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# Protocol for Study M16-142

# Indication: Exocrine Pancreatic Insufficiency (EPI) in Pancreatic Cancer Subjects

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| VERSION: | 3.0 | DATE: | 22 November 2019 |
| SPONSOR: | AbbVie Inc.* | NUMBER OF SITES: | Approximately 35 |
| ABBVIE INVESTIGATIONAL PRODUCT: | Pancrelipase – enteric-coated capsule – oral | | |

FULL TITLE: CREON® (pancrelipase) therapy for subjects with exocrine pancreatic insufficiency (EPI) due to pancreatic cancer: A double-blind, randomized, parallel design with 2 dose cohorts of pancrelipase in resected pancreatic cancer subjects and an open-label single dose cohort in non-resected pancreatic cancer subjects

Incorporating Version 1.0, Version 2.0, Administrative Change 1, and Version 3.0

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# 1 SYNOPSIS

| Title: CREON® (pancrelipase) therapy for subjects with exocrine pancreatic insufficiency (EPI) due to pancreatic cancer: A double-blind, randomized, parallel design with 2 dose cohorts of pancrelipase in resected pancreatic cancer subjects and an open-label single dose cohort in non-resected pancreatic cancer subjects | |
|---|---|
| **Background and Rationale:** | The clinical hypothesis is that appropriate pancreatic enzyme supplementation in subjects with pancreatic cancer and exocrine pancreatic insufficiency (EPI) will result in decreased stool fat and improvement in symptoms of EPI, which may improve nutrition status and chemotherapy tolerability. |
| **Objective and Endpoints:** | **Objective**:<br>Evaluate the effects of CREON® (pancrelipase) on stool fat and EPI symptoms in subjects with resected pancreatic cancer receiving 2 dosing regimens, and one dosing regimen in non-resected pancreatic cancer subjects.<br>**Endpoints**:<br>Efficacy<br>Primary<br>• Change in stool fat from Baseline (Day 1) to Week 1 (Day 8) for each dose cohort in resected subjects<br>Secondary<br>**Resected Subjects**<br>• Difference between 2 dose cohorts in change from Baseline in stool fat at Week 1<br>• Stool frequency at Weeks 1, 5, 9, and 13 comparing to Baseline, and the difference in change from Baseline to Week 1 between 2 dose cohorts<br>• Stool consistency at Weeks 1, 5, 9, and 13 comparing to Baseline, and the difference in change from Baseline to Week 1 between 2 dose cohorts<br>• EPI symptoms at Weeks 1, 5, 9, and 13 comparing to Baseline, and the difference in change from Baseline to Week 1 between 2 dose cohorts<br>• Quality of life (QoL) (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLQ]-C30 and QLQ-PAN26) at Weeks 1, 5, 9, and 13 comparing to Baseline, and the difference in change from Baseline to Week 1 between 2 dose cohorts<br>• Body weight and body mass index (BMI) at Weeks 1, 5, 9, and 13 comparing to Baseline<br>• Chemotherapy tolerability<br>• Serum albumin and serum pre-albumin at Weeks 5, 9 and 13 comparing to Baseline<br>Additional Endpoints<br>**Non-resected Subjects**<br>A subset of the analyses to be performed on the data for resected subjects will also be performed on the data for non-resected subjects. |

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| | • Change in stool fat from Baseline to Week 1<br>• Change in stool frequency from Baseline to Weeks 1, 5, 9, and 13<br>• Change in stool consistency from Baseline to Weeks 1, 5, 9, and 13<br>• Change in EPI symptoms from Baseline to Weeks 1, 5, 9, and 13<br>• Change in QoL (EORTC QLQ-C30 and QLQ-PAN26) from Baseline to Weeks 1, 5, 9, and 13<br>• Chemotherapy tolerability<br>• Change in the following measurements from Baseline to Weeks 1, 5, 9, and 13: body weight, and BMI<br>• Change from Baseline to Weeks 5, 9, and 13 for serum albumin, serum pre-albumin<br><u>Safety</u><br>Primary<br>• Adverse events (AEs) during study participation or the 30-day safety follow-up period. |
| **Investigators:** | Investigator information on file at AbbVie. |
| **Study Sites:** | Approximately 35 sites in the United States (US), including Puerto Rico |
| **Study Population and Number of Subjects to be Enrolled:** | Subjects with moderate to severe EPI due to pancreatic cancer,<br>72 resected subjects (36 per dose cohort) and up to 20 in the non-resected cohort. |
| **Investigational Plan:** | This will be a randomized, double-blind, 2-cohort study examining the efficacy and safety of 2 pancrelipase doses in subjects with EPI due to pancreatic cancer that has been resected. This study will include resected subjects who are post pancreatic cancer surgery and a single arm cohort in non-resected subjects.<br>The investigator may decide to exclude from participation any subject he or she considers unsuitable for this study |
| **Key Eligibility Criteria:** | Key eligibility criteria include:<br>• Male or female age ≥ 21 years<br>• Diagnosed cancer of the pancreas with biopsy and/or radiography, with a life expectancy of at least 5 months at Screening<br>• Subject's pancreatic cancer must involve the head and/or neck of the pancreas.<br>• Confirmed EPI as evidenced by fecal elastase-1 (FE-1) ≤ 150 µg/g stool at Screening<br>• A positive* Sudan stain for subjects without history of fat malabsorption [fat malabsorption defined as clinical steatorrhea, or measured stool fat greater than 7 g/day, or positive stool results by Sudan stain] within 1 week of Screening.<br>*Positive stool results are defined as increased level of neutral OR total fats (normal ranges are < 60 droplets/HPF and < 100 droplets/HPF, respectively). |
| **Study Drug and** | **1. Resected Subjects** |

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| **Duration of Treatment:** | At Day 1 eligible resected subjects will be randomized in 1:1 ratio to one of following dose cohorts, and will remain on blinded therapy throughout the study:<br>• Low dose (regimen of 12,000 USP units [Lipase] with meals/6,000 USP units [Lipase] with snacks)<br>• High dose (regimen of 72,000 USP units [Lipase] with meals/ 36,000 USP units [Lipase] with snacks)<br>At Weeks 1, 5, or 9, subjects who meet dose modification criteria maintained by the interactive response technology (IRT) will be titrated once to the following regimen in a blinded fashion:<br>• Subjects in the low dose cohort will escalate to the high dose (72,000 USP units [Lipase] with meals/36,000 USP units [Lipase] with snacks).<br>• Subjects in the high dose cohort will continue on the high dose (72,000 USP units [Lipase] with meals/36,000 USP units [Lipase] with snacks).<br>**2. Non-resected Subjects**<br>Resected and non-resected subjects will receive CREON (pancrelipase) delayed-release capsules administered daily with every meal and snack (72,000 USP units [Lipase] with meals/36,000 USP units [Lipase] with snacks). Subjects will participate in the study for up to approximately 177 days (Screening up to 56 days, double-blind, or open-label treatment up to 91 days, and up to a 30-day safety follow-up period). |
| **Date of Protocol Synopsis:** | 22 November 2019 |

# 2 INTRODUCTION

## 2.1 Background and Rationale

### Why Is This Study Being Conducted

Exocrine pancreatic insufficiency (EPI) is a debilitating condition that is caused by the inadequate secretion of pancreatic fluid containing digestive enzymes and bicarbonate needed for normal digestion and is commonly associated with a wide range of chronic diseases, including cystic fibrosis (CF), chronic pancreatitis (CP), and pancreatic cancer.

Evidence suggests that pancreatic enzyme replacement therapy (PERT) with pancrelipase is an acceptable approach for the treatment of patients with EPI and associated symptoms due to pancreatic adenocarcinoma, and PERT therapy may also improve nutrition, tolerance to chemotherapy, and quality of life in these patients.[1,2] Current treatment guidelines for management of pancreatic cancer recommend that pancrelipase should be used in patients with EPI, but additional information on dosing would be helpful.

Previous studies suggest that pancrelipase doses of 72,000 USP units (Lipase) per meal and 36,000 USP units (Lipase) per snack per day have a significant effect on decreasing stool fat and improving EPI symptoms.[3,4] The treatment duration of 5 days was selected as the minimum duration needed to detect potential differences in stool fat from Baseline (Day 1). Electronic diary entries of the EPI symptoms and food intake prior to each study visit will be used.

## 2.2 Benefits and Risks to Patients

EPI can be a serious and debilitating condition. Patients with EPI due to CF, CP, or pancreatectomy (PY) represent the major patient groups currently treated with pancrelipase and are the most studied populations in terms of maldigestion. The majority of information regarding the clinical symptomatology of the disease, the degree of enzyme supplementation, and the therapeutic perspectives are based upon our understanding of EPI in these diseases.

Pancrelipase was shown to be effective in the treatment of EPI as demonstrated in both placebo-controlled and long-term studies.[3-7] Coefficient of fat absorption (CFA) values—a measure of fat absorption—exceeding 80% were achieved and maintained in patients receiving pancrelipase, representing a highly significant difference from placebo in double-blind trials. In addition to a significant increase in CFA, a significant increase in the coefficient of nitrogen absorption (CNA)—a measure of protein absorption—was also observed, while the average stool frequency was lower compared to placebo.[3-7]

The short-term efficacy of CREON was evaluated in three Phase 3 studies conducted in 103 patients with EPI. Two studies were conducted in 49 patients with EPI due to CF; one study was conducted in 54 patients with EPI due to chronic pancreatitis or pancreatectomy.[8]

Fibrosing colonopathy (FC) is a complication that has been reported in patients with CF taking high doses of PERT (≥ 10,000 USP Units [Lipase]/kg/day).[9]

Potential risks, as described in the United States prescribing information (USPI) are as follows:

- To avoid irritation of oral mucosa, do not chew CREON or retain in the mouth.
- Exercise caution when prescribing CREON to patients with gout, renal impairment, or hyperuricemia.
- There is theoretical risk of viral transmission with all pancreatic enzyme products including CREON.
- Exercise caution when administering pancrelipase to a patient with a known allergy to proteins of porcine origin.
- Adverse reactions occurring in at least 2 cystic fibrosis patients (greater than or equal to 4%) receiving CREON during clinical trials are vomiting, dizziness, and cough.
- Adverse reactions that occurred in at least 1 chronic pancreatitis or pancreatectomy patient (greater than or equal to 4%) receiving CREON during clinical trials are hyperglycemia, hypoglycemia, abdominal pain, abnormal feces, flatulence, frequent bowel movements, and nasopharyngitis.

Overall, EPI, if untreated, may have serious adverse health consequences. No alternative treatments are available. When assessing the relation of the demonstrated efficacy of pancrelipase in several disease states associated with EPI, compared to the potential consequences of not treating EPI, the benefits of pancrelipase treatment outweigh the risks.

For further details, please see findings from completed studies, including safety data, in the CREON® (pancrelipase) United States Prescribing Information (USPI).[8]

# 3 STUDY OBJECTIVES AND ENDPOINTS

## 3.1 Objectives

Evaluate the effects of CREON® (pancrelipase) on stool fat and EPI symptoms in subjects with resected pancreatic cancer receiving 2 dosing regimens, and one dosing regimen in non-resected pancreatic cancer subjects.

## 3.2 Primary Endpoint

**Resected Pancreatic Cancer Subjects**

The primary endpoint is change in stool fat from Baseline (Day 1) to Week 1 (Day 8) for each dose cohort in Resected Subjects. Stool fat is collected during the 48 hours prior to the Day 1 and Week 1 visits.

## 3.3 Secondary Endpoints

**Resected Pancreatic Cancer Subjects**

- Difference between 2 dose cohorts in change from Baseline in stool fat at Week 1
- Stool frequency at Weeks 1, 5, 9, and 13 comparing to Baseline, and the difference in change from Baseline to Week 1 between 2 dose cohorts
- Stool consistency at Weeks 1, 5, 9, and 13 comparing to Baseline, and the difference in change from Baseline to Week 1 between 2 dose cohorts
- EPI symptoms at Weeks 1, 5, 9, and 13 comparing to Baseline, and the difference in change from Baseline to Week 1 between 2 dose cohorts
- Quality of life (QoL) (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLQ]-C30 and QLQ PAN26) at Weeks 1, 5, 9, and 13 comparing to Baseline, and the difference in change from Baseline to Week 1 between 2 dose cohorts
- Body weight and body mass index (BMI) at Weeks 1, 5, 9, and 13 comparing to Baseline
- Chemotherapy tolerability
- Serum albumin and pre-albumin at Weeks 5, 9 and 13 comparing to Baseline

## 3.4 Additional Endpoints

**Non-resected Pancreatic Cancer Subjects**

- Change in stool fat from Baseline to Week 1
- Change in stool frequency from Baseline to Weeks 1, 5, 9, and 13
- Change in stool consistency from Baseline to Weeks 1, 5, 9, and 13
- Change in EPI symptoms from Baseline to Weeks 1, 5, 9, and 13
- Change in QoL (EORTC QLQ-C30 and QLQ-PAN26) from Baseline to Weeks 1, 5, 9, and 13
- Chemotherapy tolerability
- Change in the following measurements from Baseline to Weeks 1, 5, 9, and 13:
  Body weight, and BMI
- Change in the following measurements from Baseline to Week 5, 9, and 13 for serum albumin and serum pre-albumin

## 3.5 Safety Endpoints

Safety evaluations include adverse event (AE) monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology, chemistry, and urinalysis) as a measure of safety and tolerability for the entire study duration.

The primary safety endpoint is AEs reported during study participation or the 30-day safety follow-up period. There are no adverse events of special interest (AESI) for pancrelipase in this study population.

# 4 INVESTIGATIONAL PLAN

## 4.1 Overall Study Design and Plan

The schematic of the study is shown in Figure 1. Details regarding study procedures are available in the Operations Manual.

See Section 5 for information regarding eligibility criteria.

This is a Phase 4, randomized, double-blind, parallel design study with 2 dose cohorts in resected subjects, and an open-label single dose cohort in non-resected subjects with EPI due to pancreatic cancer.

Resected subjects are defined as subjects who had a surgery to remove the pancreatic cancer.

Non-resected subjects are defined as unresectable, resectable, and borderline resectable or pancreatic cancer subjects who did not have a pancreatectomy of the cancer and do not plan to undergo such a surgery during study participation.

At Day 1, eligible resected subjects will be randomized in 1:1 ratio to one of following dose cohorts, and will remain on blinded therapy throughout the study:

1. Low dose (regimen of 12,000 USP units (Lipase) with meals/6,000 USP units (Lipase) with snacks)
2. High dose (regimen of 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks)

At Weeks 1, 5, or 9, subjects who meet dose modification criteria maintained by the IRT will be titrated once to the following regimen in a blinded fashion:

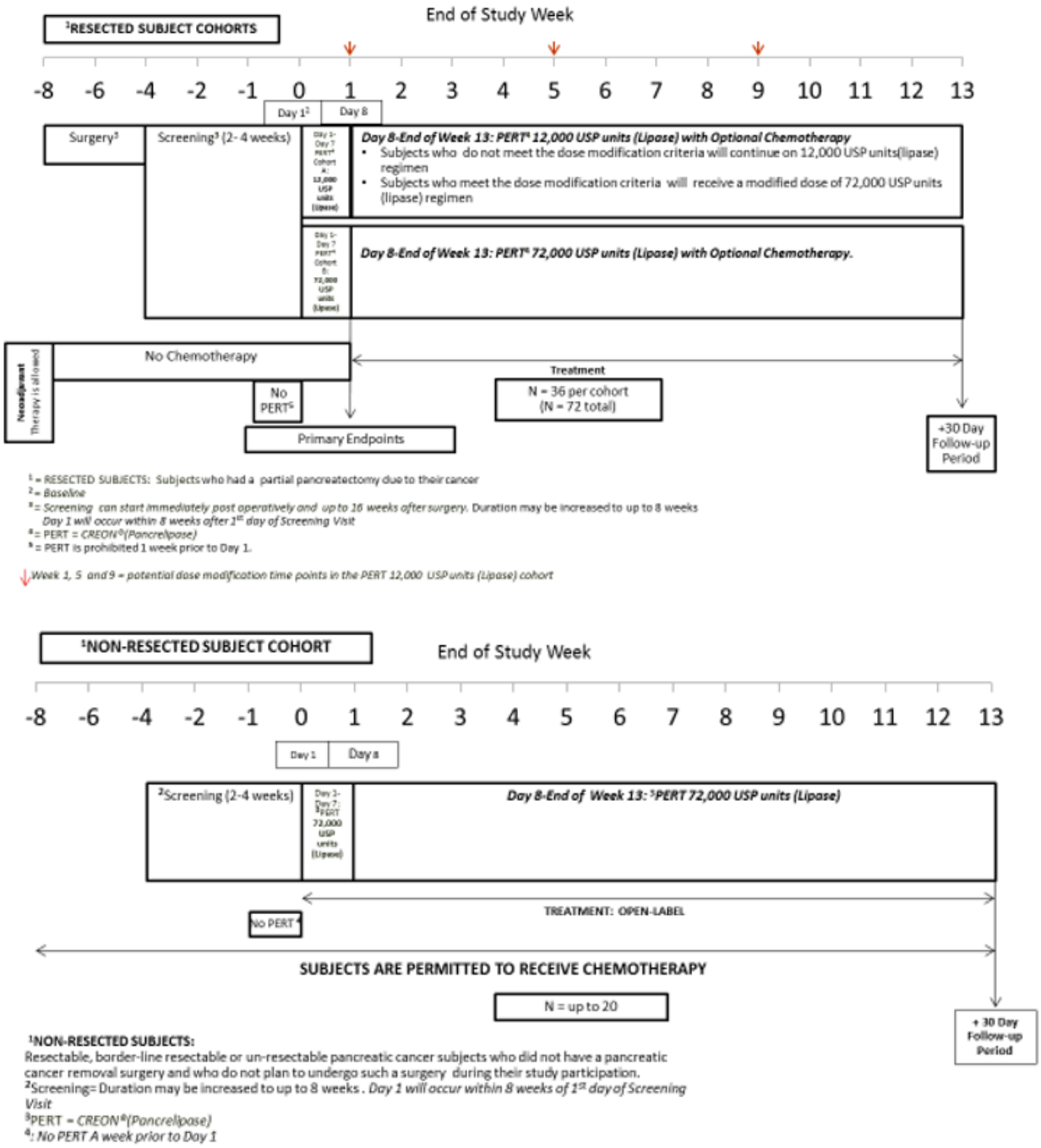
- Subjects receiving the lower dose will escalate to pancrelipase 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks.
- Subjects receiving the high dose will continue receiving the high dose throughout the study. In order to maintain the blind of the study, subjects in the high dose group will also receive a matching placebo and will not exceed the maximum dose per the USPI.[8]

Non-resected subjects in the open-label cohort will receive pancrelipase at a dose of 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks during the entire duration of the study.

No interim analyses are currently planned. Study sites and resected subjects in the double-blind cohorts will remain blinded for the treatment period of the study.

In support of the primary endpoints, it is critical for subjects to stop PERT a week prior to Day 1 and to initiate stool collection 48 hours prior to Day 1 and Week 1 visits.

## Figure 1. Study Schematic



## 4.2 Discussion of Study Design

### Choice of Control Group

Placebo use in the study is for blinding purposes. No placebo control will be used in this study because pancrelipase is an approved treatment and standard of care for EPI. The cohort receiving 12,000 USP units (Lipase) with meals/6,000 USP units (lipase) with snacks will be the control group in this study. The double-blind period compares 2 doses of pancrelipase in eligible resected subjects with EPI due to pancreatic cancer, who will be randomly assigned to treatment with pancrelipase at 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks, or treatment with pancrelipase at 12,000 USP units (Lipase) with meals/6,000 USP units (Lipase) with snacks.

The uncontrolled cohort of non-resected subjects will receive treatment with pancrelipase at 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks.

### Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with EPI. All clinical and laboratory procedures in this study are standard and generally accepted.

Using stool fat to evaluate the efficacy of PERT is a well-established method for the measurement of EPI.

The EPI Symptom Questionnaire is a disease-specific tool that has been particularly developed to measure changes in gastrointestinal symptoms experienced by patients who have EPI. This is a 12-item patient-reported outcome (PRO) tool that assesses EPI symptoms over the past seven days.

The Bristol Stool Chart will be utilized to describe stool consistency.

The EORTC QLQ-C30 is a 30-item questionnaire developed to assess the quality of life of cancer patients. The questionnaire is composed of 5 domains (physical, role, social, emotional, and cognitive functioning) and 9 single items (pain, fatigue, financial impact, appetite loss, nausea/vomiting, diarrhea, constipation, sleep disturbance, and quality of life). The tool has been validated in a cancer population.

EORTC QLQ-PAN26 is the pancreatic cancer module and is intended for patients at all disease stages undergoing surgical resection, palliative surgical intervention, endoscopic palliation, or palliative chemotherapy. The tool comprises 26 questions assessing pain, dietary changes, jaundice, altered bowel habit, emotional problems related to pancreatic cancer, and other symptoms (cachexia, indigestion, flatulence, dry mouth, taste changes). The tool has been validated in a pancreatic cancer population.

### Suitability of Subject Population

This study will include resected and non-resected pancreatic cancer patients.[2]

### Selection of Doses in the Study

A starting dose of 12,000 USP units (Lipase) with meals, although lower than 500 USP units (Lipase)/kg with meals, may be appropriate in the immediate postoperative period for patients not yet eating a diet

with a normal fat content. The high-dose cohort of 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks is a safe and efficacious dose as reported in the literature and the Food and Drug Administration (FDA)-approved prescribing information (USPI) and does not exceed the maximum described in the USPI.[8]

### Visit Window

Expecting that a few of the subjects might miss the target visit dates specified in the protocol, the windows below are defined around the target visit dates. However, it is recommended that the subject should comply with the protocol timeline as best as they can.

| Target Visit Week | Window |
|---|---|
| Week 1 | + 2 days |
| Week 5 | ± 4 days |
| Week 9 | ± 4 days |
| Week 13 | ± 4 days |

# 5 STUDY ACTIVITIES

## 5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

### Consent

- 1. Subjects must voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (IRB), before the initiation of any Screening or study-specific procedures.

### Demographic and Laboratory Assessments

- 2. Adult **male or female**, must be at least 21 years of age at Screening.
- 3. Subject must be able to tolerate solid food and be able to consume a balanced diet
- 4. Subject must have FE-1 ≤ 150 µg/g stool at Screening. FE-1 test can be repeated by subjects if needed; no washout period is required in this case.
- 5. A positive* Sudan stain for subjects without history of fat malabsorption [fat malabsorption defined as clinical steatorrhea, or measured stool fat greater than 7 g/day, or positive stool results by Sudan stain] within 1 week of Screening.

  *Positive stool results are defined as increased level of neutral OR total fats (normal ranges are < 60 droplets/HPF and < 100 droplets/HPF, respectively).

  Subject is able to follow study procedures as specified in the protocol and instructed by the site personnel.

- 6. Subject must be willing and able to collect stool samples at home.
- 7. Subject must not be participating in another clinical study.
- 8. **Resected subjects only:** Must be sufficiently recovered from surgery (investigator opinion)

## Disease Activity

- 9. Subject has been diagnosed with pancreatic cancer with biopsy and/or radiography, with a life expectancy of at least 5 months at Screening Visit.
- 10. Subject's pancreatic cancer must involve the head and/or neck of the pancreas.
- 11. Subject must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 or Karnofsky performance status (PS) > 60%.
- 12. Subject must have stable organ and marrow function as defined below:
  - Absolute neutrophil count (ANC) > 500/µL;
  - Platelets > 50,000/µL;
  - Total bilirubin ≤ 4 × upper limit of normal (ULN);

## Subject History

- 13. Subject must NOT have neuroendocrine pancreatic cancer.
- 14. Subject must NOT have a history of fibrosing colonopathy
- 15. Subject must NOT have **any other malignancy** within 1 year of Screening.
- 16. No diagnosis/history of renal impairment, hyperuricemia, or uncontrolled gout, including those with a recent acute flare within 60 days of Screening that would make the subject an unsuitable candidate to receive study drug.
- 17. Subject must NOT have other significant organ or bone marrow abnormality within 60 days of Screening.

## Contraception

- 18. A **negative urine pregnancy** test for all female subjects (except postmenopausal and permanently surgically sterile) at Baseline before the first dose of study drug. If urine pregnancy test is positive, withhold dosing and perform a serum pregnancy test. Pregnant subjects must not be enrolled into the study.
- 19. **If female**, subject must be either **postmenopausal** OR permanently **surgically sterile** OR for women of childbearing potential practicing at least 1 protocol-specified **method of birth control**, that is effective from Screening through at least 30 days after the last dose of study drug.

- 20. Female who is not **pregnant, breastfeeding, or considering becoming pregnant** during the study from Screening, for approximately 30 days after the last dose of study drug.

### Concomitant Medications/Surgery

- 21. Subjects who are receiving PERT at the time of Screening and who require a Sudan stain test are willing to be off PERT for a minimum of 48 hours prior to an initial or a repeated Sudan stain specimen collection. Sudan stain test can be repeated by subjects if needed. A washout-out period of 48 hours will be required if test is repeated.
- 22. It is critical that subject not consume PERT within 1 week prior to Day 1 [starting at Day –7].
- 23. Subject must be able to safely discontinue octreotide after signing the informed consent form (ICF) and must be able to safely be off octreotide during study participation.
- 24. Non-resected subjects (unresectable, resectable, and borderline resectable) must not plan to undergo a pancreatectomy during study participation.
- 25. Subject must be willing and able to consume daily supplements and document daily food intake at home.

## 5.2 Contraception

### Contraception Requirements for Females

Postmenopausal is defined as:

- Age > 55 years with no menses for 12 or more months without an alternative medical cause.
- Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND follicle-stimulating hormone (FSH) level > 40 IU/L.

If female, subject must be either post-menopausal or permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy). If the female subject is a woman of childbearing potential (WOCBP), she must practice at least one of the following methods of birth control throughout the study and for 30 days after the last study drug dose is given.

- Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal) associated with inhibition of ovulation initiated at least 1 month before study Baseline Day 1.
- Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month before study Baseline Day 1.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Vasectomized sexual partner(s) (the vasectomized partner(s) provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the trial participant).

- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).
- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.
- A combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier method).

### Contraception Requirements for Males

Male subjects who are sexually active with a woman of childbearing potential are not required to use condoms during the study.

## 5.3 Prohibited Medications and Therapy

In addition to the medications listed in the eligibility criteria, use of non-CREON® pancreatic enzyme supplementation or over-the-counter supplements that contain lipase, protease, and amylase as active ingredients, other than the study drug, is prohibited during the treatment period until the last dose of study drug.

Subjects in Screening, who are washing out of PERT, may resume PERT after collecting Stool specimen for Sudan stain test until 1 week prior to Day 1.

**For resected subjects:** Subjects must not have started chemotherapy or radiation therapy from the time of the resection until after Week 1 of the study. However, neoadjuvant therapy prior to the resection is allowed.

## 5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of screening or receives during the study must be recorded through the Follow-up Visit and any unscheduled visits.

All chemotherapy (neoadjuvant/adjuvant therapy) drugs used during the study will be recorded and must include all drugs, doses, and date ranges of administration. Any changes in planned chemotherapy should be recorded.

No drug interactions have been identified for pancrelipase. No formal interaction studies have been conducted with pancrelipase.[8]

Subjects must be able to safely discontinue any prohibited medications as described in the eligibility criteria. Subjects must be consented for the study before discontinuing any prohibited medications for the purpose of meeting study eligibility.

### Required and Rescue Concomitant Medications/Therapy

Not applicable.

## 5.5 Withdrawal of Study Drug and/or Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from study drug administration and/or the study at any time for reasons including, but not limited to, the following:

- The subject requests to be withdrawn from the study.
- The subject becomes pregnant while on study drug.
- The investigator believes it is in the best interest of the subject, for any reason, including:
  - Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator.
- Eligibility criteria violation noted after the subject started study drug, if continuation of the study drug administration would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- Subject is significantly noncompliant with study procedures which would put the subject at risk for continued participation in the trial.

To minimize missing data, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits. Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate electronic case report form (eCRF) page. If the subject has not had a study visit 30 days after study drug has been discontinued, a 30-day follow-up phone call after the last dose of study drug will be completed to ensure all treatment-emergent AEs/serious AEs (SAEs) have been resolved.

However, study procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator considers necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether or not the subject decides to continue to participate in the study.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, 2 telephone calls must be made, and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his or her site if he or she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

**Withdrawal from Study Drug Treatment**

In the event that a subject withdraws or is prematurely discontinued from study drug treatment, the subject should complete the Premature Discontinuation Visit as soon as possible (preferably within 7 days of last dose of study drug) and undergo certain study procedures (discontinuation visit will be added). These procedures should not interfere with the initiation of any new treatments or therapeutic modalities the investigator feels are necessary to treat the subject's condition.

**Withdrawal from Study**

If a subject prematurely discontinues study participation, the procedures outlined for the premature discontinuation (PD) visit should be completed as soon as possible, preferably within 1 week, unless the reason for the premature discontinuation is withdrawal of consent.

## 5.6 Study Drug

AbbVie will provide pancrelipase as capsules. Pancrelipase will be taken orally with each meal and snack beginning at Baseline (Day 1). The study drug should be taken with food. Capsules should be swallowed whole. If subjects forget to take their pancrelipase dose at their regularly scheduled dosing time, they should take the next dose at the next scheduled dosing time. A description of study drug is provided in Table 1.

**Table 1. Description of Study Drug**

| Investigational Product | Manufacturer | Mode of Administration | Dosage Form | Strength |
|---|---|---|---|---|
| Pancrelipase | AbbVie | Oral | Delayed-Release Capsule | 6,000 USP units (Lipase), 12,000 USP units (Lipase), 36,000 USP units (Lipase) |
| Matching placebo for purpose of blinding dose cohorts | AbbVie | Oral | Capsule | Not applicable |

The non-investigational nutritional supplements, Ensure Plus® or Glucerna Hunger Shake® (for subjects with diabetes mellitus), are commercially available (standard of care) to be supplied by $R_X$ Card and should be consumed with each snack (Ensure Plus® 2 to 3 daily or Glucerna Hunger Shake® 3 to 4 daily). This service will deliver monthly supplies of nutritional supplements directly to the subject's home for the duration of their treatment. Subjects will be provided access to the service at least 1 week prior to randomization as part of screening activities to have nutritional supplements available for consumption starting 7 days prior to randomization.

Pancrelipase will be packaged in bottles and blister cards with quantities sufficient to accommodate study design. Subjects in the blinded portion of the study will receive cartons containing blister cards for

both meals and snacks. This is to maintain the blind and to make it clear which capsules are to be taken with each meal and snack.

Subjects in the open-label portion will receive pancrelipase in bottles since blinding is not needed for this portion of the study. These subjects will receive 2 capsules of pancrelipase 36,000 USP units (Lipase) (72,000 USP units [Lipase] with meals) and 1 capsule (36,000 USP units [Lipase] with snacks) during the entire duration of the study. These subjects will not receive placebo capsules and will not be titrated per protocol.

Each kit (bottle, blister card, and carton) will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each label will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. All blank spaces on the label will be completed by the site staff before dispensing to subjects. Study drug will only be used for the conduct of this study.

A description of investigational product is provided in Table 2. All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, the pancrelipase capsules and placebo capsules provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

## Table 2. Description of Investigational Product

| | Resected Subjects | | Non-resected Subjects |
|---|---|---|---|
| | Investigational Product | Investigational Product Placebo | Investigational Product |
| Investigational product name | CREON® (Pancrelipase) | Placebo | CREON® (Pancrelipase) |
| Active ingredient | Pancrelipase, a mixture of lipase (LP), protease, and amylase of porcine origin | Not applicable | Pancrelipase, a mixture of lipase (LP), protease, and amylase of porcine origin |
| Mode/route of administration | Oral | Oral | Oral |
| Formulation | Commercially manufactured pancrelipase pellets filled into Swedish Orange opaque capsules for blinding | Sugar spheres filled into Swedish Orange opaque capsules for blinding | Commercially manufactured pancrelipase |
| Dosage Form | Delayed-release capsules | Delayed-release capsules | Delayed-release capsules |
| Dose and units | A combination of 6,000 USP units (Lipase) capsules, 12,000 USP units (Lipase) capsules, and 36,000 USP units (Lipase) capsules to achieve specified doses in study schematic (Figure 1) | A combination of placebo 6,000 USP units (Lipase) capsules, placebo 12,000 USP units (Lipase) capsules, and placebo 36,000 USP units (Lipase) capsules to achieve specified doses (Figure 1) | 36,000 USP units (Lipase) capsules |
| Masking | **Resected Subjects:** Double-blind capsules Day 1 to Week 13. In order to maintain the blind, subjects will consume 3 capsules per meal (1 capsule size 2 + 2 capsules size 00E) and 2 capsules with every snack (1 capsule size 4 + 1 capsule size 00E) according to their appropriate regimen as shown in Table 3 and Figure 2. | See Figure 1 | **Non-resected Subjects:** Not applicable, as subjects will be receiving an open-label treatment. Subjects will consume 2 capsules of pancrelipase 36,000 USP units (Lipase) (72,000 USP units [Lipase] with meals) and 1 capsule (36,000 USP units [Lipase] with snacks) during the entire duration of the study. |
| Frequency of administration | Daily with each meal and snack | Daily with each meal and snack | Daily with each meal and snack |
| Storage Conditions | 15 to 25 °C. Protect from moisture. Do not freeze. | 15 to 25 °C. Protect from moisture. Do not freeze. | 15 to 25 °C. Protect from moisture |

| | Resected Subjects | | Non-resected Subjects |
|---|---|---|---|
| | Investigational Product | Investigational Product Placebo | Investigational Product |
| Additional Information | Blinded capsules packaged in blister cards | Blinded capsules packaged in blister cards | Open-label capsules in bottles |

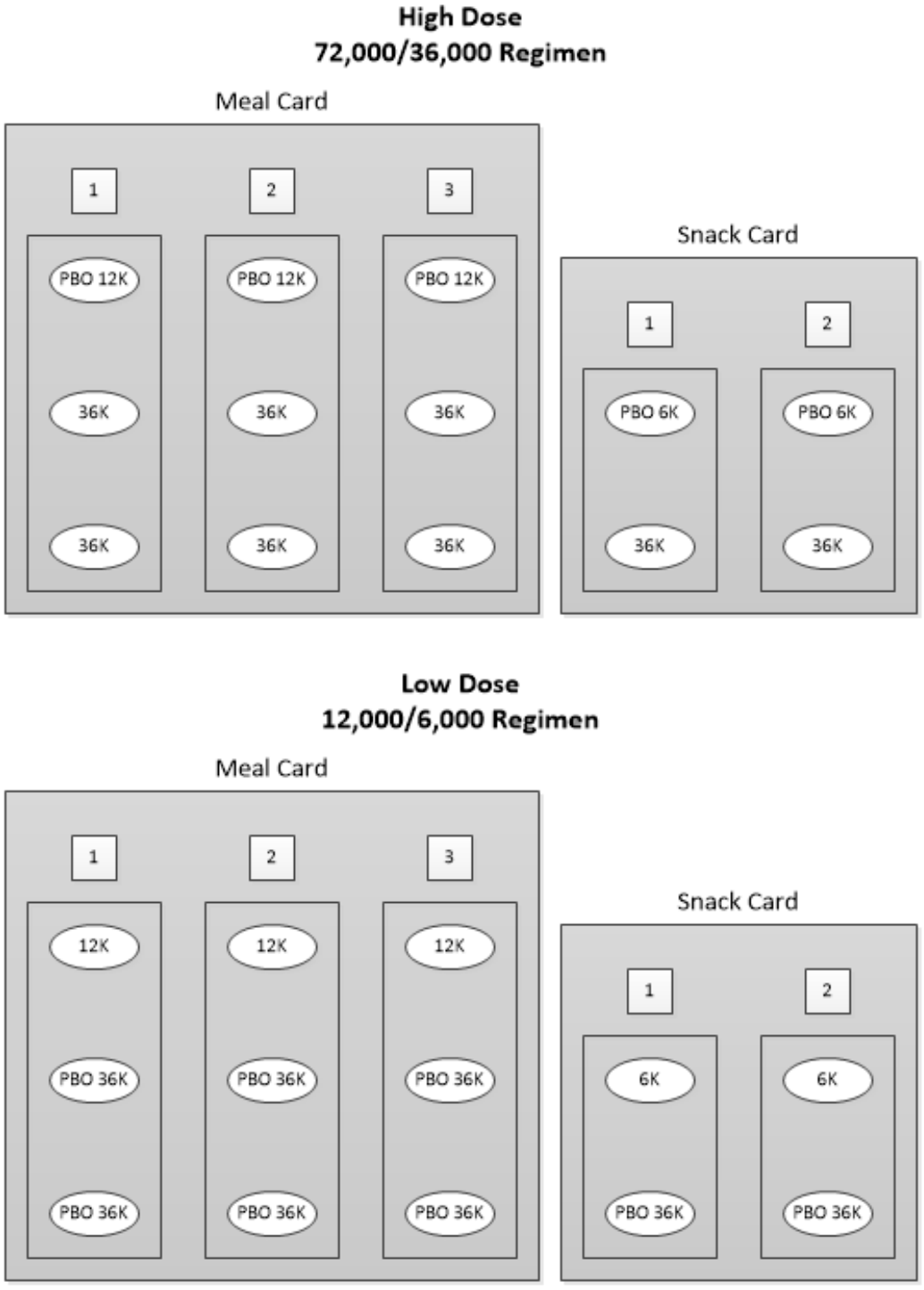
Blinding information:

In order to maintain the blind, subjects will consume 3 capsules per meal (1 capsule size 2 + 2 capsules size 00E) and 2 capsules with every snack (1 capsule size 4 + 1 capsule size 00E) according to their appropriate regimen as shown in Table 3 and Figure 2:

### Table 3. Masking of Doses

| | High Dose 72,000/36,000 Regimen | Low Dose 12,000/6,000 Regimen |
|---|---|---|
| **Meals** | | |
| **Capsule Size** | **72,000** | **12,000** |
| **2** | Placebo 12,000 | Active 12,000 |
| **00E** | Active 36,000 | Placebo 36,000 |
| **00E** | Active 36,000 | Placebo 36,000 |
| **Snacks** | | |
| **Capsule Size** | **36,000** | **6,000** |
| **4** | Placebo 6,000 | Active 6,000 |
| **00E** | Active 36,000 | Placebo 36,000 |

## Figure 2. Card Diagram of Dosing Regimen




PBO = placebo

Note: Diagrams are not to scale and are only meant as a visual representation. Actual cards may differ in color and size.

## 5.7 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. Subjects may rescreen once. For subjects who rescreen, the Screening number assigned by the IRT at the initial Screening visit should continue to be used. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

The IRT will assign a randomization number that will encode the subject's dose cohort assignment according to the randomization schedule generated by the statistics department at AbbVie.

Eligible resected subjects will be randomized to 1 of the 2 dose cohorts in a 1:1 ratio on Day 1 as indicated in Section 4.1.

For resected subjects, all AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's randomized treatment throughout the study. To maintain the blind, the pancrelipase capsules and placebo capsules provided for the study will be identical in appearance. The IRT will provide access to un-blinded subject treatment information in the case of a medical emergency.

Eligible non-resected subjects will enter the open-label cohort to receive pancrelipase at a dose of 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks during the entire duration of the study.

**Dose Modification**

Resected subjects

The dose for resected subjects in the low dose cohort (12,000 USP units (Lipase) with meals/6,000 USP units (Lipase) with snacks) may be modified to the high dose (72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks) at Weeks 1, 5, or 9 and maintained at the high dose for the rest of the study.

Only one dose modification will be permitted at Weeks 1, 5, or 9. For subjects who have experienced dose escalation, they will remain on the high dose level for the rest of the treatment duration, even if they continue to meet the dose escalation criteria in the subsequent visit(s). No further dose escalation is provided.

Dose modification criteria will be documented in the IRT specifications and implemented by IRT based upon responses to the selected questions from the EPI Symptom Questionnaire.

Non-resected subjects

Non-resected subjects in the open-label cohort will continue to receive pancrelipase at a dose of 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks during the study; there will be no dose modification.

Proton pump inhibitor (PPI) Therapy

An addition of proton pump inhibitor (PPI) therapy can be considered if all below criteria are met:

- Subjects continue to have symptoms of fat malabsorption and if the investigator deems clinically appropriate.
- Subjects are not already receiving PPI therapy.

## 5.8 Protocol Deviations

The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. AbbVie does not allow protocol waivers or intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), after the subject has been enrolled, the investigator is responsible for notifying the IEC/IRB, regulatory authorities (as applicable), and AbbVie (See Operations Manual Section 1).

## 5.9 Additional Supplies

AbbVie will provide stool collection kits, subject electronic diary (eDiary) for food intake and other subject data. Subjects will be requested to record stool data, on paper in the event the data will not be collected in the eDiary.

Sites will be provided with electronic patient-reported outcomes (ePRO) instruments for collection of EORTC QLQ-C30, QLQ-PAN26, and EPI symptom data.

# 6 SAFETY CONSIDERATIONS

## 6.1 Complaints and Adverse Events

### Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

### Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE, therefore, can be any unfavorable and unintended sign (including a clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product. Any worsening of a pre-existing condition or illness is considered an AE.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations," which must be reported whether or not associated with an AE.

There are no adverse events of special interest (AESI) for pancrelipase in this study population. The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or clinical research organization (CRO) (as appropriate) as a serious AE (SAE) within 24 hours after the site becomes aware of the SAE (refer to Section 4.3 of the Operations Manual for reporting details and contact information):

| | |
|---|---|
| **Death of Subject** | An event that results in the death of a subject. |
| **Life-Threatening** | An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form. |
| **Hospitalization or Prolongation of Hospitalization** | An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility. |
| **Congenital Anomaly** | An anomaly detected at or after birth, or any anomaly that results in fetal loss. |
| **Persistent or Significant Disability/Incapacity** | An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle). |

| | |
|---|---|
| **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** | An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, threat of loss of life, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. |

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines.

### Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE as mild, moderate, or severe.

The investigator will use the following definitions to rate the severity of each AE:

| | |
|---|---|
| **Mild** | The adverse event is transient and easily tolerated by the subject. |
| **Moderate** | The adverse event causes the subject discomfort and interrupts the subject's usual activities. |
| **Severe** | The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life threatening. |

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

**Reasonable Possibility –** After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

**No Reasonable Possibility –** After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

### Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 1 working day after the site becomes aware of the pregnancy. If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

Pregnancy in a study subject is not considered an AE. Subjects who become pregnant during the study must be discontinued (Section 5.5). The medical outcome for either the mother or infant meeting any serious criteria, including an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

## 6.2 Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product, this may include but is not limited to damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 1 business day after the study site becomes aware of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

# 7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

## 7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized before the final database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

## 7.2 Definition for Analysis Populations

The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of study drug. The FAS will be used for all efficacy and Baseline analyses. Subjects will be grouped according to treatment as randomized. Additional analysis population(s) may be used for the efficacy analysis. Details are provided in the SAP.

The safety analysis set consists of all subjects who received at least 1 dose of study drug. For the safety analysis set, subjects are assigned to a dose cohort based on the treatment actually received, regardless of the treatment randomized.

## 7.3 Statistical Analyses for Efficacy

### Primary Analysis

The primary efficacy endpoint is the change in stool fat from Baseline (Day 1) to Week 1. Within each dose cohort, a paired t-test will be performed to test the null hypothesis that the mean stool fat change is equal to zero. For comparison between dose cohorts, the change from Baseline will be analyzed using an analysis of covariance model including treatment as a fixed effect and Baseline stool fat as the covariate.

Details on the primary and other efficacy analyses are provided in the SAP.

### Sample Size Estimation

**Resected subjects:** 72 subjects total (36 subjects per dose group). After adjusting a dropout rate of 16%, the study will have 60 evaluable subjects for the evaluation of stool fat at Week 1. This sample size will have an approximately 99% power to detect a 20 gram stool fat reduction in mean stool fat from Baseline in each dose group assuming that the standard deviation for the change is 25 g or approximately 94% power to detect a 10 g stool fat reduction in mean stool fat from baseline assuming that the SD for the change is 15 g.[3,10] The type I error rate is 0.05 (2-sided).

In addition, the study will have an approximately 86% power to detect a difference of 20 g between 2 dose groups in mean stool fat change from Baseline, assuming the same standard deviation of 25 g for both dose groups. The power will drop to 63% if the difference is 15 g.

**Non-resected subjects:** Up to 20 subjects.

## 7.4 Statistical Analyses for Safety

Analysis of safety will include AEs, clinical laboratory values, and vital sign results. Details on the safety analyses are provided in the SAP.

# 8 ETHICS

## 8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB-approved.

## 8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

## 8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

# 9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

# 10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

# 11 COMPLETION OF THE STUDY

The end-of-study is defined as the time of the last subject last visit.

# 12 REFERENCES

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3. Whitcomb DC, Lehman GA, Vasileva G, et al. Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: a double-blind randomized trial. Am J Gastroenterol. 2010;105(10):2276-86.
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9. FitzSimmons SC, Burkhart GA, Borowitz D, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. N Engl J Med. 1997;336(18):1283-9.
10. Ramesh H, Reddy N, Bhatia S, et al. A 51-week, open-label clinical trial in India to assess the efficacy and safety of pancreatin 40000 enteric-coated minimicrospheres in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. Pancreatology. 2013;13(2):133-9.

# APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| ANC | Absolute neutrophil count |
| BMI | Body mass index |
| CF | Cystic fibrosis |
| CFA | Coefficient of fat absorption |
| CNA | Coefficient of nitrogen absorption |
| CP | Chronic pancreatitis |
| CRO | Clinical research organization |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| eDiary | Electronic diary |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EPI | Exocrine pancreatic insufficiency |
| ePRO | Electronic patient-reported outcomes |
| FAS | Full analysis set |
| FC | Fibrosing colonopathy |
| FDA | Food and Drug Administration |
| FE-1 | Fecal elastase-1 |
| FSH | Follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| ICH | International Council on Harmonisation |
| IEC | Independent ethics committee |
| IMP | Investigational medicinal product |
| IRB | Institutional review board |
| IRT | Interactive response technology |
| IUD | Intrauterine device |
| IUS | Intrauterine hormone-releasing system |
| LP | Lipase |
| PD | Premature discontinuation |

| | |
|---|---|
| PERT | Pancreatic enzyme replacement therapy |
| PPI | Proton pump inhibitor |
| PRO | Patient-reported outcome |
| PS | Performance status |
| PY | Pancreatectomy |
| QLQ | Quality of life questionnaire |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| ULN | Upper limit of normal |
| US | United States |
| USP | United States Pharmacopeia |
| USPI | United States prescribing information |
| WOCBP | Women of childbearing potential |

# APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-142: CREON® (pancrelipase) therapy for subjects with exocrine pancreatic insufficiency (EPI) due to pancreatic cancer: A double-blind, randomized, parallel design with 2 dose cohorts of pancrelipase in resected pancreatic cancer subjects and an open-label single dose cohort in non-resected pancreatic cancer subjects

Protocol Date: 22 November 2019

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

11. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate independent ethics committee (IEC)/institutional review board (IRB), except when necessary to protect the subject from immediate harm.
12. Personally conducting or supervising the described investigation(s).
13. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
14. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
15. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
16. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
17. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
18. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
19. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
20. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

| Signature of Principal Investigator | Date |
|---|---|

| Name of Principal Investigator (printed or typed) |
|---|

# APPENDIX C. LIST OF PROTOCOL SIGNATORIES

| Name | Title | Functional Area |
|---|---|---|
| [redacted] | Director | Medical Writing |
| [redacted] | Therapeutic Area Physician | General Medicine and Virology |
| [redacted] | Executive Medical Director | General Medicine and Virology |
| [redacted] | Medical Director | General Medicine and Virology |
| [redacted] | Statistics Therapeutic Area Head | Data and Statistical Sciences |
| [redacted] | Senior Research Statistician, Statistics | Data and Statistical Sciences |
| [redacted] | Study Project Manager | Clinical Program Development |

# APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the 8 subject encounters. The individual activities are described in detail in the **Operations Manual** (Appendix F).

## Study Activities Table

| Activity | Screening | Weeks –2 and –1 | Day 1 | Week 1 | Week 5 | Week 9 | Week 13/PD visit | 30 days FU Phone visit | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|
| Subject Information and Informed Consent<br>(Subject must be consented prior to discontinuing any prohibited medications or conducting any other study activity.) | ✓ | | | | | | | | |
| Order nutritional supplements (Ensure Plus® 2 – 3 daily or Glucerna Hunger Shake® 3 – 4/daily) for subjects to consume daily starting on Day -7 through last visit. (initial order should be placed 2 weeks prior to randomization). | | ✓ | | ✓ | ✓ | | | | |
| Eligibility criteria | ✓ | ✓ | ✓ | | | | | | |
| Medical history (including history of nicotine) | ✓ | | | | | | | | |
| Drug and alcohol screen | ✓ | | | | | | | | |
| Adverse event (AE) assessment | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| FSH | ✓ | | | | | | | | |
| EPI Symptoms (EPI Symptom Questionnaire) | | | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Prior/concomitant therapy | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| eDiary (hand-held device): ePRO Patient-Reported Outcomes:<br>1. Starting at Day –1, collection of Food Intake **daily** for **a week** for the entire Treatment Period.<br>2. Starting at Day 1- Collection of drug intake **daily** for the **entire** treatment period of the study<br>Device will be provided during Screening and collected at the last visit. | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Starting 1 week prior to Day 1: Stool frequency, stool consistency and incidences of diarrhea will be collected either by ePRO or by paper **daily** for a week prior to each visit | | | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLQ]-C30 and QLQ-PAN26 (on-site at scheduled visits) | | | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| CBC, Chemistry, and UA dipstick | ✓ | | ✓ | | | | ✓ | | |
| Serum albumin and pre-albumin | | | ✓ | | ✓ | ✓ | ✓ | | |
| Biomarker and/or Additional Laboratory Tests Sampling (for future potential nutritional analysis.) | | | ✓ | | ✓ | ✓ | ✓ | | |

| Activity | Screening | Weeks –2 and –1 | Day 1 | Week 1 | Week 5 | Week 9 | Week 13/PD visit | 30 days FU Phone visit | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|
| Fecal elastase-1 (FE-1). FE-1 test can be repeated by subjects if needed; no washout-out period is required in this case. | ✓ | | | | | | | | |
| Sudan stain test. Sudan Stain test can be repeated by subjects if needed. A washout-out period of 48 hours will be required if test is repeated. | ✓ | | | | | | | | |
| Stool fat (collected for 48 hours prior to Day 1 and Week 1). Prior to Day 1 at: Day (- 2), Day (- 1), and Prior to Day 8 at Day 6 and 7. No stool collection at any other time points. Subjects will be requested to collect the stool data during the collection time points in the eDiary or on paper. | | | ✓ | ✓ | | | | | |
| 12-lead ECG | ✓ | | | | | | | | |
| Height (Day 1 only), weight (BMI), hip and waist circumference | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Vital signs | ✓ | | ✓ | | | | ✓ | | |
| Physical exam (symptom directed) | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Local urine pregnancy test | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Randomization/drug assignment | | | ✓ | | | | | | |
| Dispense study drug | | | ✓ | ✓ | ✓ | ✓ | | | |
| A one-time dose modification to pancrelipase 72,000 USP units (Lipase) (resected cohorts) in blinded fashion will be permitted. | | | | ✓ | ✓ | ✓ | | | |

# APPENDIX E. PROTOCOL SUMMARY OF CHANGES

**Previous Protocol Versions**

| Protocol | Date |
|---|---|
| Version 1.0 | 03 August 2018 |
| Version 2.0 | 27 November 2018 |
| Administrative Change 1 | 12 March 2019 |

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following:

**1. Secondary Endpoints**

Reclassified exploratory endpoints for the resected subjects as secondary endpoints (Section 2 and Section 3.3).

**Rationale**: Since the majority of subjects in the trial are likely to have resection after PC, the sample size is likely to be large enough to get good estimates for these endpoints.

**2. Exploratory Endpoints**

Removed exploratory endpoints:

- Difference between 2 dose cohorts in change from Baseline in stool frequency at Week 1
- Change in stool frequency from Baseline to Weeks 5, 9, and 13
- Change in health care resource utilization (HCRU) from Baseline to Weeks 1, 5, 9, and 13
- Change in EPI symptoms (as assessed by the EPI Symptom Questionnaire) from Baseline to Weeks 1, 5, 9, and 13
- Changes in quality of life (QoL) (EORTC QLQ-C30 and QLQ-PAN26) from Baseline to Weeks 1, 5, 9, and 13.
- Chemotherapy tolerability
- Change from Baseline to Weeks 1, 5, 9, and 13 for the following measurements:
- Body weight, and body mass index (BMI)

**Rationale**: The endpoints in the first 2 bullets are included as secondary endpoints and HCRU endpoints were removed as they are no longer of interest. The remainder of previous exploratory endpoints were removed or relocated to secondary endpoints.

### 3. Eligibility Criteria

Revised the eligibility criteria (Section 5.1) as follows: Added FE-1 test repeat by subjects, if needed. Added the criticality of stopping PERT the week prior to Day 1. Eliminated the exclusion of full pancreatectomy subjects from the eligibility criteria. Allowed exposure to octreotide prior to consenting as long as subjects are safely able to discontinue it after consenting. Prohibited diagnosis/history of renal impairment, hyperuricemia, or uncontrolled gout, including those with a recent acute flare within 60 days of Screening that would make the subject an unsuitable candidate to receive study drug.

**Rationale:** To more clearly define the subject population in the study.

### 4. Prohibited Medications and Therapy

Added the sentence "Subjects in Screening who are washing out of PERT may resume PERT after collecting stool specimen for Sudan stain until 1 week prior to Day 1" (Section 5.3).

**Rationale**: To alleviate any potential patient discomfort due to lack of PERT at Screening until Day (–)7.

### 5. Activity Schedule

Appendix D. ACTIVITY SCHEDULE

Added FSH testing at Screening. Added specific timing for collection of stool-related parameters.

**Rationale:** Changes were made to ensure FSH is collected at Screening to verify postmenopausal status.

### 6. Changes in the Operations Manual

Changes were made to the operations manual to reflect changes made to the protocol.

# APPENDIX F. OPERATIONS MANUAL

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# Operations Manual for Clinical Study Protocol M16-142

# List Indication: Exocrine Pancreatic Insufficiency (EPI) in Pancreatic Cancer Subjects

| | | | |
|---|---|---|---|
| SPONSOR: | AbbVie Inc. | ABBVIE INVESTIGATIONAL PRODUCT: | Pancrelipase enteric-coated capsule – oral |

FULL TITLE: Creon® (pancrelipase) therapy for subjects with exocrine pancreatic insufficiency (EPI) due to pancreatic cancer: A double-blind, randomized, parallel design with 2 dose cohorts of pancrelipase in resected pancreatic cancer subjects and an open-label single dose cohort in non-resected pancreatic cancer subjects

# 1 CONTACTS

| | | |
|---|---|---|
| Sponsor/ Emergency Contact | [redacted] **MD**<br>AbbVie<br>Development<br>1 N. Waukegan Road<br>[redacted]<br>North Chicago, IL 60064<br>Email: [redacted]<br>**EMERGENCY 24-hour Number:**<br>+1 973-784-6402 | Office:<br>Mobile:<br>Fax: [redacted] |
| Safety Concerns | Therapeutic Area Safety Team<br>Dept. R48S, Bldg. AP31-1<br>1 North Waukegan Road<br>North Chicago, IL 60064 | Phone: +1 847-935-7577<br>Email:<br>GPRD_SafetyManagement_Hormones@Abbvie.com |
| Serious adverse event (SAE) Reporting outside of RAVE | Email:<br>PPDINDPharmacovigilance@abbvie.com | Fax: +1 847-938-0660 |
| Protocol Deviations | [redacted]<br>Study Project Manager<br>1 North Waukegan Rd.<br>[redacted]<br>North Chicago, IL 60064 | Phone: [redacted]<br>Fax:<br>Email: |
| Certified Clinical Lab | Covance CLS<br>8211 SciCor Dr<br>Indianapolis, IN 46214 | Phone: +1 317-273-7872<br>Fax: +1 317-616-4572 |
| Additional Sample Lab | Covance CLS<br>8211, SciCor Dr.<br>Indianapolis, IN 46214 | Phone: +1 317-273-7872<br>Fax: +1 317-616-4572 |

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# TABLE OF CONTENTS

## LIST OF APPENDICES

# 2 INVESTIGATION PLAN

## 2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

SCREENING: ● ○ ○ ○ ○ ○

| | | |
|---|---|---|
| INTERVIEW | • Subject information and informed consent[a]<br>• Eligibility criteria<br>• Medical history (updated at every visit, as appropriate) | • Drug[b] and alcohol screen<br>• Adverse event assessment<br>• Prior/concomitant therapy |
| PRO | • Dispense subject electronic diary (eDiary) | • Stool frequency,[c] stool consistency,[c] incidences of diarrhea[c]<br>• Food intake recording[c] |
| EXAM | • 12-lead electrocardiogram (ECG)<br>• Weight<br>• Hip and waist circumference | • Vital signs<br>• Physical exam (symptom directed) |
| LAB | • Urinalysis [UA] dipstick[f] | • Urine pregnancy test<br>• Follicle-stimulating hormone (FSH); see criteria in the Protocol Section 5.2 |
| CENTRAL LAB | • Complete blood count [CBC], chemistry, and urinalysis [UA] microscopic[f]<br>• Fecal elastase-1[h] | • Sudan stain.[h] A positive[g] Sudan stain for subjects without history of fat malabsorption [fat malabsorption defined as clinical steatorrhea, or measured stool fat greater than 7 g/day, or positive stool results by Sudan stain] within 1 week of Screening. |

| | | |
|---|---|---|
| ℞ TREATMENT AND ASSOCIATED ACTIVITIES | • Order nutritional supplement (Ensure Plus® or Glucerna Hunger Shake®) prescription at least 2 weeks prior to randomization[d,e]<br>• Instruct subjects to nutritional supplement consumption 1 week prior to Day 1: Ensure Plus® 2 – 3 daily or Glucerna Hunger Shake® 3 – 4 daily | • Subjects on pancreatic enzyme replacement therapy (PERT), must discontinue PERT a week prior to Day 1 |

NOTES:

a. Subject must be consented prior to discontinuing any prohibited medications or conducting any other study activity.

b. Only prescribed medication is allowed.

c. Collected daily, by the subject, for 1 week prior to Day 1. Stool Consistency and Frequency and Diarrhea may need to be recorded on paper in the event the data will not be collected in ePRO.

d. The $R_X$ Card service will deliver monthly supplies of nutritional supplements directly to the subject's home for the duration of their treatment. Subjects will be provided access to the service at least 1 week prior to randomization as part of Screening (pre-randomization) activities to have nutritional supplements available for consumption starting 7 days prior to randomization. Similarly, with the monthly delivery during study participation, subjects will be provided access to the service at least 1 week prior to use. The site will be responsible for nutritional supplement re-ordering for subjects throughout the study (prior to randomization, at Week 1, and Week 5).

e. Subjects will be required to start updating data in their electronic patient-reported outcomes (ePRO) device a week prior to randomization.

f. The site will complete dipstick urinalysis at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

g. Positive stool results are defined as increased level of neutral OR total fats (normal ranges are < 60 droplets/HPF and < 100 droplets/HPF, respectively).

h. This will be provided to subjects by the site personnel.

## BASELINE (DAY 1):

| | | |
|---|---|---|
| INTERVIEW | • Eligibility criteria | • Adverse event assessment<br>• Prior/concomitant therapy |
| PRO | • EORTC QLQ-C30[d]<br>• EORTC QLQ-PAN26[d]<br>• Exocrine pancreatic insufficiency (EPI) symptoms (EPI Symptom Questionnaire)[d] | • Collection of food intake[c]<br>• Stool frequency,[c] stool consistency,[c] and incidences of diarrhea[c]<br>• eDiary review<br>• Instruct subjects to start recording study drug intake daily (eDiary) |
| EXAM | • Height, weight, body mass index (BMI)<br>• Hip and waist circumference<br>• Vital signs | • Physical exam (symptom directed) |
| LAB | | • Urine pregnancy test<br>• Urinalysis [UA] dipstick[a] |
| CENTRAL LAB | • Serum albumin and pre-albumin (part of chemistry)<br>• Serum for additional chemistry nutritional biomarkers (vitamins and minerals) will be collected for future potential nutritional analysis. | • CBC, chemistry, and urinalysis [UA] microscopic[a]<br>• Stool fat[b] (48 hours prior to Day 1) on Day (-2) and Day (-1) |
| TREATMENT AND ASSOCIATED ACTIVITIES | • Randomization/drug assignment<br>• Nutritional supplement consumption: Ensure Plus® 2 – 3 daily or Glucerna Hunger Shake® 3 – 4 daily | • Dispense study drug |

NOTES:

a. The site will complete dipstick urinalysis at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

b. Collection kits will be provided by vendor after coordination with the site personnel. Stool collection will be done for 48 hours prior to visit on Day (–2) and Day (–1). Subjects will be requested to record the stool collection data in ePRO or on paper.

c. Collected daily, by the subject, during the week prior to visit. Stool Consistency, Frequency, and Diarrhea may need to be recorded on paper in the event the data will not be collected in ePRO.

d. Collected at visit. A "Dispensation Score" will appear in electronic data capture (EDC) once Subjects have submitted the questionnaire.

WEEK 1 (+ 2 days), WEEK 5 (± 4 days), and WEEK 9 (± 4 days):

| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Concomitant therapy | |
| PRO | • EORTC QLQ-C30<br>• EORTC QLQ-PAN26<br>• EPI symptoms (EPI Symptom Questionnaire) | • Collection of food intake[a]<br>• Stool frequency,[a] stool consistency,[a] and incidences of diarrhea[a]<br>• eDiary review<br>• Subjects continue recording study drug intake daily |
| EXAM | • Weight (BMI)<br>• Hip and waist circumference | • Physical exam (symptom directed) |
| LAB | | • Urine pregnancy test |
| CENTRAL LAB | • Serum for additional chemistry nutritional biomarkers (vitamins and minerals) will be collected for future potential nutritional analysis.[c]<br>• Serum albumin and pre-albumin[c] | • Stool fat [b] (collected 48 hours prior to Day 8 on Day 6 and Day 7) |
| TREATMENT AND ASSOCIATED ACTIVITIES | • Dispense study drug<br>• Order[e] nutritional supplements<br>• Nutritional supplement consumption: Ensure Plus® 2 – 3 daily or Glucerna Hunger Shake® 3 – 4 daily | • Only 1 dose modification to pancrelipase 72,000 USP units (Lipase) (resected cohorts) (will be permitted at Week 1, 5, or 9, if applicable)[d] |

NOTES:

a. Collected daily, by the subject, during the week prior to visit.

b. Week 1 only. Collection kits will be provided by vendor. Stool collection will be done for 48 hours prior to Week 1 visit on Day 6 and Day 7. Subjects will be requested to record the stool collection data in ePRO or on paper.

c. Weeks 5 and 9 only.

d. Please refer to Section 5.7 of the study protocol for dose modification criteria. During Weeks 1, 5, and 9 dispensing, subjects will be requested to enter the responses to all questions in the EPI Symptom Questionnaire using the Site's device. A "Dispensation Score" will appear in EDC once Subjects have submitted the questionnaire. The site personnel will then need to enter the "Dispensation Score" into IRT and the subject will be assigned with the appropriate kit.

e. Week 1 and 5 only.

## WEEK 13 (± 4 days)/Premature Discontinuation Visit:

| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Concomitant therapy | |
| PRO | • EORTC QLQ-C30<br>• EORTC QLQ-PAN26<br>• EPI symptoms (EPI Symptom Questionnaire) | • Collection of food intake[a]<br>• Stool frequency,[a] stool consistency,[a] and incidences of diarrhea[a]<br>• eDiary review<br>• Collect subject eDiary device |
| EXAM | • Weight<br>• Hip and waist circumference | • Vital signs<br>• Physical exam (symptom directed) |
| LAB | • Urine pregnancy test<br>• Urinalysis [UA] dipstick[b] | |
| CENTRAL LAB | • Serum albumin and pre albumin (part of chemistry)<br>• Serum for additional chemistry nutritional biomarkers (vitamins and minerals) will be collected for future potential nutritional analysis. | • CBC, chemistry, and urinalysis [UA] microscopic[b] |

NOTES:

a. Collected daily, by the subject, during the week prior to visit.

b. The site will complete dipstick urinalysis at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones or blood greater than negative or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

## 30 Days Follow-up Phone Visit:

| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment | • Concomitant therapy |

## Unscheduled Visit:

| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment | • Prior/concomitant therapy |

# 3 STUDY PROCEDURES

## 3.1 Subject Information and Informed Consent

The investigator or his or her representative will explain the nature of the study to the subject and answer all questions regarding this study. Before any study-related Screening procedures are performed on the subject or any medications are discontinued by the subject in order to participate in this study, the informed consent statement must be reviewed, signed, and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained before any study-related procedures and that the subject received a signed copy.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

## 3.2 Medical History

A complete medical history including history of tobacco, alcohol, and drug use will be taken at Screening. The subject's medical history can be updated at each visit as appropriate.

## 3.3 Drug and Alcohol Screen

Subjects should have no history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.

Urine specimens will be tested at the Screening visit for the presence of drugs of abuse. The panel for drugs of abuse will minimally include the drugs listed below. Any positive result must be assessed for clinical significance. These analyses will be performed by the certified central laboratory chosen for the study. Prescribed medication will be allowed.

- Opiates
- Barbiturates
- Amphetamines
- Cocaine
- Benzodiazepines

- Alcohol
- Phencyclidine
- Propoxyphene
- Methadone

## 3.4 Adverse Event Assessment

Please refer to Section 4.2.

## 3.5 Patient-Reported Outcomes

Subjects will complete the self-administered patient-reported outcome (PRO) instruments (when allowed per local regulatory guidelines). Subjects should be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaire to them. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

The PRO instruments to evaluate quality of life are the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 (Appendix B) and EORTC QLQ-PAN26 (Appendix C).

The PRO instrument should be completed before drug administration on Day 1, Weeks 1, 5, and 9, as well as Week 13/premature discontinuation (PD) and before any discussion of adverse events or any review of laboratory findings.

EPI symptoms (using EPI Symptom Questionnaire) will be assessed at visits indicated in Section 2.1. The subject should complete the questionnaire before site personnel perform any clinical assessments and before any interaction with site personnel occurs to avoid biasing the subject's response. Site personnel will administer the EPI Symptom Questionnaire (Appendix D) to subjects.

Food intake, stool frequency, stool consistency and incidences of diarrhea will be collected by subjects daily for a week prior to the following visits; Day 1, Weeks 1, 5, 9, and 13. For stool consistency, subjects will select the image from the Bristol Stool Chart that represents the most frequent or average stool consistency during a past 24-hour period.

Study drug intake will be recorded daily, by subjects using the ePRO device, during the treatment period, starting on Day 1 through Week 13.

## 3.6 Pharmacokinetic Sampling

Not applicable.

## 3.7 Biomarker and/or Additional Laboratory Tests Sampling

A blood sample will be collected on Day 1, as well as Weeks 5, 9, and 13/premature discontinuation visit from each subject for a biomarker analysis.

The central laboratory, AbbVie, or its designee will provide specific instructions for preparation and storage of archive samples.

Specimen will be collected at Day 1, Weeks 5, 9, and 13/premature-discontinuation for potential nutritional analysis.

## 3.8 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at the designated study visits as specified in Section 2.1. The ECG should be performed before blood collection.

An appropriately trained physician at the site ("local reader") will evaluate the ECGs. The local reader from the site will sign and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source folder. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

## 3.9 Height, Weight, Hip, and Waist Circumference

Height will be measured at Day 1 only. Hip and waist circumference should be measured at Screening, (however, if missed, it can be recorded at the Day 1 visit), Day 1, Week 1, 5, 9, and 13/PD Visits and as specified in Section 2.1. Body weight will be measured at scheduled visits as specified in Section 2.1. The subject will wear lightweight clothing and no shoes during weighing.

Hip and waist circumference will be measured while subject is wearing light clothing and stands with feet shoulder width apart and back straight. To measure waist circumference, locate the top of the hip bone and align the bottom edge of the measuring tape with the top of the hip bone. Wrap the tape measure all the way around the waist. Have the subject take 2 normal breaths and on the exhale of the second breath tighten the tape measure. Take the measure of the waist to the nearest 0.5 centimeter (1/4 inch).

To measure hip circumference, place the measuring tape around the maximum circumference of the buttocks. The reading of the measurement should be taken at the end of gentle exhaling. The measuring tape should be held firmly, ensuring its horizontal position. Verify that the tape is horizontal all around the waist. The tape should be loose enough to allow the observer to place 1 finger between the tape and the subject's body.

## 3.10 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, and body temperature will be obtained at visits as specified in Section 2.1. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes.

## 3.11 Physical Examination

A symptom-directed physical examination will be performed at the designated study visits as specified in Section 2.1. The physical examination performed on Day 1 will serve as the Baseline physical examination for the entire study. Any significant physical examination findings after the first dose will be recorded as adverse events. All findings, whether related to an adverse event or part of each subject's medical history, will be captured on the appropriate electronic case report form (CRF) page.

At any time, a symptom-directed physical examination can be performed as the investigator deems necessary.

## 3.12 Dispense Study Drug

Study drug will be dispensed to subjects beginning at Baseline (Day 1) and as specified in Section 2.1. The first dose of study drug will be administered after all other Baseline (Day 1) procedures are completed. At the visits specified in Section 2.1, the site personnel will review the dosing diary, review returned study drug kits, and empty study drug packaging to verify compliance.

Study drug (i.e., pancrelipase) capsules to be taken orally should be dosed together and taken with food. Subjects will also be requested to start taking nutritional supplements 7 days prior to randomization.

## 3.13 Clinical Laboratory Tests

The Baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement before the initial dose of study drug unless otherwise specified in the Statistical Analysis Plan.

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained before the initiation of the study.

The central laboratory will provide instructions regarding the collection, processing, and shipping of these samples and send them to the following certified laboratory addresses:

Covance CLS
8211 SciCor Dr.
Indianapolis, IN 46214

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- Repeat the test to verify the out-of-range value;
- Follow the out-of-range value to a satisfactory clinical resolution; or
- Discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as an adverse event.

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Clinical Chemistry</th><th>Other Tests</th></tr>
<tr><td>Hematocrit<br>Hemoglobin<br>Red blood cell (RBC) count<br>Red cell distribution width (RDW)<br>RBC morphology and mean corpuscular volume (MCV)<br>White blood cell (WBC) count<br>Neutrophils<br>Bands<br>Lymphocytes<br>Monocytes<br>Basophils<br>Eosinophils<br>Platelet count (estimate not acceptable)</td><td rowspan="3">Blood urea nitrogen (BUN)<br>Creatinine<br>Total bilirubin<br>Pre-albumin<br>Albumin<br>Alanine transaminase (ALT)<br>Aspartate transaminase (AST)<br>Alkaline phosphatase<br>Sodium<br>Potassium<br>Calcium<br>Inorganic phosphorus<br>Uric acid<br>Cholesterol<br>Total protein<br>Glucose<br>Triglycerides<br>Bicarbonate/$CO_2$<br>Chloride<br>Follicle-stimulating hormone (FSH)<br>FSH (-70)<br>SERUM BETA human chorionic gonadotropin (hCG)<br>B-hCG, Qualitative<br>B-hCG, Quantitative</td><td rowspan="3">Serum albumin and prealbumin<br>Potential nutritional biomarkers<br>Fecal elastase- 1<br>Sudan Stain<br>Stool Fat</td></tr>
<tr><td>Urinalysis</td></tr>
<tr><td>Specific gravity<br>Ketones<br>pH<br>Protein<br>Blood<br>Glucose</td></tr>
</table>

## Pregnancy Tests (Urine and Serum)

A qualitative urine pregnancy test will be performed at Screening, Day 1, Weeks 1, 5, 9 and Week 13 for all women of childbearing potential (WOCBP) subjects.

Determination of postmenopausal status will be made during the Screening period.

A pregnant or breastfeeding female will not be eligible for participation or continuation in this study.

Urine pregnancy tests will be performed at visits indicated in Section 2.1.

Sites will receive supplies from the central lab to run urine pregnancy test.

If the urine pregnancy test (which is performed at the site) is negative, begin or continue dosing. If urine pregnancy test is positive, withhold dosing and perform a serum pregnancy test. Pregnant subjects must discontinue from the study.

### Urinalysis

The site will complete dipstick urinalysis at all required visits. Sites will receive supplies from the central lab to run dipstick urinalysis. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

## 3.14 Stool Fat

Stool fat sample will be collected at visits indicated in Section 2.1.

It is critical that all stool samples will be collected 48 hours prior to Day 1 and 48 hours prior to Day 8 (Week 1 visit).

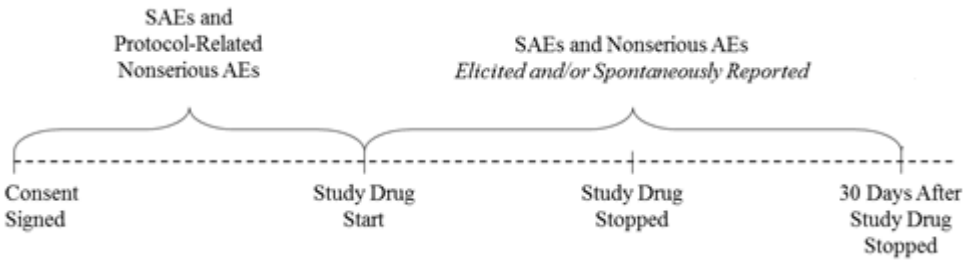
See central laboratory manual and sites' instructions for additional details regarding stool collection.

# 4 SAFETY MANUAL

## 4.1 Methods and Timing of Safety Assessment

All serious adverse events (SAEs) as well as protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 30 days after discontinuation of study treatment, all adverse events, and SAEs will be collected whether solicited or spontaneously reported by the subject.

After 30 days following completion of study treatment and throughout the Post-Treatment Period, all spontaneously reported SAEs will be collected (nonserious AEs will not be collected).




There are no adverse events of special interest (AESI) for pancrelipase in this study population.

## 4.2 Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA system organ class (SOC) and preferred term (PT). The tabulation of the number of subjects with treatment-emergent adverse events by severity grade and relationship to study drug also will be provided. Subjects reporting more than 1 adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to study drug tables. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC.

## 4.3 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours after the site becomes aware of the SAE by entering the SAE data into the electronic data capture system. SAEs that occur before the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours after the site becomes aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 938-0660

For safety concerns, contact the Therapeutic Area Safety Team at:

Therapeutic Area Safety Team
AbbVie
1 North Waukegan Road
North Chicago, Illinois 60064
Office: +1 847-935-7577
Email: GPRD_SafetyManagement_Hormones@abbvie.com

For any subject safety concerns, please contact the physician listed below:

**Primary Therapeutic Area Medical Director**
**EMERGENCY MEDICAL CONTACT:**
[redacted] **MD**
**AbbVie Inc.**
[redacted]
**1 North Waukegan Road**
**North Chicago, IL 60064**

Contact Information:

**Office:** [redacted]
**Mobile:** [redacted]
**Fax:** [redacted]
**Email:** [redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

| HOTLINE: +1 (973) 784-6402 |
|---|

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the European Union countries will be the most current version of the Investigator's Brochure.

# 5 COUNTRY-SPECIFIC REQUIREMENTS

## 5.1 Sample Retention Requirements

Not applicable.

## 5.2 SUSAR Reporting

Not applicable.

# 6 STUDY DRUG

## 6.1 Treatments Administered

The study drug (pancrelipase) will be dispensed in the form of capsules at the visits listed in Section 2.1. Subjects will be instructed to take study drugs daily with each meal or snack.

AbbVie will provide pancrelipase as capsules to be taken as a combination of 6,000, 12,000, and 36,000 USP units (Lipase).

Pancrelipase will be taken orally daily with each meal or snack from Day 1 through Week 13. Subjects in the blinded cohorts will take 3 capsules with each meal and 2 capsules with each snack. Subjects in the open-label cohort will take 2 capsules with each meal and 1 capsule with each snack.

Study drug must not be dispensed without contacting the interactive response technology (IRT) system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature Discontinuation (PD) visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

At Day 1 eligible resected subjects will be randomized in 1:1 ratio to one of following dose cohorts, and will remain on blinded therapy throughout the study:

- Low-dose (Regimen of 12,000 USP units (Lipase) with meals/6,000 USP units (Lipase) with snacks)
- High-dose (Regimen of 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks)

At Week 1, 5, or 9, resected subjects who meet the "Dose Modification Criteria" specified below will be titrated once to the following regimen in a blinded fashion:

- Subjects in the low dose cohort will escalate to the high dose (72,000/36,000 USP units [Lipase] regimen).
- Subjects in the high dose cohort will continue on the high dose (72,000/36,000 USP units [Lipase] regimen).

Non-resected (unresectable, resectable, and borderline resectable) subjects will receive pancrelipase delayed-release capsules administered daily with every meal and snack. Subjects will participate in the study for up to approximately 177 days (Screening up to 56 days, double-blind, and/or open-label treatment up to 91 days, and up to a 30-day safety follow-up period).

**Dose Modification**

Resected subjects

Resected subjects in the low dose cohort (12,000 USP units [Lipase] with meals/6,000 USP units [Lipase] with snacks) may modify to receive the high dose (72,000 USP units [Lipase] with meals/36,000 USP units [Lipase] with snacks) at Week 1, 5, or 9 and maintain it throughout the study. Resected subjects in the high dose cohort (72,000 USP units [Lipase] with meals/36,000 USP units [Lipase] with snacks) will remain on the high dose at Week 1, 5, or 9.

Only one dose modification will be permitted at Week 1, 5, or 9. For subjects who have experienced dose escalation, they will remain on the high dose level for the rest of the treatment duration, even if they continue to meet the dose escalation criteria in the subsequent visit(s). No further dose escalation is provided.

Dose modification criteria will be documented in the EDC or IRT specifications and implemented by IRT based upon responses to the selected questions from the EPI Symptom Questionnaire.

Non-resected subjects (unresectable, resectable, and borderline resectable subjects) in the open-label cohort will continue to receive pancrelipase at a dose of 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks during the study.

For subjects who continue to have fat malabsorption, addition of proton pump inhibitor (PPI) therapy can be considered, if clinically appropriate and subjects are not receiving PPI therapy.

All subjects who receive at least 1 dose of study drug and meet the discontinuation criteria will be discontinued from treatment.

The non-investigational nutritional supplements are commercially available Ensure Plus® and Glucerna Hunger Shake® (standard of care) to be supplied by $R_X$ Card. This service will deliver approximately monthly supplies of nutritional supplements directly to the subject's home for the duration of their treatment. Subjects will be provided access to the service at least 1 week prior to randomization as part of pre-randomization activities to have nutritional supplements available for consumption starting 7 days prior to randomization.

## 6.2 Packaging and Labeling

Blinded pancrelipase and matching placebo will be supplied in blister cards. Open-label pancrelipase will be supplied in bottles.

Each bottle and blister card will be labeled as required per country requirements.

The labels must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. All blank spaces on the label will be completed by the site staff before dispensing to subjects.

### Storage and Disposition of Study Drug

Pancrelipase must be stored at controlled room temperature (15° to 25°C/59° to 77°F) and protected from moisture. The pancrelipase material must not be frozen. The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

Nutritional supplements must be stored according to the conditions specified in the package insert. Storage conditions are within the subjects' responsibilities and AbbVie should not be involved with monitoring the temperature of the nutritional supplements. Any instance including, but not limited to, temperature excursions or damaged supplies, should be reported to the manufacturer of the product as specified in the product insert. Instances involving incorrect shipments or missing shipments should be reported to Rx Card, the company that handles distribution of the supplies. Extra supplies remaining after the completion of dosing should be handled by the subject.

## 6.3 Method of Assigning Subjects to Treatment Groups

This is a randomized, double-blind, 2-cohort dose-response study in subjects with EPI due to pancreatic cancer that has been resected. Eligible resected subjects will be randomized to one of the following dosing cohorts in a 1:1 ratio to receive 1 of 2 doses (12,000 USP units [Lipase] with meals/6,000 USP units [Lipase] with snacks), 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks.

Non-resected (unresectable, resectable, and borderline resectable) subjects in the open-label cohort will receive pancrelipase at a dose of 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks during the entire duration of the study.

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. For subjects who rescreen, the Screening number assigned by the IRT at the initial Screening visit should be used. For resected subjects, the IRT will assign a randomization number that will encode the subject's dose cohort assignment according to the randomization schedule generated by the statistics department at AbbVie.

Subjects who are enrolled will retain their subject number assigned at the Screening visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

## 6.4 Selection and Timing of Dose for Each Subject

All capsules of pancrelipase will be dosed at the time of snack or meal. All subjects should take all doses of study medications with food around the same time each day.

# APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

| Abbreviation | Definition |
|---|---|
| BMI | Body mass index |
| CBC | Complete blood count |
| eDiary | Electronic diary |
| ECG | Electrocardiogram |
| EDC | Electronic data capture |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EORTC QLQ-C30 | EORTC Quality of Life Questionnaire–C30 |
| EPI | Exocrine pancreatic insufficiency |
| ER | Emergency room |
| FSH | Follicle-stimulating hormone |
| hCG | Human chorionic gonadotropin |
| IRT | Interactive response technology |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MCV | Mean corpuscular volume |
| PD | Premature discontinuation |
| PPI | Proton pump inhibitor |
| PRO | Patient-reported outcome |
| PT | Preferred term |
| QLQ | Quality of life questionnaire |
| RDW | Red cell distribution width |
| SAE | Serious adverse event |
| SOC | System organ class |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| UA | Urinalysis |
| USP | United States Pharmacopeia |

# APPENDIX B. EORTC QLQ-C30

ENGLISH

## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| **During the past week:** | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

ENGLISH

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# APPENDIX C. EORTC QLQ-PAN26

ENGLISH

## EORTC QLQ - PAN26

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

| During the past week: | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|
| 31. Have you had abdominal discomfort? | 1 | 2 | 3 | 4 |
| 32. Did you have a bloated feeling in your abdomen? | 1 | 2 | 3 | 4 |
| 33. Have you had back pain? | 1 | 2 | 3 | 4 |
| 34. Did you have pain during the night? | 1 | 2 | 3 | 4 |
| 35. Did you find it uncomfortable in certain positions (e.g. lying down)? | 1 | 2 | 3 | 4 |
| 36. Were you restricted in the types of food you can eat as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 37. Were you restricted in the amounts of food you could eat as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 38. Did food and drink taste different from usual? | 1 | 2 | 3 | 4 |
| 39. Have you had indigestion? | 1 | 2 | 3 | 4 |
| 40. Were you bothered by gas (flatulence)? | 1 | 2 | 3 | 4 |
| 41. Have you worried about your weight being too low? | 1 | 2 | 3 | 4 |
| 42. Did you feel weak in your arms and legs? | 1 | 2 | 3 | 4 |
| 43. Did you have a dry mouth? | 1 | 2 | 3 | 4 |
| 44. Have you had itching? | 1 | 2 | 3 | 4 |
| 45. To what extent was your skin yellow? | 1 | 2 | 3 | 4 |
| 46. Did you have frequent bowel movements? | 1 | 2 | 3 | 4 |
| 47. Did you feel the urge to move your bowels quickly? | 1 | 2 | 3 | 4 |
| 48. Have you felt physically less attractive as a result of your disease and treatment? | 1 | 2 | 3 | 4 |

Please go to the next page

ENGLISH

| During the past week: | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|
| 49. Have you been dissatisfied with your body? | 1 | 2 | 3 | 4 |
| 50. To what extent have you been troubled with side-effects from your treatment? | 1 | 2 | 3 | 4 |
| 51. Were you worried about your health in the future? | 1 | 2 | 3 | 4 |
| 52. Were you limited in planning activities in advance (e.g. meeting friends)? | 1 | 2 | 3 | 4 |
| 53. Have you received adequate support from your health care professionals? | 1 | 2 | 3 | 4 |
| 54. Has the information given about your physical condition and treatment been adequate? | 1 | 2 | 3 | 4 |
| 55. Have you felt less interest in sex? | 1 | 2 | 3 | 4 |
| 56. Have you felt less sexual enjoyment? | 1 | 2 | 3 | 4 |

# APPENDIX D. EPI SYMPTOM QUESTIONNAIRE

**Exocrine Pancreatic Insufficiency (EPI) Symptom Questionnaire**

**Instructions:** These questions ask about symptoms you may have had during the **past 7 days**. Please answer all questions by selecting the one option that best describes your experience.

1. Rate your **abdominal pain** during the past 7 days.

☐ **None**

☐ **Mild**

☐ **Moderate**

☐ **Severe**

☐ **Very Severe**

2. Rate your **bloating (feeling like you need to loosen your clothes)** during the past 7 days.

☐ **None**

☐ **Mild**

☐ **Moderate**

☐ **Severe**

☐ **Very Severe**

3. Rate your **nausea** during the past 7 days.

☐ **None**

☐ **Mild**

☐ **Moderate**

☐ **Severe**

☐ **Very Severe**

4. Rate your **vomiting** during the past 7 days.

☐ **None**

☐ **Mild**

☐ **Moderate**

☐ **Severe**

☐ **Very Severe**

5. Rate your **gas (flatulence)** during the past 7 days

☐ **None**

☐ **Mild**

☐ **Moderate**

☐ **Severe**

☐ **Very Severe**

6. Rate your **constipation** during the past 7 days.

☐ **None**

☐ **Mild**

☐ **Moderate**

☐ **Severe**

☐ **Very Severe**

7. Rate your **foul smelling stools** during the past 7 days.

☐ **None**

☐ **Mild**

☐ **Moderate**

☐ **Severe**

☐ **Very Severe**

8. Rate your **greasy or fatty stools** during the past 7 days.

☐ **None**

☐ **Mild**

☐ **Moderate**

☐ **Severe**

☐ **Very Severe**

9. Rate your **abdominal cramps** during the past 7 days.

☐ **None**

☐ **Mild**

☐ **Moderate**

☐ **Severe**

☐ **Very Severe**

10. Rate your **diarrhea** during the past 7 days.

☐ **None**

☐ **Mild**

☐ **Moderate**

☐ **Severe**

☐ **Very Severe**

11. Rate your **lack of appetite** during the past 7 days.

☐ **None**

☐ **Mild**

☐ **Moderate**

☐ **Severe**

☐ **Very Severe**

12. Rate your **tiredness** during the past 7 days.

☐ **None**

☐ **Mild**

☐ **Moderate**

☐ **Severe**

☐ **Very Severe**

# APPENDIX E. BRISTOL STOOL CHART