M FT, Kodera Y, Nagai S, Takeda S, Nakao A: Nutritional predictors of postoperative outcome in pancreatic cancer. Br J Surg 98:268-74, 2011

11. Wooldridge JL, Heubi JE, Amaro-Galvez R, et al: EUR-1008 pancreatic enzyme replacement is safe and effective in patients with cystic fibrosis and pancreatic insufficiency. J Cyst Fibros 8:405-17, 2009

12. Stern RC, Eisenberg JD, Wagener JS, et al: A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. Am J Gastroenterol 95:1932-8, 2000

13. Sabater L, Ausania F, Bakker OJ, et al: Evidence-based Guidelines for the Management of Exocrine Pancreatic Insufficiency After Pancreatic Surgery. Ann Surg 264:949-958, 2016

14. Saito T, Hirano K, Isayama H, et al: The Role of Pancreatic Enzyme Replacement Therapy in Unresectable Pancreatic Cancer: A Prospective Cohort Study. Pancreas Publish Ahead of Print, 9000

APPENDIX A EQ-5D-5L Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- ☐ **I have no problems in walking about**
- ☐ **I have slight problems in walking about**
- ☐ **I have moderate problems in walking about**
- ☐ **I have severe problems in walking about**
- ☐ **I am unable to walk about**

SELF-CARE

- ☐ **I have no problems washing or dressing myself**
- ☐ **I have slight problems washing or dressing myself**
- ☐ **I have moderate problems washing or dressing myself**
- ☐ **I have severe problems washing or dressing myself**
- ☐ **I am unable to wash or dress myself**

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- ☐ **I have no problems doing my usual activities**
- ☐ **I have slight problems doing my usual activities**
- ☐ **I have moderate problems doing my usual activities**
- ☐ **I have severe problems doing my usual activities**
- ☐ **I am unable to do my usual activities**

PAIN / DISCOMFORT

- ☐ **I have no pain or discomfort**
- ☐ **I have slight pain or discomfort**
- ☐ **I have moderate pain or discomfort**

☐ **I have severe pain or discomfort**

☐ **I have extreme pain or discomfort**

ANXIETY / DEPRESSION

☐ **I am not anxious or depressed**

☐ **I am slightly anxious or depressed**

☐ **I am moderately anxious or depressed**

☐ **I am severely anxious or depressed**

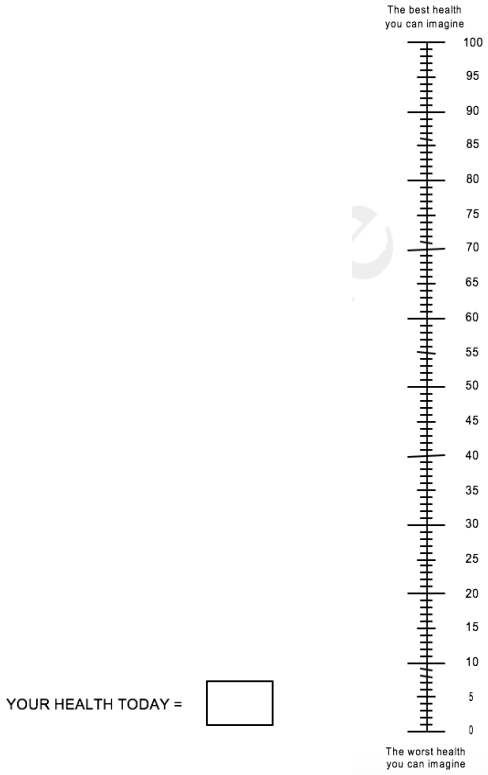
☐ **I am extremely anxious or depressed**

We would like to know how good or bad your health is TODAY. This scale is numbered from 0 to 100.

100 means the <u>best</u> health you can imagine. 0 means the <u>worst</u> health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

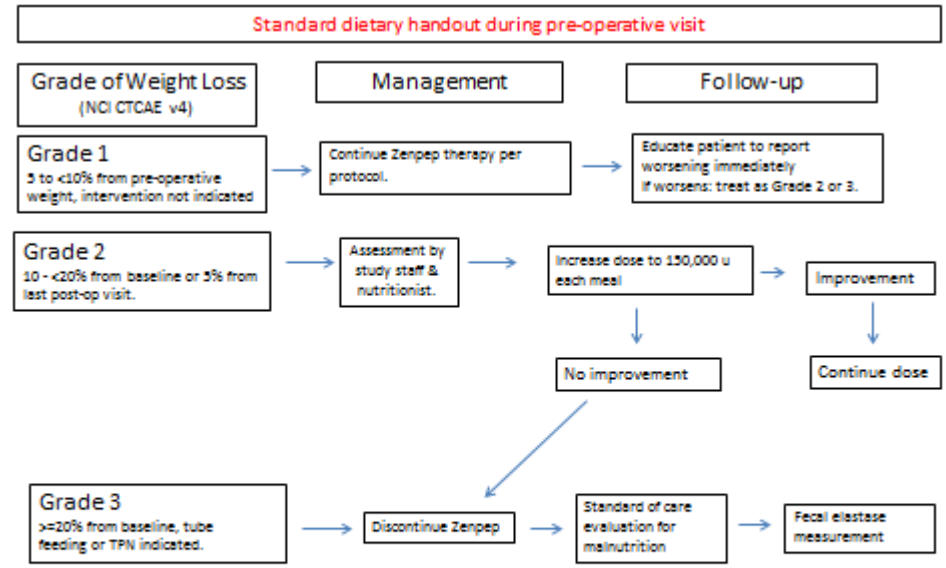
Now, please write the number you marked on the scale in the box below.

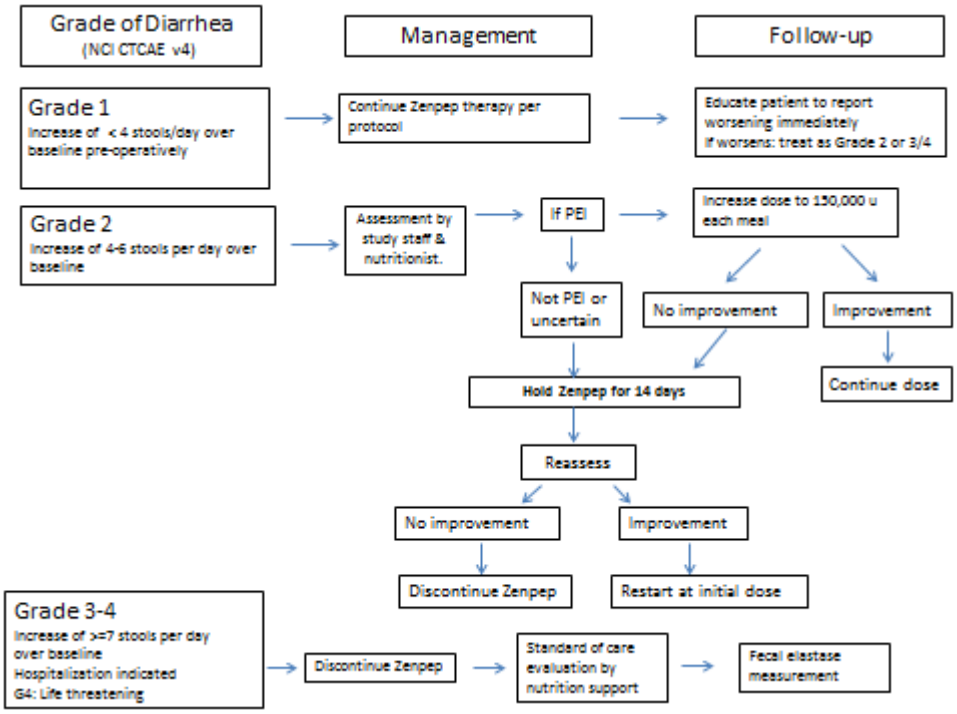


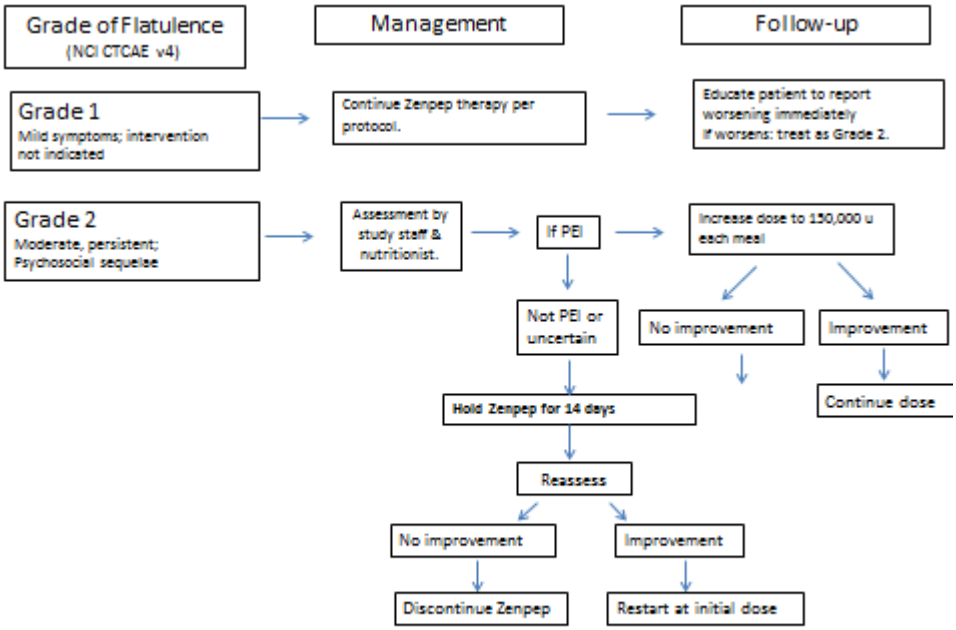
APPENDIX B: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX C Algorithm for Weight Loss, Diarrhea and Flatulence Management






Grade of Flatulence
(NCI CTCAE v4)
Management
Follow-up
Grade 1
Mild symptoms; intervention not indicated
Continue Zenpep therapy per protocol.
Educate patient to report worsening immediately
If worsens: treat as Grade 2.
Grade 2
Moderate, persistent; Psychosocial sequelae
Assessment by study staff & nutritionist.
If PEI
Increase dose to 150,000 u each meal
Not PEI or uncertain
No improvement
Improvement
Continue dose
Hold Zenpep for 14 days
Reassess
No improvement
Improvement
Discontinue Zenpep
Restart at initial dose

Appendix D – Clavien-Dindo Complication Index

Full Scale			Contracted Form	
Grades	Definition		Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.		**Grade I:**	Same as for Full Scale
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.		**Grade II:**	Same as for Full Scale
Grade III:	Requiring surgical, endoscopic or radiological intervention		**Grade III:**	Grades IIIa & IIIb
Grade III-a:	intervention not under general anesthesia			
Grade III-b:	intervention under general anesthesia			
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management		**Grade IV:**	Grades IVa & IVb
Grade IV-a:	single organ dysfunction (including dialysis)			
Grade IV-b:	multi organ dysfunction			
Grade V:	Death of a patient		**Grade V:**	Same as for Full Scale
Suffix 'd':	If the patients suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.			