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Protocol for Study M21-432

Exocrine Pancreatic Insufficiency (EPI): Phase 4 Study of Symptoms of EPI in Subjects Treated with Creon® (Pancrelipase) with an Alternate Source of Active Pharmaceutical Ingredient

VERSION:	1.0	DATE:	19 May 2021
SPONSOR:	AbbVie Inc.	PLANNED NUMBER OF SITES:	15
ABBVIE INVESTIGATIONAL PRODUCT:	Pancrelipase	EudraCT:	Not applicable

FULL TITLE: A Phase 4 Study to Assess Symptoms of Exocrine Pancreatic Insufficiency in Subjects with Cystic Fibrosis or Chronic Pancreatitis Treated with Creon® (Pancrelipase) with an Alternate Source of Active Pharmaceutical Ingredient

PRINCIPAL INVESTIGATOR(S): Investigator information is on file at AbbVie.

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*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority. Additional study contact information can be found in the Operations Manual (Appendix E).

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1 SYNOPSIS

Title: A Phase 4 Study to Assess Symptoms of Exocrine Pancreatic Insufficiency in Subjects with Cystic Fibrosis or Chronic Pancreatitis Treated with Creon® (Pancrelipase) with an Alternate Source of Active Pharmaceutical Ingredient	
Background and Rationale:	The purpose of this study is to evaluate the clinical symptoms of EPI in subjects with cystic fibrosis (CF) or chronic pancreatitis (CP) treated with pancrelipase with API from SPL (**CREON-SPL**).
Objective and Endpoints:	This is a descriptive, exploratory study. The objective of this study is to evaluate the clinical symptoms of EPI in subjects treated with **CREON-SPL**. The Pharmacodynamic endpoints are: • Total Symptom Score (TSS) as defined in the Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q) at Days 1, 8, 15, 29 and 85. • Abdominal Symptom Domain Score (ASDS) as defined in PEI-Q at Days 1, 8, 15, 29 and 85. • Bowel Movement Symptom Score (BMSS) as defined in PEI-Q at Days 1, 8, 15, 29 and 85. Safety will be assessed by the description of treatment-emergent adverse events (TEAEs).
Investigators:	Multicenter
Study Sites:	Approximately 15 sites from the United Sites are expected to participate.
Study Population and Number of Subjects to be Enrolled:	The study population is adult subjects with CF or CP. Approximately 30 subjects will be enrolled.
Investigational Plan:	This is a Phase 4, prospective, single-arm, single-blinded study. As this study is descriptive and exploratory, no clinical hypothesis is being tested.
Key Eligibility Criteria:	Key eligibility criteria include: adult male or female subjects; a previous diagnosis of CF or CP; a previous diagnosis of EPI that is currently clinically controlled; current treatment with a Creon dosing regimen including the 24,000 LU strength for at least 3 months prior to Screening; a Total Symptom Score (TSS) < 1.8 on PEI-Q at Screening; no malignancy involving the digestive tract in the last 5 years, or other significant disease or medical condition that may interfere with EPI symptom assessment.
Study Drug and Duration of Treatment:	Single-blinded study drug (**CREON-SPL** or **CREON-ABT**) is provided as 24,000 lipase units (LU) capsules. Throughout the study, subjects will maintain the same stable individual dose per LU of Creon that they were on before initiating screening. Study drug will be taken orally with each meal and snack (as per patient's usual practice).
Date of Protocol Synopsis:	19 May 2021

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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, delivery or activity of pancreatic 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. There are approximately 190,000 patients in the United States (US) managing their EPI with pancreatic enzyme replacement therapy (PERT).[1]

Pancreatic enzyme replacement therapy is the cornerstone of EPI treatment. Without PERT, patients may suffer from maldigestion and malabsorption and associated consequences, such as weight loss, malnutrition and sarcopenia.[2-4] Pancrelipase delayed-release (DR) capsules is a PERT currently approved and marketed in the US by AbbVie as Creon® for the treatment of EPI due to CF, CP, pancreatectomy or other conditions.[5] Currently approved and marketed Creon is manufactured using active pharmaceutical ingredient (API) produced at [redacted].

In order to protect Creon's supply chain through site and geographic diversity, AbbVie invested in new equipment and manufacturing site expansion to replicate the manufacturing process for pancrelipase DR API at an alternate site [redacted], in order to produce Creon using SPL API (**CREON-SPL**). This study is being conducted to evaluate the clinical symptoms of EPI in subjects treated with the Creon manufactured with SPL API (**CREON-SPL**).

Information on **CREON-ABT** and **CREON-SPL** can be found in Section 5.9. Further information on pancrelipase DR currently marketed as Creon® in the US can be found in the US Product Information (USPI).[5]

2.2 Benefits and Risks to Subjects

All subjects enrolled in this study will receive treatment for EPI during the study. This is the primary benefit to subjects for this study.

The safety and efficacy of Creon has been well described in subjects with EPI. The safety data describe a well-tolerated regimen, and the use of Creon is supported by a favorable benefit-risk profile. Risks of study participation include those currently listed in the USPI for Creon,[5] and are not expected to be different for **CREON-SPL**.

For further details, please see the current Creon Investigator's Brochure and the current product insert.[5]

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3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

This is a descriptive, exploratory study.

The objective of this study is to evaluate the clinical symptoms of EPI in subjects treated with **CREON-SPL**. No clinical hypothesis is being tested.

3.2 Pharmacodynamic Endpoints

- Total Symptom Score (TSS) as defined in the Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q) at Days 1, 8, 15, 29 and 85.
- Abdominal Symptom Domain Score (ASDS) as defined in PEI-Q at Days 1, 8, 15, 29 and 85.
- Bowel Movement Symptom Score (BMSS) as defined in PEI-Q at Days 1, 8, 15, 29 and 85.

3.3 Safety Endpoints

Safety evaluations include monitoring of treatment-emergent adverse events (TEAEs).

A TEAE compatible with the clinical symptoms of EPI will be considered an adverse event of special interest (AESI) for this study and will be summarized separately.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 4, prospective, single-arm, single-blinded study (subject will not be aware of the order in which study drugs are dispensed). Approximately 30 subjects will be enrolled.

Female subjects of childbearing potential who have a positive pregnancy test during Screening, are not eligible to rescreen. Subjects who fail screening due to other reasons can be rescreened once. In the event of rescreening, only prior disqualifying criterion/criteria will need to be repeated.

This study will consist of 4 periods as follows:

Screening Period: Subjects have up to 14 days following the Screening Visit to confirm eligibility and enroll into the study at the Run-In Visit (RIV). If all eligibility criteria can be verified during the Screening Visit, the RIV can occur on the same day as the Screening Visit, and the subject can be enrolled in the study and be dispensed **Creon-ABT**. If full eligibility cannot be confirmed at the Screening Visit, the subject will schedule the RIV on a separate date.

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Run-in Period:

At the RIV, after eligibility is confirmed, the subject will be dispensed blinded Creon 24,000 lipase units (LU) manufactured with Abbott API (**CREON-ABT**) to be used for the duration of the Run-in Period (28 days) at the same stable individual dose of Creon he/she was on before Screening. This assures that the Day 1 assessment reflects the symptoms on stable **CREON-ABT** use.

Treatment Period: Subjects who complete the Run-in Period will be assessed for the continuation criteria at Day 1. Only subjects who meet all continuation criteria will be dispensed additional study drug. Blinded **CREON-ABT** study drug from the Run-In Period will be returned, and the subject will be dispensed blinded Creon 24,000 LU manufactured with SPL API (**CREON-SPL)** to use at the same stable individual dose per LU of Creon he/she was on before Screening and during the Run-in Period. This assures that the treatment assessments after Day 1 reflect the symptoms on **CREON-SPL**. Symptoms will be assessed at Day 1 and over both short- (Day 8) and long-term (Days 15, 29, and 85). Study procedures, including assessment of EPI symptoms and adverse events (AEs), will be conducted at each visit.

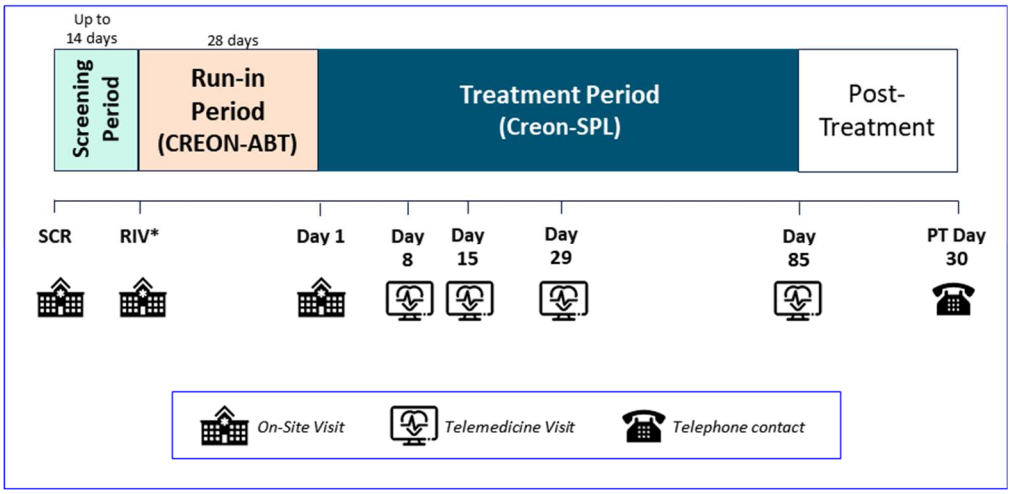
Post-Treatment Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 30 days, through a safety follow-up telephone contact, to assess symptoms and to verify the subject's well-being.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual.

See Section 5.1 for information regarding eligibility criteria.

See Section 5.2 for information regarding the continuation criteria.

Figure 1. Study Schematic



CREON-ABT = Creon using active pharmaceutical ingredient produced at [redacted]; **CREON-SPL** = Creon using active pharmaceutical ingredient produced [redacted]; PT = post treatment; SCR = Screening; SB = single-blinded; RIV = Run-in Visit

* If all eligibility criteria can be confirmed at the SCR Visit, RIV can occur at the same day as the SCR Visit.

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Study completion for each subject is defined as the date of the follow-up telephone contact or the premature study discontinuation visit, whichever comes later. The maximum duration of study participation is approximately 157 days for each subject.

4.2 Discussion of Study Design

A single-arm, single-blind, prospective, longitudinal design is considered appropriate to evaluate symptoms, as the assessments being performed are reported by the subject (patient reported outcome [PRO]). The 7-day recall period of the PEI-Q instrument assures that the measurement obtained at Day 1 reflects the symptoms under **CREON-ABT**, i.e., before the switch to **CREON-SPL**. Providing **CREON-ABT** for 28 days before Day 1, assures the stability of the effect of **CREON-ABT** at the time it is assessed at Day 1. Because of the subjective nature of symptom assessment, the subjects will be blinded to which study drug they are receiving at each point in the study. The investigators will know the sequence of assignment of study drug but must not inform the subject of this assignment.

Additionally, a study with a simple design (e.g., utilizing telemedicine visits, avoiding confinement period, diet standardization or stool collection) was chosen to facilitate study execution during the current SARS-CoV-2 epidemic, in alignment with the study objective. The number of in-person visits was minimized to essential visits where labs are collected, or study drug is dispensed/reconciled. Most study visits will be conducted remotely via a telemedicine visit or a phone call.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All pharmacodynamic and safety-related measurements in this study are standard for assessing disease activity in subjects with CF or CP. All clinical and laboratory procedures in this study are standard and generally accepted.

The pharmacodynamic assessments will be conducted using an EPI-specific PRO measure – the PEI-Q. The PEI-Q is an 18-item PRO measure designed to assess EPI symptoms and associated impact.[6,7] The PEI-Q has demonstrated good content validity, reliability, and psychometric properties via the conduct of qualitative concept elicitation, cognitive debriefing interviews and quantitative psychometric evaluation studies in EPI patients due to CF and CP.[6,7]

Suitability of Subject Population

Male and female subjects with EPI and CF or CP who meet all of the eligibility criteria at the RIV will be eligible to enroll into the study. Subjects who meet the continuation criteria at Day 1 will be allowed to initiate the Treatment Period of the study. The instrument that will be used to assess EPI symptoms (PEI-Q) was developed in a population of CF and CP patients. As subjects are required to be clinically controlled in their current PERT regimen, and subjects with a TSS ≥ 1.8 are most likely poorly clinically controlled, those subjects will be excluded.

Selection of Doses in the Study

This study does not select a specific dose of pancrelipase. The individualized dose that the subject is using before and during Screening will be maintained throughout the Run-in and Treatment Periods, as

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specified in the eligibility criteria (see Section 5.1). The subject's total daily dose should not exceed the approved dose of 4,000 LU/g fat/day or 10,000 LU/kg/day.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be enrolled 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 form (ICF)**, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures. The use of Legally Authorized Representatives (LARs) is prohibited for this protocol.

Demographic

- 2. Adult **male or female**, at least 18 years old at the time of ICF signature.
- 3. Are willing and able to comply with all procedures required in this protocol.
- 4. Subject must be able to read, and must be willing and capable to use the electronic patient reported outcome (ePRO) device and the platform needed for remote assessment and telemedicine visits.

Disease/Condition Activity

- 5. Subject has a previous diagnosis of Cystic Fibrosis (CF) or Chronic Pancreatitis (CP).
  - A diagnosis of CF is defined by:
    - sweat chloride test result ≥ 60 mmol/L, **and/or**
    - documented CF-causing CFTR mutations and clinical features of CF.[8,9]
  - A diagnosis of CP is defined by presence of definite or probable evidence of CP in a patient with history and physical examination suspicious for CP, as described in the 2014 APA Practice Guidelines in CP.[10]
- 6. Subject has a previous diagnosis of EPI that is currently clinically controlled (no clinically overt steatorrhea or diarrhea) with a Creon dosing regimen for more than 3 months prior to Screening.
- 7. Subject has a Total Symptom Score (TSS) < 1.8 on PEI-Q at Screening.

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Subject History

- 8. Subject is on an individualized, stable (no change in the prescribed total daily dose in LU for at least 3 months before Screening) dose regimen of commercially available Creon that includes the use of the 24,000 LU capsule strength (up to a maximum of sixteen 24,000 LU capsules per day). The subject's total daily dose should not exceed 4,000 LU/g fat/day or 10,000 LU/kg/day.
- 9. Subject does not have any medical history of any type of malignancy involving the digestive tract in the last 5 years, nor any of the following medical conditions:

  At any time prior to Screening:

  - fibrosing colonopathy
  - celiac disease
  - bariatric surgery or partial/total gastrectomy
  - inflammatory bowel disease
  - irritable bowel syndrome
  - lactose intolerance not controlled with diet
  - previous bowel surgery (other than minor resection that does not result in malabsorption syndromes)
  - any other clinically significant disease or medical condition that may interfere with the EPI symptom assessment, as per the investigator's judgment

  Within 6 months prior to or during screening:

  - distal intestinal obstruction syndrome episode
  - *Clostridioides (Clostridium)* difficile infection
  - Small intestine bacterial overgrowth
  - acute pancreatitis
- 10. Subjects must not have a diagnosis/history of renal impairment, hyperuricemia, or uncontrolled gout, including those with a recent acute gout flare within 60 days of Screening that would make the subject an unsuitable candidate to receive study drug in the investigator's opinion.
- 11. Subjects must not have any history of an allergic reaction or significant sensitivity to pork, or constituents of Creon (and its excipients) and/or other products in the same class.
- 12. Subject did not have a recent history, in the 7 days prior to or at the RIV, of uncontrolled diabetes mellitus or any acute illness.
- 13. Subject should not have any signs or symptoms associated with COVID-19 infection during Screening or at the RIV.

Contraception

- 14. If female, subject must be either:

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- postmenopausal, defined as either:
  - female with age > 55 years with no menses for 12 or more months, without an alternative medical cause.
  - female with age ≤ 55 years with no menses for 24 or more months without an alternative medical cause

OR

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy) or premenopausal female with permanent sterility (non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals)

OR

- For females of childbearing potential, practicing at least one protocol-specified method of birth control, as specified in Section 5.3, that is effective from study Screening through at least 7 days after the last dose of study drug.

15. Females of child-bearing potential must have a negative urine pregnancy test at Screening and at the RIV (prior to the first dose of study drug).
16. Female subjects should not be pregnant, or breastfeeding, or considering becoming pregnant or donating eggs during the study or for approximately 7 days after the last dose of study drug.

Concomitant Medications

17. Subject did not initiate new antibiotic therapy (except for inhaled antibiotics) within 10 days prior to the RIV.
18. Subject has not used narcotic medications for at least 3 months prior to Screening.
19. Subject should not require, or should be able to safely discontinue, the medications or supplements listed below prior to the RIV throughout the end of the treatment period.
    - Anti-diarrheal and antispasmodic drugs
    - Stimulant or lubricant laxatives
    - Antacids containing aluminum, magnesium, or calcium
    - Fiber supplements (e.g., psyllium, calcium polycarbophil)
    - Immunosuppressive drugs (not including steroids)
    - Any pancreatic enzyme preparations other than the study drug (except for any other Creon strength, besides the 24,000 LU strength, that the subject was taking as part of their stable regimen before study, which must be continued along with the 24,000 LU study drug)
    - Nutritional supplementation via tube feeding (nasogastric, gastrostomy, jejunostomy)

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- 20. If the medications below are used, the subject should be able to safely keep the same stable dose used at the RIV throughout the end of the treatment period. If not used, the investigator should not be planning to initiate these drugs from the RIV throughout the end of the treatment period:
  - proton pump inhibitors, H2-blockers
  - Antacids containing bicarbonate only
  - Cholestyramine, sucralfate
  - Prokinetics (e.g., domperidone, bromopride, metoclopramide, sulpiride)
  - Prostaglandins, Somatostatin
  - Prebiotics or probiotic drugs or supplements
  - Immunosuppressive steroids (local or systemic)
  - Osmotic laxatives
  - Oral iron supplementation
- 21. Subject must not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the RIV, or be currently enrolled in another clinical study, or have been previously enrolled in this study.

5.2 Continuation Criteria

At the Day 1 visit, the subject will be assessed for the following continuation criteria and will only be able to initiate the Treatment Period at Day 1 (i.e., start **CREON-SPL**) if the following criteria are met:

- Subject continues to be willing and capable to use the ePRO device and the platform needed for remote assessment and telemedicine visits throughout the rest of the study.
- Subject has a TSS on PEI-Q < 1.8 at Day 1.
- Subject has not been identified as non-compliant with study drug administration, as per the investigator's assessment.
- Subject did not have a recent history, starting within 7 days prior to or at Day 1, of uncontrolled diabetes mellitus or any acute illness.
- Subject does not have any signs or symptoms associated with COVID-19 infection at Day 1.
- Females of child-bearing potential have a negative urine pregnancy test at Day 1, prior to the initiation of **CREON-SPL**.
- Subject did not initiate new antibiotic therapy (except for inhaled antibiotics) within 10 days prior to Day 1.
- Subject does not have any other clinically significant disease or medical condition that may interfere with the EPI symptom assessment, as per the investigator's judgment.

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5.3 Contraception Recommendations

Contraception Requirements for Females

Female subjects should not be pregnant, breastfeeding or considering becoming pregnant during the study or for approximately 7 days after the last dose of study drug.

Subjects must follow the following contraceptive guidelines as specified:

Females, Non-Childbearing Potential

Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
   - Permanent surgical sterility due to a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy
   - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
2. Postmenopausal female
   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 24 or more months without an alternative medical cause

Females, of Childbearing Potential

Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 7 days after the last dose of study drug. Females of childbearing potential must commit to one of the following methods of birth control:

- Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation-initiated at least 30 days prior to Screening.
- Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to Screening.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation **is not** the primary mode of action, initiated at least 30 days prior to Screening.
- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).

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- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
- 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).
- Practice true abstinence, defined as: 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).

Contraception Requirements for Males

Male subjects are not required to use contraception methods during the study.

5.4 Prohibited Medications and Therapy

The following medications/therapies are prohibited from the RIV to the end of the Treatment Period:

- Anti-diarrheal and antispasmodic drugs
- Stimulant or lubricant laxatives
- Antacids containing aluminum, magnesium, or calcium
- Fiber supplements (e.g., psyllium, calcium polycarbophil)
- Immunosuppressive drugs (not including steroids)
- Nutritional supplementation via tube feeding (nasogastric, gastrostomy, jejunostomy)
- Any pancreatic enzyme preparations other than the study drug (except for any other Creon strength, besides the 24,000 LU strength, that the subject was taking as part of their stable regimen before study, which must be continued along with the 24,000 LU study drug)

The following medications/therapies are prohibited from 30 days or 5 half-lives of the drug (whichever is longer) prior to the RIV, until the end of the study:

- Any investigational drugs

Narcotic analgesics can be used only if necessary for management of an AE, such as acute pain management.

Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

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5.5 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.

Any questions regarding concomitant or prior therapy should be raised to the Sponsor Medical contact.

5.6 Prior and Post Treatment PERT Therapy

The total daily dose of Creon® taken prior to the RIV will be recorded in the electronic case report form (eCRF).

The total daily dose of Creon® taken during the Post-Treatment 30-day Period will be recorded in the eCRF.

5.7 Withdrawal of Subjects and Discontinuation of Study

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

- The subject requests to be withdrawn from the study.
- Any intake of pancreatic enzyme preparations in addition or substitution to the study drug during the study.
- When continuation of the study drug would place the subject at risk, as determined by the Investigator.
- Subjects who become pregnant during the study.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the study.
- Subject does not meet all continuation criteria at Day 1.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. 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/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID 19 pandemic, it may be necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Refer to Section 2 and Section 3.1 of the Operations Manual in Appendix E.

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5.8 Follow-Up After Subject Discontinuation of Study Drug or from Study

To minimize missing data for study assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation Visit (PD Visit) should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/serious adverse events (SAEs) have been resolved.

5.9 Study Drug

Study drug will only be shipped to clinical sites that have provided the sponsor (or an authorized representative) with all required study documents, including Independent ethics committee/institutional review board (IEC/IRB) approval, and have signed a clinical study agreement.

Study drug capsules (**CREON-ABT** or **CREON-SPL**) will be taken orally with each meal and snack (as per patient's usual practice) with enough fluids to swallow the capsules completely. Capsules must be swallowed whole (capsules must not be crushed, chewed, or opened). Subjects will maintain throughout the study the same stable individual dose per LU of Creon they were on before initiating Screening.

If the Screening Visit and the RIV do not occur on the same day, subjects will continue their existing stable dose of commercial Creon until the RIV.

At the RIV, eligible subjects will be dispensed blinded Creon 24,000 LU manufactured with Abbott API (**CREON-ABT**) for the Run-in Period. At the RIV, and for the duration of the study, eligible subjects will stop using the commercial Creon 24,000 LU capsules they were taking before the RIV and begin taking the same corresponding number of capsules at meals and snacks (maintaining the same daily dosing as prescribed by their doctor), using the 24,000 LU capsules dispensed as study drug. If the subject is using more than one strength of commercial Creon capsules, the subject will keep taking the commercial Creon capsules of any other strength besides the 24,000 LU strength at the same previous dose and will switch the 24,000 LU capsules from the commercial Creon they were using before Screening to the 24,000 LU capsules dispensed as study drug.

At Day 1, subjects will return all the bottles dispensed at the RIV. Subjects who meet all continuation criteria at Day 1 will be dispensed blinded Creon 24,000 LU manufactured with SPL API (**CREON-SPL**) for the Treatment Period at the same dose used during the Run-in Period.

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The subjects will be blinded to the type of study drug they will be receiving; therefore, site personnel **MUST NOT** inform the subject whether they are receiving **CREON-ABT** or **CREON-SPL** at each dispensation visit, in order to maintain the single-blind of the study.

If a subject forgets to take their study drug dose at their regularly scheduled dosing time, they should take the next dose at the next snack or meal. Information on the study drugs is provided in Table 1. AbbVie-provided study drug must not be substituted. Direct-from-patient shipping at Day 85/PD Visit is also described in the Operations Manual (Appendix E).

The subject will be instructed to return all drug containers (even if empty) to the study site personnel at the completion of the Run-in and Treatment Periods. The study site personnel will document study drug usage.

Pancrelipase (**CREON-ABT** or **CREON-SPL**) will be packaged in bottles with quantities sufficient to accommodate the study design. Each kit 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 kit 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. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

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Table 1. Study Drug Information

	Investigational Product	
Investigational product name	**CREON-SPL**	**CREON-ABT**
Product Blinded /Labeled name	Pancrelipase 24,000 USP Units (Lipase) (Creon-ABT or Creon-SPL) Delayed-Release Capsule	Pancrelipase 24,000 USP Units (Lipase) (Creon-ABT or Creon-SPL) Delayed-Release Capsule
Type of Blinding	Single-blind (subject)[a]	Single-blind (subject)[a]
Active ingredient	Pancrelipase, a mixture of lipase, protease and amylase of porcine origin manufactured by SPL	Pancrelipase, a mixture of lipase, protease and amylase of porcine origin manufactured by ABT
Mode/Route of Administration	Oral	Oral
Formulation	Pancrelipase pellets manufactured using the commercial process, with pancrelipase API sourced from SPL, filled into commercial transparent capsules with orange caps with the imprint "CREON 1224"	Pancrelipase pellets manufactured using the commercial process, with pancrelipase API sourced from ABT, filled into commercial transparent capsules with orange caps with the imprint "CREON 1224"
Dosage Form	Delayed-release Capsules	Delayed-release Capsules
Strength	24,000 USP units (lipase) capsules	24,000 USP units (lipase) capsules
Frequency of administration	Daily with each meal or snack	Daily with each meal or snack
Excipients	Capsule Shell: Gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide Drug Product: cetyl alcohol, dimethicone, hypromellose phthalate, polyethylene glycol, and triethyl citrate	Capsule Shell: Gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide Drug Product: cetyl alcohol, dimethicone, hypromellose phthalate, polyethylene glycol, and triethyl citrate
Storage Conditions	Store between 15°C to 25°C (59°F to 77°F). See clinical label for additional details.	Store between 15°C to 25°C (59°F to 77°F). See clinical label for additional details.

[redacted]

USP = United States Pharmacopoeia

a. Subject will not be informed whether they are receiving **CREON-ABT** or **CREON-SPL.** Study drug capsules and bottles will look identical, identifiable only by the IRT kit number.

Additional information on the investigational products is provided in Operations Manual Section 6.

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Digital Health Tools Accountability

The investigator or his/her representative will verify that the digital health tools (e.g., PRO devices) are received intact and in the correct amounts. A proof of receipt or similar document will be kept in the site files as a record of what was received.

In addition, sites will maintain records of traceability, accountability, and return including but not limited to date received/dispensed/returned, subject number, and the identification of the person dispensing/returning the digital health tools.

5.10 Drug Assignment

This is a single-arm study, and all eligible subjects will receive both study drugs (**CREON-ABT** during the Run-in Period; **CREON-SPL** during the study Treatment Period). However, to blind subjects to the sequence of study drugs, the IRT system will be used to allocate drug.

All subjects will be assigned a unique subject identification number by the IRT at the Screening Visit. For subjects who rescreen, the subject number assigned by the IRT at the initial Screening Visit should be used.

AbbVie personnel, the investigator, study site personnel, and anyone with access to the full protocol, will be unblinded to the sequence of study drug assignment. Only subjects will remain blinded to their treatments throughout the study. To maintain the subject blind, the **CREON-SPL** and **CREON-ABT** capsules provided for the study will be identical in appearance. The investigator, study site personnel **must not** inform the subject of the order they will receive the 2 study drugs. The subject should remain blinded even if the subject experiences an AE.

5.11 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

5.12 Data Monitoring Committee

The external, independent data monitoring committee (DMC) will review unblinded safety data during the study. The DMC Charter for Study M21-432 will include, but is not limited to, the following: the frequency and scope of data reviews, the suggested relevant data to be included in the review, the DMC responsibilities, and the DMC members and their credentials.

Since this is a single-arm, single-blinded study and the sponsor is unblinded, the sponsor will be responsible for performing the DMC analyses described in the DMC Charter as well as any additional analyses requested by the DMC.

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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.

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 damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

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 can therefore be any unfavorable and unintended sign (including an abnormal 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.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

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/or the surgery/procedure has

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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 any of the following events are reported, then the following supplemental reports must be completed.

Event	Supplemental Report
TEAEs compatible with clinical symptoms of EPI	EPI Symptom CRF
Covid-19 Diagnosis	COVID -19 Supplemental Signs/Symptoms CRF COVID-19 Status Form CRF

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as an SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.2 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, life threatening, 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.

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All AEs reported from the time of first 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, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

Adverse events will be monitored throughout the study to identify any of special interest for this study.

Adverse Events of Special Interest

The following TEAEs compatible with clinical symptoms of EPI will be considered AESI for this study:

- Diarrhea
- Abdominal pain
- Abdominal bloating
- Flatulence
- Steatorrhea

Patients with signs and symptoms suggestive of worsening EPI should be evaluated and treated as clinically indicated by the investigator.

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 to Creon 24,000 LU dispensed as **CREON-ABT** or **CREON-SPL**.
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 to Creon 24,000 LU dispensed as **CREON-ABT** or **CREON-SPL**.

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Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.7). If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Management of COVID-19 Infection

Clinical management of confirmed or suspected COVID-19 infection during the study will be handled by the investigator according to treatment guidelines and local standard of care.

For suspected COVID-19 infection, prompt and comprehensive evaluation should be performed to confirm COVID-19 infection or exclude other causes (e.g., influenza). For negative COVID-19 results, the investigator should consider re-testing based on clinical suspicion (exposures, clinical findings).

All cases of suspected or confirmed COVID-19 infection **must** be discussed with the Sponsor/Emergency Medical Contact regarding additional COVID-19 testing, alternative etiologies and/or study visit disposition (including but not limited to the possibility of screen fail due to an expiring screening window, premature discontinuations, etc.).

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on high level description of the statistical analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

The planned analyses will be conducted after all subjects have completed the study or prematurely discontinued from the study.

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all enrolled subjects who received at least 1 dose of study drug of **CREON-SPL**. The FAS will be used for the summary of subject disposition and baseline characteristics.

A Per-Protocol (PP) Population includes all enrolled subjects who received at least 1 dose of study drug of **CREON-SPL**, had Day 1 (baseline) PEI-Q scores collected, and had at least one post-baseline PEI-Q scores collected during the Treatment Period (Days 8, 15, 29, and 85). The pharmacodynamic endpoints will be analyzed in the PP Population.

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The Safety Analysis Set for **CREON-ABT** (SAS-CREON-ABT) consists of all subjects who received at least 1 dose of **CREON-ABT** study drug during the Run-in Period. The Safety Analysis Set for **CREON-SPL** (SAS-CREON-SPL) consists of all subjects who received at least 1 dose of **CREON-SPL** study drug.

7.3 Handling Potential Intercurrent Events for the Study Endpoints

The pharmacodynamic endpoints (TSS, ASDS and BMSS) will be analyzed based on the PP population and the following potential intercurrent events will be addressed:

- Subjects who did not receive any dose of study drug **CREON-SPL** will be excluded from the PP population.
- Subjects who did not have baseline (Day 1) PEI-Q score data or did not have any post-baseline PEI-Q score data will be excluded from the PP population.

Subjects who have missing PEI-Q data for the visit will be excluded from the analysis of that visit.

7.4 Statistical Analyses for Pharmacodynamic Endpoints

Summary and Analysis of the Pharmacodynamic Endpoints

Analyses of the pharmacodynamic endpoints will be conducted on the PP population. Descriptive statistics (N, mean, standard deviation [SD], median, minimum, and maximum) will be used to summarize the TSS as well as the symptom score for each domain of abdominal symptoms and bowel movement symptoms from PEI-Q. The summaries will be provided for the Screening Visit, Baseline Visit (Day 1), each Post-Baseline Visit (Days 8, 15, 29, 85), and the change from baseline for each. Two-sided 95% confidence interval based on t-distribution will also be provided for the mean estimate of each score at each visit, and the mean change from baseline for each post-baseline visit.

7.5 Statistical Analyses for Safety

Safety analyses will be provided based on safety analysis sets. Number and proportion of subjects reporting a TEAE during the Run-in Period (**CREON-ABT**) and Treatment Period (**CREON-SPL),** will be summarized separately using SAS-CREON-ABT and SAS-CREON-SPL, respectively. A TEAE compatible with the clinical symptoms of EPI (see Section 6.1) will be considered an AESI and will be summarized separately. Details of the safety analyses will be provided in the SAP.

Adverse event will be coded using MedDRA. A -TEAE is defined as an AE with an onset date on or after the first dose of corresponding study drug and within 30 days after the last dose of study drug or initiation of the next study drug, whichever is earlier. The number and percentage of subjects experiencing TEAEs will be tabulated using MedDRA system organ class (SOC) and preferred term (PT), as well as by severity and by relationship to the study drug as assessed by the investigator. Summaries (i.e., number and percentages) of TEAEs, SAEs, deaths, AEs leading to discontinuation, and AESIs will be provided.

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7.6 Overall Type I Error Control

Not applicable for this study as the study will provide descriptive statistics with no hypothesis testing.

7.7 Sample Size Determination

Approximately 30 subjects will be enrolled at the RIV. The sample size is calculated based on the descriptive statistics for the TSS based on PEI-Q. No formal statistical hypothesis testing is planned. Assuming a dropout rate of 20% after the RIV, the number of evaluable subjects will be around 24 for the analysis of pharmacodynamic endpoints.

Based on Johnson CD, et al,[6] the average TSS from PEI-Q was estimated to be 1.4 (SD = 0.7) for CP and CF subjects with EPI symptoms. Assuming the covariance between the TSS at baseline and post-baseline after switching to **CREON-SPL** to be 0.365, the SD for the change of the TSS between baseline and post-baseline is estimated to be 0.5. A sample size of 24 evaluable subjects will provide a precision of ± 0.2 in terms of half-length of the 95% confidence interval for the estimate of change in TSS based on PEI-Q.

8 ETHICS

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

The protocol, ICF, recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the ICF 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.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators

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should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

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). During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be 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 date of the last subject's last visit.

12 REFERENCES

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8. Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr. 2008;153(2):S4-S14.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ABT	[redacted]
AE	adverse event
AESI	adverse event of special interest
API	active pharmaceutical ingredient, synonym: drug substance
ASDS	Abdominal Symptom Domain Score
BMSS	Bowel Movement Symptom Score
CBC	complete blood count
CF	cystic fibrosis
CP	chronic pancreatitis
[redacted]	[redacted]
[redacted]	[redacted]
CRF	case report form
DFP	direct from patient
DMC	Data Monitoring Committee
DR	delayed-release
eCRF	electronic case report form
EDC	electronic data capture
EPI	Exocrine Pancreatic Insufficiency
ePRO	electronic patient reported outcome (device)
FAS	full analysis set
GCP	Good Clinical Practice
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IMP	Investigational Medicinal Product
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
LARs	Legally Authorized Representatives

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LU	lipase units
MedDRA	Medical Dictionary for Regulatory Activities
PD	premature discontinuation (visit)
PEI-Q	Pancreatic Exocrine Insufficiency Questionnaire
PERT	pancreatic enzyme replacement therapy
PP	per-protocol
PRO	patient reported outcome
PT	preferred term
RIV	Run-in Visit
SAE	serious adverse event
SAP	statistical analysis plan
SAS-CREON-ABT	safety analysis set for **CREON-ABT**
SAS-CREON-SPL	safety analysis set for **CREON-SPL**
SD	standard deviation
SOC	system organ class
SPL	[redacted]
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TSS	Total Symptom Score
US	United States
USP	United States Pharmacopoeia
USPI	US Product Information

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APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M21-432: A Phase 4 Study to Assess Symptoms of Exocrine Pancreatic Insufficiency in Subjects with Cystic Fibrosis or Chronic Pancreatitis Treated with Creon® (Pancrelipase) with an Alternate Source of Active Pharmaceutical Ingredient

Protocol Date: 19 May 2021

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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:

1. 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. 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.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. 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).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. 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.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. 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.
10. 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)	

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APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Study Project Manager	Clinical Program Development
[redacted]	Principal Medical Writer	Medical Writing
[redacted]	Medical Director	General Medicine and Virology
[redacted]	Statistics Therapeutic Area Head	Statistics
[redacted]	Director, Statistics	Statistics

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APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the eight subject encounters. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed within the Operations Manual.

Study Activities Table

Period	Screening Period	Run-in Period	Treatment Period					Post-Treatment (PT) Period
Visit Name	Screening (SCR)	Run-in Visit (RIV)	Day 1	Day 8	Day 15	Day 29	Day 85/ Premature Discontinuation (PD)	Day 115/PT Day 30
Visit Type	On-Site	On-Site	On-Site	Telemedicine	Telemedicine	Telemedicine	Telemedicine	Phone Call
INTERVIEWS & QUESTIONNAIRES								
Informed consent	✓							
Eligibility criteria	✓	✓						
Continuation criteria			✓					
Medical/surgical history	✓	✓						
Alcohol and nicotine use	✓							
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓
Patient reported outcome (PRO): Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q)	✓		✓	✓	✓	✓	✓	
Study drug usage			✓	✓	✓	✓	✓	
Dispense ePRO device			✓					
Return ePRO device (shipped after the completion of the visit)							✓	
LOCAL LABS & EXAMS								
Height (screening only) and weight	✓	✓	✓					
Vital signs	✓	✓	✓					
Physical examination	✓	✓	✓					
Urine pregnancy test	✓	✓	✓					

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Period	Screening Period	Run-in Period	Treatment Period					Post-Treatment (PT) Period
Visit Name	Screening (SCR)	Run-in Visit (RIV)	Day 1	Day 8	Day 15	Day 29	Day 85/ Premature Discontinuation (PD)	Day 115/PT Day 30
Visit Type	On-Site	On-Site	On-Site	Telemedicine	Telemedicine	Telemedicine	Telemedicine	Phone Call
CENTRAL LABS								
Clinical chemistry	✓							
Hematology (complete blood count [CBC])	✓							
TREATMENT								
Dispense study drug		✓	✓					
Retrieve study drug (at Day 85/PD, shipped after the completion of the visit)			✓				✓	
Study drug accountability (at Day 85/PD, performed after the study drug is received by the site)			✓				✓	

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