1.0 Title Page

Clinical Study Protocol M16-111

A Phase 4 Study to Compare US Marketed Creon® Drug Product with Drug Product Manufactured with a Modernized Process at an Alternate Manufacturing Site and with Drug Product Manufactured with the Approved Manufacturing Process at an Alternate Active Pharmaceutical Ingredient Site, in Subjects with EPI due to Cystic Fibrosis

Incorporating Amendments 1, 2, 3, 4, 5, 6, and 7

AbbVie Investigational Product:	Pancrelipase (ABT-SLV-245) Delayed Release capsules/enteric coated modernized process uniform coated pellets drug product Pancrelipase (ABT-SLV-245) Delayed Release capsules with API from an alternate manufacturing site
Date:	15 September 2021
Development Phase:	4
Study Design:	Two-Part, Double-Blind, Randomized, Active-Controlled, Two-Period, Two-Sequence Crossover design
EudraCT Number:	2017-000578-12
Sponsor:	AbbVie*
Sponsor/Emergency Contact:	[redacted] MD Medical Director Specialty Development 1 N. Waukegan Road North Chicago, IL 60064 Phone: Mobile: Fax: [redacted]

*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.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	19 May 2017
Administrative Change 1	03 August 2017
Amendment 1	29 June 2018
Amendment 2	10 December 2018
Amendment 3	27 February 2019
Administrative Change 2	15 May 2019
Amendment 4	10 October 2019
Administrative Change 3	21 January 2020
Administrative Change 4	21 February 2020
Amendment 5	04 June 2020
Administrative Change 5	29 June 2020
Amendment 6	26 January 2021

The purpose of this amendment is to:

- Updated throughout the protocol that General Medicine at AbbVie has changed to Specialty Development

  Rationale: *To update the name of the Therapeutic Area for Creon studies.*
- Update Section 5.1, Overall Study Design and Plan: Description: Updated the target number of screened subjects to 30, enrolled subjects to 20 and evaluable subjects to 18 for Part 2.

  Rationale: *To align with the updates from the Sample Size Determination in Section 8.2.2*
- Update Section 5.1, Overall Study Design and Plan: Description: Added language to clarify that open label study drug is given to subjects during the follow up period.

  Rationale: *To add clarity*

- Update Section 5.5.1, Treatments Administered: Description: Added language to clarify that open label study drug is given to subjects during the follow up period.

  Rationale: *To add clarity*

- Update Section 8.1.2, Primary and Secondary Endpoint Analyses: Added reference to the Statistical Analysis Plan (SAP) description of estimand attributes and supplementary analyses of primary endpoint.

  Rationale: *To add awareness*

- Update Section 8.2.2, Samples Size Determination: Description: Updated the target number of screened subjects to 30, enrolled subjects to 20 and evaluable subjects to 18 for Part 2, based on revised assumptions.

  Rationale: *To update sample size determination for Part 2 based on revised assumptions (e.g., within-subject standard deviation of treatment difference) based on the results from the Part 1 Blinded Sample Size Re-estimation (BSSR).*

- Update Section 8.2.3, Blinded Sample Size Re-Estimation (BSSR): Description: Updated initial planned sample size and revised within-subject standard deviation assumption for Part 2. Provided rationale for revised assumption.

  Rationale: *To align with updates from the Sample Size Determination in Section 8.2.2.*

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-111
Name of Study Drug: Pancrelipase.	**Phase of Development:** 4
Name of Active Ingredient: Pancrelipase	**Date of Protocol Synopsis:** 15 September 2021
Protocol Title: A Phase 4 Study to Compare US Marketed Creon® Drug Product with Drug Product Manufactured with a Modernized Process at an Alternate Manufacturing Site and with Drug Product manufactured with the Approved Manufacturing Process at an Alternate Active Pharmaceutical Ingredient Site, in Subjects with EPI due to Cystic Fibrosis	
Objectives: The objective of Part 1 is to demonstrate non-inferiority of pancrelipase Delayed Release (DR) capsules Modernized Process (MP) 24,000 USP Units (lipase) drug product compared to the active control (pancrelipase DR capsules 24,000 USP Units (lipase) currently marketed in the US as Creon®) in subjects with Exocrine Pancreatic Insufficiency (EPI) due to Cystic Fibrosis (CF), as measured by Coefficient of Fat Absorption (CFA). The objective of Part 2 is to demonstrate non-inferiority of delayed-release capsules of pancrelipase manufactured with the Approved Manufacturing Process at an **A**lternate **A**ctive **P**harmaceutical **I**ngredient **S**ite (AAPIS) 24,000 USP Units (lipase) compared to the active control (Creon®) in subjects with EPI due to CF, as measured by CFA.	
Investigators: Multi-center	
Study Site(s): Approximately 16 sites	
Study Population: Subjects aged 12 years or older with CF and EPI.	
Number of Subjects to be Enrolled: Part 1: 22 evaluable subjects (Approximately 26 subjects randomized) Part 2: 18 evaluable subjects (Approximately 20 subjects randomized) Subjects will participate in either part 1, part 2 or may choose to participate in both.	

Methodology:

After eligibility is confirmed, the subject will be enrolled to one of the two Study Parts. For each Part, eligible subjects will be randomized into one of the two treatment sequences, as shown in the study schematic. Randomization for Part 1 and Part 2 are independent. After the completion of the participation in the Part they were originally enrolled to, the subjects may be offered the opportunity to participate in the other Part. This participation is optional. If the subject agrees to participate in the other Part, the subject will be kept on open label Creon® while eligibility to that Part is confirmed and the subject can initiate the next confinement period. Subjects who participate in the other Part of the study will be re-randomized in that Part.

Part 1 is designed to test pancrelipase DR MP for non-inferiority compared to an active control (Creon®) in a DB, randomized, active controlled, two-period, two-sequence crossover design in subjects 12 years or older with EPI due to CF, as measured by CFA. Safety will also be assessed.

Part 2 is designed to test pancrelipase DR AAPIS for non-inferiority compared to an active control (Creon®) in a DB, randomized, active controlled, two-period, two-sequence crossover design in subjects of 12 years or older with EPI due to CF, as measured by CFA. Safety will also be assessed.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject is 12 years or older at the time of informed consent/assent form signature.
2. Subject has a documented diagnosis of CF previously confirmed by:
   a. a sweat chloride test ≥ 60 mmol/L, and/or
   b. documented CF-causing CFTR mutations and clinical features of CF.*
3. Diagnosis of moderate to severe EPI, as determined by Fecal Elastase 1 (FE-1) < 15 µg/g at screening.
4. Subject has EPI that is currently clinically controlled (no clinically overt steatorrhea or diarrhea) under treatment with a commercially available Pancreatic Enzyme Replacement Therapy (PERT), on an individually established dose regimen for more than 3 months prior to Screening, with a daily dose not exceeding 4,000 LU/g fat/day or 10,000 LU/kg/day.
5. Subject is available for two (if participating in one of the parts) or four (if participating in both parts) hospitalization/confinement periods of 6 to 8 days each during the expected study window.
6. Subject is able to consume a diet with 100 g fat/day, a minimum of 1 g/kg of protein/day and normal to low fiber content.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion:

1. BMI percentile for age less than 10% in patients less than 18 years of age.
2. Subject has a history of any of the following gastrointestinal disorders:
   a. acute pancreatitis within 6 months prior to SV1 or
   b. chronic pancreatitis, or
   c. fibrosing colonopathy, or
   d. distal intestinal obstruction syndrome (DIOS) within 6 months prior to SV1, or
   e. *C. difficile* infection within 6 months prior to SV1, or
   f. celiac disease, or
   g. gastric bypass or partial/total gastrectomy, or
   h. Crohn's disease or other inflammatory bowel disease, or
   i. small bowel surgery (other than minor resection due to meconium ileus without resultant malabsorption syndrome), or
   j. any type of malignancy involving the digestive tract in the last 5 years.
3. Subject has a history of any clinically significant endocrine, respiratory (except mild asthma or CF-related lung disease), neurological, cardiac, renal, hepatic (including Hepatitis B or C), hematologic or psychiatric disease or disorder, or any other uncontrolled medical illness which might limit participation in or completion of the study.
4. Subject requires concomitant treatment with any medication not allowed by the protocol or a prohibited medication is expected to be needed during the study.
5. Subject is currently receiving nutritional supplementation via tube feeding (nasogastric, gastrostomy, jejunostomy).
6. Subject has clinically significant (as per Investigator's judgment) abnormalities in clinical chemistry, hematology, or urinalysis (excluding findings that are associated with CF) such as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels ≥ 3 times the upper limit of normal values, or clinically significant (investigator opinion) elevation of uric acid.

Investigational Product(s):	For Part 1: • Pancrelipase DR capsules MP 24,000 USP Units (lipase) • Creon® [pancrelipase DR 24,000 USP Units (lipase)] For Part 2: • Pancrelipase AAPIS 24,000 USP Units (lipase) • Creon® [pancrelipase DR 24,000 USP Units (lipase)]
Dose(s):	The study drug total daily dose, calculated based on the maximum dose of 4,000 LU/g of fat/day, as recommended in the current US Creon® capsules 24,000 USP units label, will be administered orally, divided proportionally based on three meals and two snacks.
Mode of Administration:	Oral

Criteria for Evaluation:

Pharmacodynamics:

The primary pharmacodynamic variable will be the CFA which measures fat absorption. Secondary pharmacodynamic variables will include the Coefficient of Nitrogen Analysis Absorption (CNA) (measuring protein absorption), stool fat content, and stool weight. Additional exploratory variables will include stool frequency and consistency, diarrhea, abdominal pain, bloating and flatulence.

Safety:

The safety variables include:

- Clinically significant physical examination findings and laboratory values
- Proportion of subjects reporting treatment-emergent adverse events (TEAEs).

Statistical Methods:

Pharmacodynamics:

The primary pharmacodynamic variable will be the CFA. The primary pharmacodynamic variable will be analyzed in all subjects who complete the 2 crossover treatment periods in the corresponding study Part. The CFA measured at the end of each cross-over period will be analyzed using a mixed effects model including sequence, period and treatment group as fixed effects and subjects within sequence as a random effect. From this model, the mean CFA difference between two treatment groups will be estimated, along with a two-sided 99% confidence interval (CI) that will be compared with a non-inferiority margin of 12%.

The secondary pharmacodynamic variables will be the CNA, stool fat, and stool weight. These variables will also be analyzed separately using a mixed effects model including sequence, period and treatment group as fixed effects and subjects within sequence as a random effect. All comparisons for all secondary pharmacodynamic variables between the treatment groups will be descriptive.

Safety:

Safety analyses will be carried out using the safety population. The safety population includes all subjects who received at least one dose of study drug at any time during the study. Treatment-emergent AEs and SAEs, including pre- and post-treatment SAEs, will be summarized and reported.

Pharmacodynamic and safety analyses will be performed separately for Part 1 and Part 2.

* 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): S4-14.

Smyth AR, Bell SC, Bojcin S, et al. European cystic fibrosis society standards of care: best practice guidelines. J Cyst Fibros. 2014;13 (Suppl 1):S23-42.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

API	Active pharmaceutical ingredient
AAPIS	Delayed-release capsules of pancrelipase manufactured with the approved manufacturing process at an **A**lternate **A**ctive **P**harmaceutical **I**ngredient **S**ite
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
CF	Cystic Fibrosis
CFA	Coefficient of Fat Absorption
CI	Confidence Interval
CNA	Coefficient of Nitrogen Absorption
Cork	AbbVie Fournier Laboratories, County Cork, Ireland
DB	Double-Blind
DIOS	Distal Intestinal Obstruction Syndrome
DR	Delayed-Release
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EPI	Exocrine Pancreatic Insufficiency
EudraCT	European Clinical Trials database
EU	European Union
FDA	US Food and Drug Administration
FD&C	US Food, Drug and Cosmetics
FE-1	Fecal Elastase-1
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
LU	Lipase Units

MedDRA	Medical Dictionary for Regulatory Activities
MP	Modernized process uniform coated pellets manufactured in the large-scale suite
PERT	Pancreatic Enzyme Replacement Therapy
RSI	Reference Safety Information
SAE	Serious Adverse Events
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Drug Reaction
TA	Therapeutic Area
TEAE	Treatment Emergent Adverse Events
USPI	US Product Information

Definition of Terms

Screening Period	Variable duration up to 35 days while confirming eligibility criteria. During this period subjects will receive open label Creon® (Pancrelipase) 24,000 USP units (lipase) with every meal and snack until eligibility is confirmed and subject can be randomized.
Part 1 DB Treatment Periods 1 and 2	Periods during which subjects are taking study drug Creon® (pancrelipase) Delayed Release capsules 24,000 USP Units (lipase) or pancrelipase Delayed Release capsules MP 24,000 USP Units (lipase) every day at the time of meals/snacks. Part 1 DB Treatment Period 1 starts at Visit 2 and ends at Visit 3 and is separated by an interval of up to 28 days from DB Treatment Period 2, which starts at Visit 4 and ends at Visit 5.
Part 2 DB Treatment Periods 1 and 2	Periods during which subjects are taking study drug Creon® (pancrelipase) Delayed Release capsules 24,000 USP Units (lipase) or pancrelipase DR capsules manufactured with an **A**lternate **A**ctive **P**harmaceutical **I**ngredient **Site** (AAPIS) 24,000 USP Units (lipase) every day at the time of meals/snacks. Part 2, DB Treatment Period 1 starts at Visit 2 and ends at Visit 3 and is separated by an interval of up to 28 days from DB Treatment Period 2, which starts at Visit 4 and ends at Visit 5.
Post-Treatment Follow-up Period for subjects participating in only one study Part (Part 1 or Part 2)	Interval between the last dose of study drug (Visit 5) and the safety follow-up telephone contact (Visit 6). During this period subjects will receive open label Creon® (Pancrelipase) 24,000 USP units (lipase).

Post-Treatment Follow-up Periods for subjects participating in both study Parts (Part 1 and Part 2)	Interval between the last dose of study drug (Visit 5) of the study Part the subject was originally assigned to and Visit 6 of that Part, or Visit 1 of the next study Part, whichever comes first. This period is variable in duration, and can last up to 30 days. During this period, subjects will receive open label Creon® (Pancrelipase) 24,000 USP units (lipase). If visit 1 of the next Part does not occur within 30 days of the last dose of study drug (Visit 5) of the previous part, the subject will not receive any additional open label Creon® (Pancrelipase) 24,000 USP units (lipase) past the provided for the first 30 days, and the subject will need to be re-consented and rescreened for the next study part. Once the subject has completed Visit 5 of the next study Part, the follow up period of that next Part is the interval between the last dose of study drug (Visit 5) and the safety follow-up telephone contact (Visit 6) and is 30 days. During this period subjects will receive open label Creon® (Pancrelipase) 24,000 USP units (lipase).

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3.0 Introduction

Pancreatic enzyme replacement therapy (PERT) is the cornerstone of nutritional management of exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF), chronic pancreatitis (CP), partial or complete pancreatectomy (PY) or other conditions. Without pancreatic enzyme replacement, the patients may suffer from severe symptoms of maldigestion and malabsorption.

PERT is critical to achieve optimal growth in patients with EPI due to CF and resulting maldigestion. In patients with CF, abnormally thick mucus blocks the pancreatic duct in the pancreas. The pancreatic digestive enzymes from acinar cells and bicarbonate from ductal cells are not secreted into the intestine, thus preventing the normal digestion of starch, fat and protein. This results in steatorrhea, abdominal pain, flatulence, changes in bowel habits and often, failure to thrive.

Pancrelipase Delayed-Release (DR) capsules is a PERT currently marketed in United States as Creon® for the treatment of EPI due to CF, CP, PY and other conditions. AbbVie has modernized the current drug product process for manufacturing the enteric coated drug product into uniform coated pancrelipase pellets at a new manufacturing site in Cork, Ireland. Part 1 of this study is being conducted to determine whether the modernized process (MP) uniform coated pellets formulation from the large-scale suite [pancrelipase DR capsules MP 24,000 USP Units (lipase)] manufactured at the Cork facility results in similar clinical pharmacodynamics and safety as the current US marketed Creon®, and is thus appropriate to be administered for the same indication and patient populations as Creon®.

In order to protect CREON's supply chain through site and geographic diversity, AbbVie invested in new equipment and facility expansion to duplicate the approved Abbott Neustadt Active Pharmaceutical Ingredient (API) process used to manufacture Creon® currently marketed in the US, to manufacture pancrelipase DR capsules at an **Alternate** **A**ctive **P**harmaceutical **I**ngredient **S**ite (**AAPIS**) in Waunakee, Wisconsin (Scientific Protein Laboratories, SPL). The approved source countries of the starting material for the

manufacture of pancrelipase is the same for both manufacturing sites. Part 2 of this study is being conducted to determine whether AAPIS 24,000 USP Units (lipase) results in similar clinical pharmacodynamics and safety as the current US marketed Creon®, and is thus appropriate to be administered for the same indication and patient populations as Creon®.

Information on Creon®, the MP formulation and the AAPIS formulation can be found in Section 5.5.2. Further information on pancrelipase DR currently marketed as Creon® in the US can be found in the US Product Information (USPI).

The dose of study drug selected in each Part of this study is based on ~4,000 lipase units (LU) per gram fat/day, corresponding to the maximum dose of Creon® in CF patients as per current US label, and according to the upper limit of the US Cystic Fibrosis Consensus Committee.[1,2] Each subject will consume a predetermined study diet that contains 100 g fat/day and a minimum of 1 g/kg protein/day, under the supervision of a registered dietitian. The study drug dose will be individualized to this diet for each subject.

3.1 Differences Statement

Unlike typical efficacy and safety studies previously conducted with Creon®, which demonstrated superiority to placebo, this study aims to determine whether the drug products tested in each Part [pancrelipase DR capsules MP 24,000 USP Units (lipase) for Part 1 or pancrelipase AAPIS 24,000 USP Units (lipase) for Part 2] are non-inferior to the current US marketed drug product (Creon®) as measured by the coefficient of fat absorption (CFA).

3.2 Benefits and Risks

All subjects randomized in this study will receive treatment for EPI during the study at a safe and effective dose. This is the primary benefit to subjects for this study. Risks of study participation include those currently listed in the USPI for Creon®, and are not

expected to be different for the pancrelipase DR capsules MP 24,000 USP Units (lipase) or Pancrelipase AAPIS 24,000 USP Units (lipase) drug products.

4.0 Study Objective

The objective of Part 1 is to demonstrate non-inferiority of pancrelipase DR capsules MP 24,000 USP Units (lipase) drug product compared to the active control [pancrelipase DR capsules 24,000 USP Units (lipase) currently marketed in the US as Creon®] in subjects with EPI due to CF, as measured by CFA.

The objective of Part 2 is to demonstrate non-inferiority of delayed-release capsules of pancrelipase AAPIS 24,000 USP Units (lipase) compared to an active control [pancrelipase DR capsules 24,000 USP Units (lipase) currently marketed in the US as Creon®] in subjects with EPI due to CF, as measured by CFA.

Safety will also be evaluated.

5.0 Investigational Plan

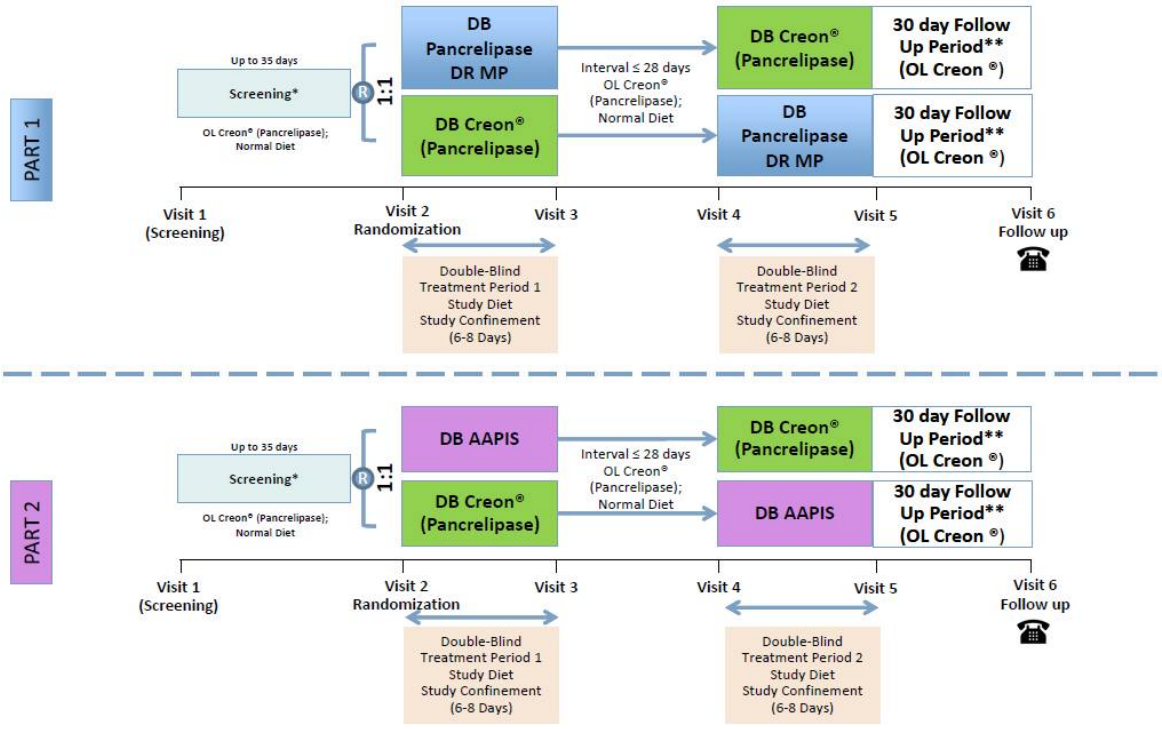
5.1 Overall Study Design and Plan: Description

For study Part 1, the target number of evaluable subjects is 22, with a screening of approximately 36 subjects and enrollment/randomization of approximately 26 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects, in alignment with ethical considerations. Therefore, if the target number of evaluable subjects in Part 1 (22) has completed the study, there is a possibility that additional subjects in screening will not be enrolled in that Part.

For study Part 2, the target number of evaluable subjects is 18, with a screening of approximately 30 subjects and enrollment/randomization of approximately 20 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects, in alignment with ethical considerations. Therefore, if the target number of evaluable subjects in Part 2 (18) has completed the study, there is a possibility that additional subjects in screening will not be enrolled in that Part.

The study will be conducted in the US. See Figure 1.

Figure 1. Study Schematic



OL = Open Label DB; = Double-Blind; R = Randomization

Pancrelipase DR MP = Pancrelipase Delayed Release Modernized Process capsules 24,000 USP Units (lipase); Pancrelipase AAPIS = delayed-release capsules of pancrelipase manufactured at an Alternate Active Pharmaceutical Ingredient Site; Creon® (pancrelipase) = Us approved and marketed Creon® (pancrelipase) Delayed Release capsules 24,000 USP Units (lipase)

* Subjects who participate in both Part 1 and Part 2 may not need to repeat screening.

** For subjects who participate in both Part 1 and Part 2, the follow up period of the first Part will end at Visit 6 of the current Part or the day before Visit 1 of the next study Part, whichever comes first.

Note: First blue dye marker administered bedtime of study confinement Day 2 and stools collection starts once subject passes first blue dye marker. Second blue dye marker administered on study confinement Day 5 and stool collection continues until the appearance of the next blue dyed stool and stool collection will then stop.

Enrollment in the DB Treatment Period of study Part 1 will continue until at least 22 subjects are evaluable for the analysis of coefficient of fat absorption (CFA).

Enrollment in the DB Treatment Period of study Part 2 will continue until at least 18 subjects are evaluable for the analysis of coefficient of fat absorption (CFA).

After eligibility is confirmed, the subject will be enrolled to one of the two Study Parts. For each Part, eligible subjects will be randomized into one of the two treatment sequences, as shown in the study schematic. Randomization for Part 1 and Part 2 are independent. After the completion of the participation in the Part they were originally enrolled, the subject may be offered to participate in the other Part. This participation is optional. If the subject agrees to participate in the other Part and has completed consent to do so, the subject will be kept on OL Creon®, for a period of up to 30 days, while eligibility to that Part is confirmed and the subject can initiate the next confinement period. If visit 1 of the next Part does not occur within 30 days of the last dose of study drug (Visit 5) of the previous part, the subject will not receive any additional open label Creon® (Pancrelipase) 24,000 USP units (lipase) past the amount provided for the first 30 days, and the subject will need to be re-consented/rescreened for the next study part. Subjects who participate in the other Part of the study will be re-randomized in that Part.

Subjects who have already completed Part 1 at the time of implementation of this amendment will need to re-consent and rescreen (except for FE-1) for participation in Part 2.

Pharmacodynamic and safety analyses will be performed separately for Part 1 and Part 2.

An external data monitoring committee (DMC) composed of persons independent of AbbVie and with relevant expertise in their field will review unblinded safety data from the ongoing study. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

A separate DMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC members, frequency of data reviews, relevant safety data to be assessed, and expectations for blinded communications.

Methodology:

Part 1 is designed to test pancrelipase DR MP for non-inferiority compared to Creon® in a DB, randomized, active-controlled, two-period, two-sequence crossover design in subjects of 12 years or older with EPI due to CF, as measured by CFA. Safety will also be assessed.

Part 2 is designed to test pancrelipase AAPIS for non-inferiority compared to Creon® in a DB, randomized, active-controlled, two-period, two-sequence crossover design in subjects of 12 years or older with EPI due to CF, as measured by CFA. Safety will also be assessed.

Pancrelipase DR 24,000 USP Units (Lipase) capsules, commercially available in US as Creon®, will be administered as double-blind drug as the active control for the study and will be administered as open-label drug at the screening visit and will be taken by the subject until the subject randomizes into the study. Open-label Creon® will also be given during the interval between treatment Periods 1 and 2 of each Part and during the follow-up period.

Screening Period (35 Days Maximum)

At the Screening Visit (Visit 1) and during the screening period, subjects will be evaluated for eligibility to enter the DB Treatment Period. Written informed consent will be signed before any study-related procedures are performed. Written consent will need to be signed by a parent and/or guardian for minor subjects. Written assent for minor study participants will also need to be signed where indicated by local requirements.

A stool sample for FE-1 testing will be obtained during the screening period to check for subject eligibility. A pre-screening consent may also be obtained from the subject prior to the screening visit so a stool sample can be collected and brought to the study site at the Screening Visit. If a sample cannot be provided at the Screening Visit, the subject will be given a FE-1 testing kit and will be given instructions to return the sample during the screening period as soon as possible.

After completing the Screening Visit, while waiting on FE-1 results to confirm eligibility, subjects will receive open label Creon® at their usual pre-study PERT dose (lipase units) to be taken during the screening period. Subjects who decide to participate in both Study Parts and have been consented to do so and it has been ≤ 30 days since the subject completed Visit 5 of the previous Part will not need to repeat all screening procedures for the second study Part. Eligibility should be re-confirmed at the start of the next study Part; however, subjects do not need to repeat the FE-1 or serum pregnancy (if applicable) tests. Urine pregnancy tests still need to be performed as per Appendix C. Subjects who participate in both Parts can complete the Screening Visit (Visit 1) to re-confirm eligibility and Visit 2 on the same day.

Subjects who decide to participate in both Study Parts and have been consented to do so and it has been > 30 days since the subject completed Visit 5 of the previous Part will need to repeat screening procedures (except FE-1, which does not need to be repeated) and should complete the Screening Visit as a separate visit.

Site to discuss/consult with AbbVie in regards to the planned confinement location in the study prior to screening their first subject or if there is any change in confinement location during the study.

Rescreening

Subjects who have FE-1 > 15 µg/g at Screening or female subjects of childbearing potential who have a positive serum pregnancy test at screening are not eligible to rescreen or retest. Subjects who screen-failed for other reasons may be re-screened (only once per study part) within 6 months of when they were originally screened. Subjects must sign a new ICF and be rescreened for all eligibility criteria (except for an eligible FE-1 value, which does not need to be repeated), not just those that were exclusionary. The investigators are encouraged to consult with the AbbVie TA MD when considering rescreening subjects.

For subjects do not meet the study eligibility criteria upon retest/rescreen, the site personnel must contact the Interactive Response System (IRT) and identify the subject as a screen failure.

Subjects who screen-fail due to COVID-19 infection (as per Inclusion Criteria 10 and Exclusion Criteria 12, Section 5.2.1) may only rescreen if the following criteria are met:

- *If the subject had symptomatic infection:* At least 2 consecutive negative COVID-19 tests, ≥ 24 hours apart after at least 7 days have passed since recovery, defined as resolution of fever without use of antipyretics **and** improvement in respiratory symptoms (e.g., cough, shortness of breath).
- *If the subject had asymptomatic infection:* At least two negative COVID-19 tests in a row, ≥ 24 hours apart after at least 7 days have passed since prior positive test result.

Please see Section 5.3.1.1 for directions on retesting/rescreening after a positive COVID-19 test.

Re-screened subjects will sign a new ICF and all Screening Visit procedures (except FE-1) have to be repeated.

Double-Blind Treatment Period for Study Part 1 and/or Study Part 2

Once study eligibility has been confirmed, subjects will be enrolled into the DB Treatment Period of either Part 1 or Part 2. After they complete the Part they were initially enrolled in, the subject may elect to participate in the other Part.

DB Treatment Period 1 (Visit 2 to Visit 3)

Eligible subjects will be admitted to the clinical site or designated confinement location, in the morning (prior to breakfast) of Visit 2 or in the evening (after dinner) on the previous day and will be hospitalized/confined at the clinical site or designated confinement location for approximately 6 to 8 days, depending on each subject's gastrointestinal motility.

At Visit 2 (DB Treatment Period 1 Day 1), subjects will be allocated into Study Part 1 or Part 2 and randomized in a 1:1 ratio to 1 of the 2 treatment sequence arms within their study Part, as shown below:

Part 1:

Sequence Arm	Treatment Period 1	Treatment Period 2
A	Pancrelipase DR capsules **MP**	Creon® (Pancrelipase) DR
B	Creon® (Pancrelipase) DR capsules	Pancrelipase DR capsules **MP**

DR = Delayed release; MP = Modernized Process uniform coated pellets, large scale

Part 2:

Sequence Arm	Treatment Period 1	Treatment Period 2
C	Pancrelipase DR capsules **AAPIS**	Creon® (Pancrelipase) DR capsules
D	Creon® (Pancrelipase) DR capsules	Pancrelipase DR capsules **AAPIS**

AAPIS = Delayed-release capsules of pancrelipase manufactured at an Alternate Active Pharmaceutical Ingredient Site; DR = Delayed release

Before any study drug administration on DB Treatment Period 2 Day 1 (Visit 4), the subject's weight will be confirmed to be 40 kg or more. Then subjects will stop their open label Creon® treatment and will receive DB treatment with study drug and an individualized diet with 100 grams daily fat content, a minimum of 1 g/kg of daily protein and normal to low fiber content for 6 – 8 days. They will consume the specified diet with pre-specified fat and protein content during all DB treatment periods, although the actual foods consumed may differ. Each subject's diet for the two treatment periods of each study Part (if applicable) will be created at the same time by a site-based dietitian using ABVDiet, (see Section 5.3.1.1 Diet Plan Design) after an interview with the subject, and reviewed and approved by a central dietitian, prior to Visit 2.

During the hospitalization/confinement, dietary surveillance and stool collection will be accurately performed to allow for the evaluation of CFA and CNA. Subjects must adhere to the individualized study meal plan. Therefore, no food or drink outside of the

prescribed diet will be allowed. Site personnel will encourage subjects to eat all of the food served at each meal or snack.

The stool collection period will be demarcated with a stool marker consisting of 2 capsules of 250 mg of food dye (coloring according to FDA Food, Drug and Cosmetics – FD&C Blue No. 2/European E132).

After the last food intake on hospitalization/confinement Day 2 (bedtime), the first blue dye marker (2 capsules) will be administered orally, and food intake recording will begin with hospitalization/confinement Day 3 breakfast. After subjects pass the first blue dye marker, all bowel movements (excluding the first blue dyed stool) will be collected.

After the last food intake on hospitalization/confinement Day 5 (bedtime), the second blue dye marker (2 capsules) will be administered, and dietary recording will be stopped (Day 5 last food intake will be included in the dietary recording). Stool collection will continue until the appearance of the next blue dyed stool. The last collected stool will be the first blue dyed stool after the second blue dye marker administration. Depending on each subject's gastrointestinal motility, the stool collection period may be longer than 72 hours.

Subject will stop DB treatment and will be discharged from the clinical site or designated confinement location, (or begin preparation for DB Treatment Period 2) after the first blue dyed stool following the second dye administration is collected (Visit 3). This could be hospitalization/confinement Day 6, 7 or 8, depending on each subject's gastrointestinal motility.

If subject chooses to leave the clinical site or designated confinement location after DB Treatment Period 1, subject will re-start his/her usual diet and will be given a supply of open label Creon® at the dose of open label Creon® they received for the screening period to be taken during this period, until returning to the clinical site or designated confinement location, for DB Treatment Period 2. The interval between DB Treatment Period 1 and DB Treatment Period 2 will last up to a maximum of 28 days: In exceptional

circumstances, such as impact by COVID-19-related activities, this period may be extended upon specific consultation with the sponsor. If the subject elects to continue directly into DB Treatment Period 2, and site capacity allows, Visit 4 will be the day following Visit 3.

DB Treatment Period 2 (Visit 4 to Visit 5)

Subject will again be hospitalized/confined (or continue to be hospitalized/confined) at the clinical site or designated confinement location, for approximately 6 to 8 days, starting in the morning (prior to breakfast) of Visit 4 or in the evening (after dinner) on the previous day.

Before any study drug administration on DB Treatment Period 2 Day 1 (Visit 4), subject's weight will be confirmed to be 40 kg or more. Then subjects will stop current open label Creon® (if receiving it) and will receive DB study drug and an individualized diet with 100 grams daily fat content, a minimum of 1 g/kg of daily protein and normal to low fiber content for 6 - 8 days. Each subject's diet for the two treatment periods will be created at the same time by a site-based dietitian using ABVDiet, after an interview with the subject, and reviewed and approved by a central dietitian, prior to Visit 2. Dietary surveillance and stool collection will be performed as during DB Treatment Period 1.

Subjects will stop DB treatment and will be discharged from the clinical site or designated confinement location, after the first blue dyed stool following the second dye administration is collected (Visit 5). This could occur at hospitalization/confinement Day 6, 7 or 8, depending on each subject's gastrointestinal motility.

Subjects who withdraw during any Part of the study will immediately enter the Post-Treatment Follow-Up Period, and will undergo early discontinuation activities as specified in Appendix C, Visit 5.

After completing the Part to which the subject was originally enrolled, the subjects may be given the opportunity to participate in the other Study Part. If the subject agrees to participate in the other study Part, he/she will re-start his/her usual diet and will be given a

supply of open label Creon®, at the dose they received during the screening period, to be taken during this period of up to 30 days, while eligibility for the other Part is re-assessed. The subject will then return to the clinical site or designated confinement location for randomization into the other Study Part. If visit 1 of the next Part does not occur within 30 days of the last dose of study drug (Visit 5) of the previous part, the subject will not receive any additional open label Creon® (Pancrelipase) 24,000 USP units (lipase) past the amount provided for the first 30 days, and the subject will need to be re-consented/rescreened for the next study part.

Post-Treatment Follow-Up Period (Visit 5 to Visit 6)

During the follow-up period for both study parts, subjects will be given at Visit 5 a supply of open label Creon® at the dose they received during the screening period to be taken during this period, along with their usual diet.

A safety follow-up telephone contact (Visit 6) will be performed 30 days after discharge upon completion of DB Treatment Period 2 (or following study withdrawal) to verify the subject's well-being and to assess for AEs and changes in concomitant medication use. If a subject is participating in both study Parts and they are starting the second study Part ≤ 30 days following completion of DB Treatment Period 2 of the previous Part, Visit 6 can be completed on the same day as the start of the next study Part.

Study completion for each subject is defined as the date of the follow-up telephone contact (Visit 6) for the last Part the subject participated in. The maximum duration of study participation is approximately 109 days for each subject participating in one study Part only and approximately 183 days for each subject participating in both study parts.

5.2 Selection of Study Population

Male and female subjects aged 12 years or older, who meet all of the inclusion criteria and none of the exclusion criteria, will be eligible for enrollment into the DB Treatment Periods of the study.

Each Investigator will employ his/her clinical judgment in conjunction with protocol specified inclusion/exclusion criteria to determine if subject meets eligibility. Questions should be directed to the AbbVie Therapeutic Area (TA) MD listed on the Title Page and in Section 6.1.5 if further clarification is required.

5.2.1 Inclusion Criteria

A subject will be eligible for randomization if he/she meets ALL of the following criteria:

1. Subject has voluntarily signed and dated an informed consent form (ICF) approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to any study specific procedures. For subjects aged less than 18 years, the subject has provided voluntary assent and the subject's legal representative has voluntarily signed and dated an ICF, approved by an IEC/IRB, prior to screening and all study related procedures. If indicated by local requirements, written assent will also need to be signed.
2. Subject is 12 years or older at the time of informed consent/assent form signature.
3. Subject has a documented diagnosis of CF previously confirmed by:
   a. a sweat chloride test ≥ 60 mmol/L, and/or
   b. documented CF-causing CFTR mutations and clinical features of CF.[3,4]
4. Diagnosis of moderate to severe EPI, as determined by Fecal Elastase 1 (FE-1) < 15 µg/g at screening.
5. Subject has EPI that is currently clinically controlled (no clinically overt steatorrhea or diarrhea) under treatment with a commercially available PERT, on an individually established dose regimen for more than 3 months prior to Screening, with a daily dose not exceeding 4,000 LU/g fat/day or 10,000 LU/kg/day.
6. Subject is available for two (if participating in one of the Parts) or four (if participating in both Parts) hospitalization/confinement periods of 6 to 8 days each.

7. Subject is able to consume a diet with 100 g of fat/day, a minimum of 1 g/kg of protein/day and normal to low fiber content.
8. If female, subject must be either postmenopausal, 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 an FSH level > 40 IU/L.

     OR
   - Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

     OR
   - For females of childbearing potential, practicing at least one protocol specified method of birth control (Section 5.2.4).
9. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1 of Visit 2.

   Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing.
10. Subjects must have a negative viral test (e.g., PCR, antigen) for COVID-19 done within 7 days before V2.
11. At Screening (Visit 1) and Visit 2, before dosing, subject weight is 40 Kg or more.

Rationale for Inclusion Criteria:

1	In accordance with harmonised Good Clinical Practices (GCP)
2 – 7	To select the adequate subject population with appropriate disease severity for the evaluation of the study drug
8, 9, 10	For the safety of the study subjects

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets ANY of the following criteria:

1. BMI percentile for age less than 10% in patients less than 18 years of age.
2. Subject has a history of any of the following gastrointestinal disorders:
   a. acute pancreatitis within 6 months prior to SV1, or
   b. chronic pancreatitis, or
   c. fibrosing colonopathy, or
   d. distal intestinal obstruction syndrome (DIOS) within 6 months prior to SV1, or
   e. *C. difficile* infection within 6 months prior to SV1, or
   f. celiac disease, or
   g. gastric bypass or partial/total gastrectomy, or
   h. Crohn's disease or other inflammatory bowel disease, or
   i. small bowel surgery (other than minor resection due to meconium ileus without resultant malabsorption syndrome), or
   j. any type of malignancy involving the digestive tract in the last 5 years.
3. Subject has a history of any clinically significant endocrine, respiratory (except mild asthma or CF-related lung disease), neurological, cardiac, renal, hepatic (including Hepatitis B or C), hematologic or psychiatric disease or disorder, or any other uncontrolled medical illness which might limit participation in or completion of the study.
4. Subject requires concomitant treatment with any medication not allowed by the protocol or a prohibited medication is expected to be needed during the study.
5. Subject is currently receiving nutritional supplementation via tube feeding (nasogastric, gastrostomy, jejunostomy).

6. Subject has clinically significant (as per Investigator's judgment) abnormalities in clinical chemistry, hematology, or urinalysis (excluding findings that are associated with CF) such as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels ≥ 3 times the upper limit of normal values, or clinically significant (investigator opinion) elevation of uric acid.
7. Subject is currently participating in any other interventional clinical study or has taken any experimental drug (other than for this study) within 30 days prior to Screening.
8. Subject has a known hypersensitivity and/or contraindication to pancrelipase (also named pancreatin) of any source or inactive ingredients (excipients) of study drugs, or to Federal Food, Drug, and Cosmetic (FD & C) Blue No. 2/European E132 dye marker.
9. Subject has experienced problems or lack of efficacy with prior Creon® treatment.
10. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 7 days after the last dose of study drug.
11. Subject presents any other factor/condition which, in the opinion of the investigator, would pose a significant risk for the subject, invalidate the informed consent process or interfere with the ability of the subject to comply with study requirements or interfere otherwise with the conduct of the study.
12. Subject has signs or symptoms associated with COVID-19 infection at V2.

Rationale for Exclusion Criteria:

1, 2, 3, 4, 8, 9, 10, 11, 12	To ensure safety of the subjects throughout the study
3, 5, 6, 7	To avoid bias for the evaluation of non-inferiority by concomitant diseases or conditions
8	To avoid bias for the evaluation of non-inferiority by previous use

5.2.3 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 along with the specific reason for use (e.g., bronchodilators for CF-related lung disease, vitamin supplements for CF-related hypovitaminosis), date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.1 Prior and Inter Treatment Interval PERT Therapy

The daily dose of PERT taken prior to the Screening Visit will be recorded in the eCRF.

The daily dose of Open Label Creon® taken during the Screening Period (Visit 1 to Visit 2) will be recorded in the eCRF.

The daily dose of Open Label Creon® taken during the interval between Visit 3 and Visit 4 will be recorded in the eCRF.

The daily dose of Open Label Creon® taken during the Follow up Period (Visit 5 to Visit 6) will be recorded in the eCRF.

5.2.3.2 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) taken by the subject during their study participation (from signing the ICF [Visit 1] through follow-up call [Visit 6]) is to be recorded on the Concomitant Medication form of the eCRF, except for the study drug(s). Subjects who are taking concomitant medications should have corresponding entries in the Medical History and/or Adverse Event forms of the eCRF to document the need for the

medications. Reason for use for concomitant medications should be as specific as possible, e.g., bronchodilators used for chronic bronchitis or bronchiectasis, not CF.

Any intake of enzyme preparations in addition or in substitution to the study drug, starting at screening (Visit 1) and throughout the completion of both DB Treatment Periods (of all the Parts the subject agrees to participate in), is not allowed and will lead to the exclusion of the subject from the study.

The following concomitant medications or nutritional supplements **CAN BE GIVEN** during the Screening Period, the study drug treatment periods and the interval between study Parts (if applicable) **under specified circumstances:**

- Concomitant medications influencing duodenal pH
  - H2-receptor antagonists
  - Antacids containing **only bicarbonate** *(examples: Alka Seltzer, Alkaligen, Bicarbonato de Sosa TM, Bicarbonato Sod Agadrian, Bicarbonato Sod Cinfa, Bicarbonato Sod Grifols, Bicarbonato Sod Serra, Bicarbonato Sod Viviar, Bicarbonato Sodico Braun, Bicarbonato Sodico Mein, Hospal, Justegas, Natrium bicarbonicum Polpharma, Natrium-Hydrogen-Carbonicum Pharmamagist, Natrium-Hydrogen-Carbonicum Pharmamagist 8.4%, Natrium-Hydrogenkarbonat Braun, sodium bicarbonate, Venofusin Bicarb Sodico)*
  - Sucralfate
  - Proton-pump-inhibitors
  - Prostaglandins
  - Somatostatin
  - Anticholinergic agents.
- Drugs acting on gastric emptying (e.g., metoclopramide or erythromycin).
- Prebiotic or probiotic drugs.
- Immunosuppressive steroids (local or systemic).
- Osmotic laxatives (e.g., Miralax).

- Flax seeds or chia seeds taken for nutritional supplementation or bowel regularity.

The specified circumstances are:

- The medication is commercially available and is prescribed according to the recommended dose range.
- The medication has been taken by the subject for more than 4 weeks before start of the study in the prescribed dose and is planned to be kept at a stable dose during the conduct of the study.
- Any nutritional supplements are accounted for in the subject Diet Plan.

5.2.3.3 Prohibited Therapy

Medications prohibited during the DB Treatment Periods are:

- fat or protein containing nutritional supplements (e.g., Ensure, Glucerna, protein shakes), unless they are accounted for in the study Diet Plan,
- narcotic analgesics,
- antidiarrheals, antispasmodics, non-osmotic laxatives,
- antacids containing aluminum (US)/aluminium (EU), magnesium or calcium carbonate,
- oral fiber supplements (e.g., Psyllium plantago, Metamucil),
- immunosuppressive drugs (not including steroids).
- Tube feeding

The use of prohibited therapies during the DB Treatment Periods will lead to the exclusion of the subject from the study.

Note: These medications are **NOT** prohibited during the Screening Period, during the interval between Treatment Periods 1 and 2 or during the interval between Parts (if applicable), if the subjects leave the clinical site or designated confinement location.

5.2.4 Contraception Recommendations and Pregnancy Testing

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) OR a Women of Childbearing Potential, practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 30 days after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to screening.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to screening.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 1 month prior to screening.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided that the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, and is the sole sexual partner of the female of childbearing potential trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Male or female condom with or without spermicide.
- Cap, diaphragm or sponge with spermicide.
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier method).
- 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 subjects who are sexually active with a woman of childbearing potential are not required to use contraception methods during the study.

5.3 Pharmacodynamic and Safety Assessments/Variables

The primary pharmacodynamic variable will be the CFA which measures fat absorption. Secondary pharmacodynamic variables will include the CNA (measuring protein absorption), stool fat content, stool weight. Additional exploratory pharmacodynamic variables include assessment of EPI symptoms.

The safety variables assessed will include clinically significant physical examination findings, laboratory values and AE's.

5.3.1 Pharmacodynamic and Safety Measurements Assessed and Flow Chart

Study procedures, with the exception of treatment compliance monitoring (Section 5.5.6), collection of concomitant medication (Section 5.2.3.2) and AE information collection (Section 6.1), are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

5.3.1.1 Study Procedures

Informed Consent

At the Screening Visit, signed informed consent (and subject's assent as applicable) will be obtained from the subject before beginning any study-specific procedure. A pre-screening consent may also be obtained from the subject prior to the screening visit so a stool sample can be collected and brought to the study site at the Screening Visit. Details on how informed consent/assent will be obtained and documented are provided in Section 9.3.

Subjects who have signed informed consent/assent and do not complete the study-specific procedures during the Screening Period will be considered screen failures. The reason(s) for screen failure will be documented in the source documents and will be captured in the eCRF.

Medical History

A complete medical history, including documentation of any clinically significant medical conditions and medications (including history of tobacco, nicotine-containing products and alcohol use) will be collected during the Screening Visit of the first part the subject is participating in. The Medical History form of the eCRF must contain all diseases/conditions for which the subject is taking concomitant medications.

For subjects who are participating in more than 1 study Part, the medical history will be reviewed at the screening visit for the next part the subject is participating in and updated for any new information available.

Pancreatic Enzyme Replacement Therapy (PERT)

Under the direction of their usual treating physician, at the screening visit subjects will start receiving open label Creon® at their usual established dose until all eligibility criteria are confirmed and the subject randomized, or until the subject is screen-failed.

For subjects who enter DB Treatment Period 2 directly from DB Treatment Period 1 (without leaving the hospital/confinement site): during the 24 h period until Treatment Period 2 can be started, subjects will be maintained at their usual diet and will be administered open label Creon® at the dose they received during the screening period. This daily dose of open label Creon® should be recorded in the eCRF.

For subjects who do not enter DB Treatment Period 2 directly from DB Treatment Period 1 (i.e., leave the hospital/confinement site): if a subject chooses to leave the clinical site or designated confinement location after DB Treatment Period 1, the subject will re-start his/her usual diet and will be given a supply of Creon® at the dose they received for the screening period to be taken until returning to the clinical site or designated confinement location for DB Treatment Period 2. The daily dose of open label Creon® will be recorded in the eCRF.

Subjects participating in both Parts and who decide to enter the second study Part directly after the first Part will be given a supply of open label Creon® at the dose they received during the screening period to be taken during this time, along with their usual diet, for 24 hours. The dose of open label for these 24 hours should be recorded in the eCRF.

Subjects participating in both Parts and who choose to leave the clinical site or designated confinement area after completion of the Part they were originally enrolled will re-start his/her usual diet and will be given a supply of Creon® at the dose they received for the screening period to be taken until returning to the clinical site or designated confinement location, for DB Treatment Period 1 of the other study Part they are participating in. The dose of open label Creon® will be recorded in the eCRF.

During the follow up period Subjects will be given a supply of open label Creon® at the dose they received during the screening period to be taken during this time, along with their usual diet.

Physical Examination

A physical examination will be performed at the Screening Visit after the ICF is signed. A physical examination update will be performed at Visit 2, Visit 3, Visit 4 (unless subject has directly entered DB Treatment Period 2 from DB Treatment Period 1, in which case the physical examination at Visit 3 will suffice for this requirement at Visit 4) and a complete final physical examination will be performed at Visit 5. Subjects participating in both Parts and who decide to enter the second study Part directly after the first Part will not need a physical examination done at Visit 1 of the next study Part they are participating in, as long as it has been < 30 days between Visit 5 and Visit 1 of the next study part. The physical examination at Visit 5 of the previous study Part will suffice for this requirement at Visit 1 of the next study Part.

The physical examination at Visit 2 of each Part will serve as the baseline physical examination for that Part of the study.

Height

Height will be measured at the Screening Visit only, with the subjects not wearing shoes.

Body Weight and BMI

Body weight will be measured, with the subjects in light weight clothing without shoes, at the Screening Visit, on Day 1 of the 2 study drug treatment periods for each study Part and at Visit 3 and 5 preferably using the same calibrated weighing scale at all visits. The body weight should be assessed in the morning prior to any food intake and to any blood sampling.

The body weight measured at Visit 2 of each Part will serve as the baseline measurement for clinical assessment during DB Treatment Periods 1 and 2 for that study Part.

The BMI will be calculated as follows: body weight (kg)/height^2 (m).

Vital Signs

Vital sign determinations of sitting blood pressure, heart rate and body temperature will be obtained at the Screening Visit, Visit 2, Visit 3, Visit 4 and Visit 5 for each study Part.

The blood pressure and heart rate measurements should be taken prior to scheduled blood collections. Body temperature measurements should be assessed using the same modality consistently throughout the study, e.g., oral, aural, axillary, etc., and the modality will be reported in the source documentation and eCRF.

The vital signs measurements prior to dosing on Visit 2 of each Part will serve as the baseline measurements for clinical assessment during DB Treatment Periods 1 and 2 for that study Part.

Pregnancy Testing

For females of childbearing potential, a serum pregnancy test will be performed at the Screening Visit and a urine pregnancy test will be performed by designated study site personnel at Visit 2 and at Visit 4 (only if subject has not continued confinement from Visit 3), for each study Part.

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing.

Subjects with a positive pregnancy test at the Screening Visit or at Visit 2 or Visit 4 for either study Part may not continue participation in the study and must be discontinued.

Subjects who completed the study Part they were originally enrolled in and agree to participate in the other study Part and it has been ≤ 30 days since Visit 5 of the first Part they participated in will not need to repeat the serum pregnancy test, but will still need to perform the urine pregnancy test as required in Appendix C.

Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in Table 1 at the Screening Visit and at Visit 2, Visit 3, Visit, 4 (except if ≤ 24 hours post Visit 3) and Visit 5 (ref to Appendix C) for each study Part.

Subjects participating in both Parts and who decide to enter the second study Part directly after the first Part will not need Clinical Laboratory tests done at Visit 1 of the next study Part they are participating in, as long as it has been < 30 days between Visit 5 and Visit 1 of the next study part. The Clinical Laboratory tests done at Visit 5 of the previous study Part will suffice for this requirement at Visit 1 of the next study Part.

Blood draws will be performed after (or at least 30 minutes prior to) vital sign measurements during a visit.

The clinical chemistry should be preferably performed following a fast of a minimum of 8 hours except at the Screening Visit which may be performed in the non-fasting state. Fasting conditions will be reported in the eCRF.

A central laboratory contracted by AbbVie will be utilized for the clinical laboratory tests. Instructions regarding the collection requirements, processing, and shipping of these samples will be provided by the central laboratory.

Table 1. Clinical Laboratory Tests

Hematology	**Clinical Chemistry**	**Urinalysis**
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Albumin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphate Uric acid Cholesterol Total protein Glucose Triglycerides Bicarbonate/CO_2 Chloride	Specific gravity Ketones pH Protein Glucose Blood **Other Tests** COVID-19

The laboratory results will be provided by the central laboratory to the investigative site where they will be reviewed, signed, and dated by the Investigator. For any value outside of the reference range, the investigator will indicate on the report if the result is clinically significant (CS) or not clinically significant (NCS). The Investigator will receive Sponsor defined laboratory alerts from the central lab. The Investigator will review the laboratory alerts and assess clinical significance for potential AEs.

All screening laboratory results must be reviewed prior to Visit 2.

Covid-19 Testing

COVID-19 tests will be performed locally prior to each confinement period to confirm whether or not the subject has known COVID-19 infection. If a site does not have access to testing locally, or if the turn-around-time of the local test is greater that the central laboratory, the central laboratory can be used. The site will also have the option to have the tests collected at the subject's home by a qualified home health nurse.

Initiation of Confinement Periods

Subjects must have a negative viral test (e.g., PCR, antigen) for COVID-19, from a test done within 7 days prior to each Confinement period (V2 and V4). The test can be performed locally or via central laboratory, considering availability and whichever may provide faster turnaround time, as well as no signs or symptoms associated with COVID-19 infection.

If a subject has confirmed or suspected COVID-19 infection between confinement periods, the subject can only enter the next confinement period if the following criteria are met prior to the next dose scheduled confinement:

For symptomatic subjects:

- At least two consecutive COVID-19 tests, ≥ 24 hours apart after at least 7 days have passed since recovery, defined as resolution of fever without use of antipyretics **and** improvement in respiratory symptoms (e.g., cough, shortness of breath)

For asymptomatic subjects:

- At least two negative COVID-19 tests in a row, ≥ 24 hours apart after at least 7 days have passed since prior positive test results

Subjects who enter DB Treatment Period 2 less than 7 days at the end of DB Treatment Period 1 do not need to perform a COVID-19 test unless otherwise directed by the

investigator. Subjects must have no signs or symptoms associated with COVID-19 infection at Day 1 of DB Treatment Period 2.

Subjects participating in both study Parts do not need to perform a COVID-19 test to begin Treatment Period 1 of the other Part (unless directed by the investigator) if they:

- do not leave the confinement location following completion of the Part they were originally enrolled into and decide to enter the other study Part directly following the original Part, or;
- enter DB Treatment Period 1 of the other Part within 7 days after the end of DB Treatment Period 2 of the Part they were originally enrolled into.

Diet Plan Design

A prospective individualized diet plan that will meet the subject's calorie and protein requirements will be designed by a clinical site dietitian for the screening confinement period and each of the treatment periods in consultation with each subject before V2 and will include food items which the subject prefers so that compliance with the consumption requirements is met.

The diet plan must be designed ensuring:

- a total protein intake of a minimum of 1 g/kg/day;
- a normal to low fiber content;
- a total daily fat intake of 100 grams.
  The fat intake should be distributed proportionally across:
  - 3 meals with 25 grams fat per meal (± 3 grams is acceptable, if needed), and
  - 2 snacks with 12.5 grams fat per snack (± 2 grams is acceptable, if needed),

The subject's individualized diet plan will be implemented by the clinical site dietitian during each of the 2 treatment periods for each study Part (beginning at Visit 2 and

restarting at Visit 4, if subject is discharged between the two DB treatment periods), only after review and approval by the central dietitian.

The individualized diet plan should be similar for each of the two treatment periods for each study Part with the same daily amount of fat and protein, and the same fat distribution across meals and snacks.

A web-based dietary program (ABVDiet) has been developed by AbbVie to track nutrition information of foods and beverages, diet plans and subject food consumption. ABVDiet will be utilized by the site dietitians to design and implement the diet plan for each study subject prior to each confinement period. ABVDiet is designed to send automatic email alerts to the designated individuals and to streamline diet plan approvals by the central dietitian, and will also record the amount of food not consumed during meals and snacks.

Assignment of Subject Number and Randomization

The site will access the Interactive Response Technology (IRT) system at the Screening Visit to obtain a 4-digit subject number once the subject has signed the informed consent. Consecutive and unique subject numbers will be assigned. The same 4-digit subject number will be used to identify the subject throughout Screening, DB Treatment Periods 1 and 2 for all study Parts (if a subject is participating in both Parts) and the Post-Treatment Follow-Up Period. If the subject is not enrolled into the study, the reason for screen failure will be documented in the eCRF and the site will access the IRT system to register the subject as a screen failure.

All inclusion/exclusion criteria must be reviewed prior to the hospitalization/confinement at Visit 2 for each study Part. For subjects entering the DB treatment periods, subjects who meet all of the eligibility criteria will be enrolled to one of the study Parts and randomized to one of the 2 treatment sequence arms on Day 1 of DB Treatment Period 1 (Visit 2) of the enrolled study Part by accessing the IRT system and providing the 4-digit subject number assigned at the Screening Visit (Visit 1).

During the randomization contact at Visit 2 for each study Part the subject is being enrolled to, a 5-digit randomization number (only used within the system for treatment assignment) and a 6-digit study drug kit number will be assigned by the IRT system for DB Treatment Period 1 of the enrolled Part according to a randomization schedule generated by the statistics department at AbbVie (see Section 5.5.3). At Visit 4, the site will access the IRT system to obtain the 6-digit study drug kit number allocated for DB Treatment Period 2 of that study Part. Randomization for study Part 1 and Part 2 are independent.

In the event study drug becomes lost or damaged, or if additional drug is needed, the site can access the IRT system to obtain an unscheduled re-supply of study drug kit numbers to dispense. Sites will also register the Post-Treatment Follow-Up Visit (Visit 6).

Diet Administration and Dietary Records

For each study Part the diet will be administered from each confinement period Day 1 (Visit 2 and Visit 4) until the last stool has been collected (Visit 3 and Visit 5) during each of the 2 confinement periods (or 4 confinement periods for subjects participating in both Parts). The subjects must be encouraged to eat all food provided and will not be allowed to eat anything in addition to the 3 meals and 2 snacks provided within the diet plan. Fat or protein containing nutritional supplements (e.g., nutritional shakes, fish oil supplements, omega fatty acids) not included in the diet plan are not allowed to be taken. If the study diet does not provide sufficient food to prevent hunger, a third snack may be consumed by the subject and the sites will be provided with a list of examples of low-calorie, low-fat foods that subjects may consume. The calories and nutrients from these foods will not need to be included in the diet plan. The fat content of this additional snack should be $\leq$ 2 grams/serving and the protein content should be $\leq$ 4 grams/serving.

During all study confinement periods, subjects will be actively monitored by site personnel for compliance with the diet consumption requirements. Subjects must be encouraged and instructed to consume all food provided as per the planned diet during hospitalization/confinement with specific reference to Days 3, 4 and 5.

ABVDiet is designed to calculate the consumed amounts of fat, protein and calories. The proportion of food provided in the diet that is consumed each day on Day 3 (starting from first food intake), Day 4 and Day 5 (ending with last food intake) will be determined and recorded in ABVDiet by specifically assigned site personnel. Non-consumed meals, snacks and any other deviations to the diet requirements will be determined and will be recorded similarly in ABVDiet. The preferred method to quantify the amount of uneaten food is by weight or volume, as appropriate for the individual solid or liquid food, respectively. Thus, food selections in meals/snacks should be of a type which can be easily measured. The same calibrated food scale should be used for weighing the subjects' meals/uneaten food. The total daily fat and protein intake will be determined from the quantity of food actually consumed and will be recorded in the eCRF.

In the event that not all food in the planned diet is consumed on Days 3, 4 and 5, non-compliance will exist when either of the following occur:

- the subject consumes less than 80% of the planned fat consumption, or
- the difference in fat consumption in the two treatment periods is more than 10% based on the lower amount consumed.

Human Fecal Elastase

A stool sample for fecal elastase testing will be collected as a pre-screening activity or during the screening period and will be evaluated in spot stool sample in a specialty lab contracted by AbbVie (monoclonal antibody test). Instructions regarding the collection requirements, processing, and shipping of these samples will be provided by the central laboratory. Results of Fecal Elastase will be electronically transferred from the central laboratory to the study database using validated software.

Stool Collection

Stool collection will be performed during each of the treatment periods (see Appendix C) for both study Parts. In order to ensure accurate collection of stool samples corresponding

to a known food intake, each subject will be administered stool dye markers orally on two occasions, separated by 72 hours, in order to mark the beginning and end of the stool collection period.

AbbVie will supply stool dye markers (250 mg capsules of encapsulated FD&C Blue No. 2/E132) packaged in high density polyethylene (HDPE) bottles. Each bottle will contain 50 capsules, will be labeled per local requirements and must be stored at controlled room temperature (15° to 25°C or 59° to 77°F).

For each study Part the subjects will be hospitalized/confined on Day 1 of each treatment period (Visit 2 and Visit 4) until the stool collection is completed (Treatment Period Day 6, 7 or 8). The stool dye markers will be administered as follows:

- the 1st stool dye marker (2 capsules) will be administered after the last food intake on the hospitalization/confinement Day 2 (bedtime); subjects will not be allowed to eat anything after the stool dye marker intake until breakfast on the hospitalization/confinement Day 3;
    - If a subject does not excrete the first blue dyed stool by hospitalization/confinement Day 5 following the 1st stool dye marker intake on Day 2, the subject will not be administered the second stool dye marker and will be discontinued from the study.
- the 2nd stool dye marker (2 capsules) will be administered after the last food intake on the hospitalization/confinement Day 5 (bedtime); subjects will not be allowed to eat anything after the stool dye marker intake until breakfast on the hospitalization/confinement Day 6.
    - If a subject does not excrete the second blue dyed stool by hospitalization/confinement Day 8, following the 2nd stool dye marker intake on Day 5, the subject will be discontinued from the study.

During the confinement periods, subjects will be actively monitored by site personnel for compliance with the stool collection requirements, including reporting stool excretion data in the stool collection log.

The subjects will be given appropriate containers for stool collection. Stool collection will begin after appearance of the first stool dye marker, excluding the 1st blue dyed stool, and end with the first stool sample containing the 2nd stool dye marker, including the blue dyed stool. Each stool will be collected in a separate container. Instructions regarding the collection, processing and shipping of the stool samples will be provided by the central laboratory.

Food intake will be recorded by clinical site personnel on Day 3 (from first food intake), Day 4 and Day 5 (ending with last food intake). Although the timing of the stool collection in this protocol is noted as being 72 hours, individual subjects may experience different durations depending on their intestinal transit time.

Results of stool analyses during the DB Treatment Periods will be electronically transferred from the central laboratory to the study database using validated software.

The stools collected during the stool collection periods will be analyzed by a specialty lab contracted by AbbVie for the following:

- Stool Weight.

  Total stool weight will be determined from the net weight of the stool samples collected.
- Stool Fat Content.

  Stools will be analyzed by a central laboratory for fat according to the method of Van de Kamer[5] to allow for the CFA determination.
- Stool Nitrogen Content.

  Stools will be analyzed by a central laboratory for nitrogen according to the Kjeldahl[6] method to allow for the CNA determination.*

* Stool nitrogen content will not be measured for the screening confinement period.

Patient EPI Symptom Diary

A paper EPI symptoms diary, which will collect information on stool frequency, stool consistency, diarrhea, abdominal pain, bloating and flatulence, will be provided to all subjects to complete on each day during each of the confinement periods. The EPI symptom diary should be completed before the subject receives the first study drug dose, prior to breakfast on each day. The clinical site personnel should remind subjects to complete the diary as instructed.

5.3.2 Drug Concentration Measurements

Since pancrelipase is not absorbed from the intestine, there will be no drug concentration measurements in this study.

5.3.3 Pharmacodynamic Variables

5.3.3.1 Primary Variable

The primary pharmacodynamic variable is the CFA measured at the end of each confinement period.

The CFA is calculated as 100•[fat intake – fat excretion]/fat intake.

Fat intake will be determined from fat content of food consumed. Fat excretion will be determined from the fat content in the stool(s) collected between the two dye markers.

5.3.3.2 Secondary Variables

The secondary pharmacodynamic variables include:

- CNA, measured at the end of each treatment period.
  - The CNA is calculated as 100•[nitrogen intake – nitrogen excretion]/nitrogen intake.
  - Nitrogen intake will be determined from protein content of food consumed. Based on the assumption that all proteins are polypeptide chains with a

mass containing 16% nitrogen on average, calculated protein intake is to be converted into nitrogen intake by multiplying the grams of protein ingested by 0.16. Nitrogen excretion will be determined from the nitrogen content in the stool(s) collected between the two dye markers.

- Stool fat.
- Stool weight.

5.3.3.3 Additional Exploratory Variables

Additional exploratory pharmacodynamic variables include:

- Stool frequency
- Stool consistency
- Diarrhea
- Abdominal pain
- Bloating
- Flatulence

5.3.4 Safety Variables

The safety variables include:

- Clinically significant physical examination findings or laboratory values
- Proportion of subjects reporting treatment-emergent adverse events (TEAEs).

5.4 Removal of Subjects from Therapy or Assessment

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an AE or noncompliance with the protocol. In the event that a subject withdraws or is discontinued

from the study, the primary reason for discontinuation and any other reason(s) for the discontinuation from the study will be recorded according to the following definitions:

- AE: discontinuation due to any AE with a corresponding entry reflected on the Adverse Events form in the eCRF.
- Lack of pharmacodynamic effect: subject fails to respond to the study drug at an acceptable level where the subject or the Investigator feels it is in the best interests of the subject to seek another treatment.
- Lost to follow-up: the subject fails to return to the study site for scheduled visits and does not respond to telephone or written attempts to contact.
- Withdrew consent: subject decides to stop his/her participation in the study for any reason or is unable to complete the study as described in the clinical study protocol (e.g., subject is relocating to another location).
- Other

5.4.1 Discontinuation of Individual Subjects

For each study Part, a subject may voluntarily withdraw or be withdrawn at any time for reasons including, but not limited to, the following:

- The subject requests to be withdrawn from the study.
- Any intake of enzyme preparations in addition or substitution to the study drug during the study.
- The subject does not excrete the first blue dyed stool by hospitalization/confinement Day 5, following the 1st blue dye marker intake on Day 2.
- The subject does not excrete the second blue dyed stool by hospitalization/confinement Day 8, following the 2nd blue dye marker intake on Day 5.
- The subject does not consume study drug as specified in Treatment Compliance, Section 5.5.6.
- The subject does not consume the study specific diet as specified in Diet Administration and Diet Records, Section 5.3.1.1.

- Introduction of prohibited therapies during any confinement period.
- When continuation of the study drug would place the subject at risk as determined by the Investigator.
- Subjects who become pregnant during the study must be discontinued (Section 5.3.1.1).

For subjects discontinued from one of the study Parts, the PI must assess if the reason for discontinuation does not preclude the subject from adhering to the procedures on the next study Part before offering the subject participation in the other Part. Also, the PI is encouraged to consult with the AbbVie Therapeutic Area MD before enrolling the subject in the next Part.

Compliance with stool collection is also important, as missing even 1 stool collection can invalidate the results for the CFA endpoint. Subjects will be considered compliant only if all specified stools (100%) of each confinement period are collected (see Section 5.3.1.1 for specifics of stool collection requirements). Subjects who do not have 100% stool collection compliance during any confinement period will be excluded and will not be able to begin the subsequent confinement period within that Part.

In the event that a subject withdraws or is prematurely discontinued before completion of the DB Treatment Period 2 for the study Part they are participating in, he/she must have a final evaluation according to the procedures required at Visit 5 as well as a safety follow-up call 30 days after the last study drug intake. The investigator should schedule blood samples with the subject before premature withdrawal or within the week following the premature withdrawal. The results of these evaluations and observations, and a clear reason for the subject's withdrawal, must be recorded in the eCRF.

If a subject is discontinued from the study with an ongoing AE, the investigator will attempt to follow up until a satisfactory resolution of the AE is achieved or the subject returns to a stable state medically, or the database is locked.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or its Parts, or at any study site, for reasonable cause, provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination to allow for transfer of care of enrolled subjects. Advance notice is not required by either party if the study is stopped due to safety concerns. If the investigator terminates the study at a site for safety reasons, the investigator must notify the AbbVie monitor immediately (within 24 hours), who will then notify the study team. The AbbVie monitor will notify the site in writing of any instructions from the study team for study termination. If AbbVie terminates the study for safety reasons, the AbbVie monitor will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

Study drug will only be shipped to clinical sites which have provided the Sponsor (or an authorized representative) with all required study documents, including IEC/IRB approval, and have signed a clinical study agreement.

5.5.1 Treatments Administered

On completion of the screening visit the subject will be given a 30 day supply of open label Creon® at their usual pre-study daily dose (lipase units) of PERT to be taken until the subject comes back for Treatment Period 1 (if considered eligible). In exceptional circumstances, such as impact by COVID-19-related activities, this period may be extended by an additional 30 days upon specific consultation with the sponsor. Once results have been received and if it is deemed that a subject is not eligible, they will not receive any more open label Creon® and will be considered a screen failure.

For Part 1 of the study, study drug, consisting of Pancrelipase delayed release capsules MP 24,000 USP Units (Lipase) or Creon® (Pancrelipase) delayed release capsules

24,000 USP Units (Lipase) blinded capsules (same size, color and appearance), will be administered during DB Treatment Period 1 (Visit 2 to Visit 3) and DB Treatment Period 2 (Visit 4 to Visit 5) by the clinical site personnel at the time of each meal/snack as follows, depending on the treatment sequence arm the subject will be randomized to, as shown below:

Sequence Arm	Treatment Period 1	Treatment Period 2
A	Pancrelipase DR capsules **MP**	Creon® (Pancrelipase) DR capsules
B	Creon® (Pancrelipase) DR capsules	Pancrelipase DR capsules **MP**

DR = Delayed release; MP = Modernized Process uniform coated pellets, large scale

For Part 2 of the study, study drug, consisting of Pancrelipase DR capsules AAPIS, 24,000 USP Units (Lipase) or Creon® (Pancrelipase) delayed release capsules 24,000 USP Units (Lipase) blinded capsules (same size, color and appearance), will be administered during DB Treatment Period 1 (Visit 2 to Visit 3) and DB Treatment Period 2 (Visit 4 to Visit 5) by the clinical site personnel at the time of each meal/snack as follows, depending on the treatment sequence arm the subject will be randomized to, as shown below:

Sequence Arm	Treatment Period 1	Treatment Period 2
C	Pancrelipase DR capsules **AAPIS**	Creon® (Pancrelipase) DR capsules
D	Creon® (Pancrelipase) DR capsules	Pancrelipase DR capsules **AAPIS**

AAPIS = Delayed-release capsules of pancrelipase manufactured at an Alternate Active Pharmaceutical Ingredient Site; DR = Delayed release

For each study Part the 2 DB treatment periods will be separated by a maximum of 28 days, unless the subject elects to directly enter DB Treatment Period 2 from DB Treatment Period 1. In exceptional circumstances, such as impact by COVID-19-related activities, this period may be extended upon specific consultation with the sponsor.

At the end of DB Treatment Period 1 (between Visit 3 and Visit 4), the subjects will be given a 30 day supply of open label Creon® at the dose they received for the screening period to be taken during this period. In exceptional circumstances, such as impact by COVID-19-related activities, this period may be extended by an additional 30 days upon

specific consultation with the sponsor. If the subject elects to directly enter DB Treatment Period 2, the duration between Visit 3 and Visit 4 will be ≤ 24 hours.

During the follow up period for both study parts, subjects will be given, at Visit 5, a supply of open label Creon® at the dose they received during the screening period to be taken during this period, along with their usual diet.

The study drug total daily dose, calculated based on the maximum dose of 4,000 LU/g of fat/day, as recommended in the current Creon® (Pancrelipase) delayed release capsules 24,000 USP Units (Lipase) label, will be administered orally, divided proportionally based on three meals and two snacks as follows:

Study diet g fat/day	# Capsules/ Meal	# Capsules/ Snack	Total # Capsules/Day	LU/Meal	LU/Snack	Total Daily Dose
100	4	2	16	96,000	48,000	384,000

For each of the treatment periods, the study drug intake will start on Treatment Period Day 1 at breakfast and will continue with each meal/snack until the last stool has been collected. Individual subjects may experience different treatment durations due to the fact the stool collection period depends on their intestinal transit time.

The study drug capsules must be swallowed intact (capsules must not be crushed, chewed or opened), and will be taken during the meal or snack (as per patient's usual practice), with enough fluids to swallow the capsules completely.

All scheduled doses must be taken. Subjects must be encouraged and instructed to consume all food provided as per the individualized diet during hospitalization/confinement.

5.5.2 Identity of Investigational Products

Information about the study drug formulations used in this study is presented in Table 2.

Table 2. Identity of Investigational Product

Study Part(s)	Part 1	Part 1	Part 2	Part 2	Parts 1 and 2	Parts 1 and 2
Investigational Product Name	**DB Creon® (Pancrelipase orange/orange capsules)**	**DB Pancrelipase MP**	**DB Creon® (pancrelipase clear/orange capsules)**	**DB Pancrelipase AAPIS**	**FD&C Blue No. 2 (E132)**	**OL Creon® (Pancrelipase)**
API Manufacturing site	Abbott Neustadt, Germany	Abbott Neustadt, Germany	Abbott Neustadt, Germany	Scientific Protein Laboratories, USA	Neelikon, India	Abbott Neustadt, Germany
Drug product Manufacturing site[a]	Abbott Neustadt, Germany	AbbVie Cork, Ireland	Abbott Neustadt, Germany	Abbott Neustadt, Germany	Almac Group LTD, United Kingdom	Abbott Neustadt, Germany
Type of Blinding	Double-blind[b]	Double-blind[b]	Double-blind	Double-blind	Open-label	Open-label
Active ingredient	Pancrelipase a mixture of lipase (LP), protease and amylase of porcine origin	Pancrelipase a mixture of lipase (LP), protease and amylase of porcine origin	Pancrelipase a mixture of lipase (LP), protease and amylase of porcine origin	Pancrelipase a mixture of lipase (LP), protease and amylase of porcine origin	FD&C Blue No. 2 (E132)	Pancrelipase a mixture of lipase (LP), protease and amylase of porcine origin
Mode/route of administration	Oral	Oral	Oral	Oral	Oral	Oral

Table 2. Identity of Investigational Product (Continued)

Study Part(s)	Part 1	Part 1	Part 2	Part 2	Parts 1 and 2	Parts 1 and 2
Investigational Product Name	**DB Creon® (Pancrelipase orange/orange capsules)**	**DB Pancrelipase MP**	**DB Creon® (pancrelipase clear/orange capsules)**	**DB Pancrelipase AAPIS**	**FD&C Blue No. 2 (E132)**	**OL Creon® (Pancrelipase)**
Formulation	Commercially manufactured pancrelipase pellets filled into Swedish Orange opaque capsules for blinding	Pancrelipase pellets MP filled into Swedish Orange opaque capsules for blinding	Commercially manufactured pancrelipase pellets manufactured using commercial process filled into commercial transparent capsules with orange caps	Pancrelipase pellets manufactured using commercial process, with pancrelipase API sourced from alternate manufacturing site, filled into transparent capsules with orange caps	FD&C Blue No. 2 (E132) powder, filled into hard capsules	Commercially manufactured pancrelipase pellets and capsules
Dosage Form	Delayed-release capsules	Delayed-release capsules MP	Delayed-release capsules	Delayed-release capsules	Hard gelatin capsules	Delayed-release capsules
Dose and units	24,000 USP units (Lipase) capsules	24,000 USP units (Lipase) capsules	24,000 USP units (Lipase) capsules	24,000 USP units (Lipase) capsules	250 mg	24,000 USP units (Lipase) capsules

Table 2. Identity of Investigational Product (Continued)

Study Part(s)	Part 1	Part 1	Part 2	Part 2	Parts 1 and 2	Parts 1 and 2
Investigational Product Name	**DB Creon® (Pancrelipase orange/orange capsules)**	**DB Pancrelipase MP**	**DB Creon® (pancrelipase clear/orange capsules)**	**DB Pancrelipase AAPIS**	**FD&C Blue No. 2 (E132)**	**OL Creon® (Pancrelipase)**
Excipients	Capsule Shell: Gelatin, red iron oxide, titanium dioxide, and sodium lauryl sulfate Drug Product: cetyl alcohol, dimethicone, hypromellose phthalate, polyethylene glycol, and triethyl citrate	Capsule Shell: Hypromellose, red iron oxide, and titanium dioxide 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	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, and titanium dioxide Drug Product: Each capsule contains 250 mg of FD&C Blue #2, with no additional 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

FD&C = US Food, Drug & Cosmetics Act; MP = modernized process uniform coated pellets

a. Capsule filling may occur at Catalent Germany Schorndorf, GmbH, Germany.

b. Facilitated by the Unblinded Pharmacist.

5.5.2.1 Packaging and Labeling

For the blinded treatment period of Part 1, AbbVie will supply to all sites open label study drug packaged in high density polyethylene (HDPE) bottles for Creon® (Pancrelipase) 24,000 USP Units (Lipase) delayed release capsules and Pancrelipase 24,000 USP Units (Lipase) delayed release capsules (MP). Each bottle will contain 100 capsules and will be labeled per local regulatory requirements. The blinding will be facilitated by a local Unblinded Pharmacist.

For the blinded treatment period of Part 2, AbbVie will supply to all sites double-blinded study drug packaged in high density polyethylene (HDPE) bottles for Creon® (Pancrelipase) 24,000 USP Units (Lipase) delayed release capsules and Pancrelipase 24,000 USP Units (Lipase) delayed release capsules (AAPIS). Each bottle will contain 100 capsules and will be labeled per local regulatory requirements.

For the screening period and for the interval between treatment Period 1 and treatment Period 2 (up to 28 days) for each study Part, open-label commercial Creon® (Pancrelipase) 24,000 USP units (Lipase) delayed release capsules will be provided in 250 ct bottles and labeled per local regulatory requirements. All labels must remain affixed to the bottle and the bottle should be kept closed except when dispensing study medication.

AbbVie will provide open label FD&C Blue No. 2 (E132) packaged in high density polyethylene (HDPE) bottles. Each bottle will contain 50 capsules and will be labeled per local requirements. Labels must remain affixed to the bottle and the bottle should be kept closed except when dispensing study medication.

5.5.2.2 Storage and Disposition of Study Drugs

All pancrelipase drugs must be stored at controlled room temperature (15° to 25°C or 59° to 77°F) and protected from moisture and freezing. The minimum and maximum temperature must be recorded on business days to document proper storage conditions. Temperature excursions must be reported to AbbVie. For the pancrelipase drug for the

screening period, for the interval between treatment periods, and for the interval between Parts (if applicable), subjects should be instructed to keep the bottle tightly closed between uses to protect from moisture.

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 conditions specified on the label until dispensed for subject use or returned to AbbVie or representative. Under necessary circumstances, sites will be allowed to ship open-label study drug to a subject's house using AbbVie's preferred courier, Marken. Other courier services, selected by the site, may be used if Marken is not available.

The clinical site will maintain accurate records of the disposition of all clinical drug supplies received during the study. These records shall include the amounts of drug supplied and the dates on which drug supplies were received from the Sponsor (or an authorized representative), dispensed to the subject, returned by the subject and returned to the Sponsor (or an authorized representative). If errors or damages in the clinical drug supply shipments occur, the clinical site must contact the Sponsor (or an authorized representative) immediately.

5.5.2.3 Preparation of Dosage Form

The preparation of blinded doses for the DB Treatment Periods for Part 1 only will need to be performed by an unblinded pharmacist or qualified designee.

5.5.3 Method of Assigning Subjects to Treatment Groups

For each study Part, all subjects enrolling into the DB Treatment Periods will be centrally randomized using an IRT system. Before the study is initiated, contact information and user guidelines for the IRT system will be provided to each site.

As subjects undergo the Screening Visit (Visit 1) of the first study Part, a unique subject number will be assigned to each subject by the IRT system. This unique subject number will be used only for the assigned subject throughout the study.

At the start of each study Part, after confirming that the subject has met all eligibility criteria on Day 1 of DB Treatment Periods 1, each subject will be randomly assigned to one of the treatment sequence arms in a 1:1 ratio, as outlined in Section 8.4.

For enrollment of eligible subjects into the study, the site will utilize the IRT system in order to receive unique study drug kit numbers. The study drug kit numbers will be assigned according to schedules that were computer-generated for each Part before the start of each Part of the study by the AbbVie Statistics Department, North Chicago, IL.

Randomization for study Part 1 and Part 2 are independent.

A copy of all of the randomization schedules will be kept by the Statistics Department at AbbVie and a copy will be forwarded to the IRT system provider. Study drug may only be dispensed after contacting the IRT system and only to subjects enrolled in the study according to kit numbers provided by the IRT system.

5.5.4 Selection and Timing of Dose for Each Subject

During each DB treatment period, subjects will receive 96,000 LU with each of the 3 planned meals and 48,000 LU with each of the 2 planned snacks, with a total of 384,000 LU per day. Study drug will be administered to subjects by study site staff at each meal/snack time during the 2 treatment periods for each Study Part.

5.5.5 Blinding

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management and AbbVie unblinded Site Monitor), the investigator, study site personnel (with the exception of the site unblinded pharmacist for study Part 1) and the subject, will remain blinded to each subject's

treatment and until completion of the study for all subjects. The IRT system will provide access to blinded subject treatment information in the case of a medical emergency.

The study blind may be broken if, in the opinion of the Investigator, it is in the subject's best interest. AbbVie must be notified before breaking the blind unless identification of the study drug is required for emergency therapeutic measures. If an emergency therapeutic measure is necessary which warrants breaking of the blind, AbbVie must be notified within 24 hours of the blind being broken.

The date and reason for blind break must be recorded in source documentation and on the appropriate eCRF.

If one study Part (Part 1 or Part 2) is completed earlier than the other study Part, the database lock and formal unblinded analysis for the completed study Part will be performed. Analysis of one Part will not unblind the other. The AbbVie study team will review the efficacy and safety results from the unblinded analysis of the completed Part and an interim study report for the corresponding study Part may be prepared for regulatory submission.

5.5.5.1 Blinding of Data for Independent Data Monitoring Committee (IDMC)

The external independent DMC will review unblinded safety data during the study. The frequency and the scope of data reviews and suggest relevant data for review and full details of DMC responsibilities and members and credentials will be included in the DMC Charter for Study M16-111.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

During each of the treatment periods, the subjects will be actively monitored by site personnel for compliance with the study drug intake requirements.

Subjects will be considered compliant if at least 90% of scheduled blinded study drug doses are taken during each of the blinded treatment periods. The Study Coordinator or other site personnel will keep an inventory of the study drug and document compliance for each individual study medication intake.

5.5.7 Drug Accountability

The investigator or representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt or similar document or via direct recording in the IRT system. An accurate (running) inventory of study drug will be kept by the site, and will include the lot number, Proof of Receipt number(s), the number of capsules dispensed, subject number, initials of person who dispensed/administered the drug, and the date study drug was dispensed/administered for each subject. An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the study and at the site close-out visit. All study drug unit doses must be inventoried, accounted for, and returned to AbbVie or destroyed per instructions from AbbVie and according to local regulations. A copy of the Drug Accountability Form, in accordance with instructions provided by the AbbVie monitor, will also be included in the shipment.

The investigator and/or named sub-investigators agree not to supply study medication to any persons not enrolled in the study. They also agree not to supply study medication to subjects who have completed their participation in the study (after Visit 6).

Intake of blue dye capsules and study drug compliance check will be recorded in the eCRF.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The study Part 1 utilizes a cross-over as the optimal design to demonstrate non-inferiority for pancrelipase formulated as pancrelipase DR capsules MP 24,000 USP Units (lipase) as compared to Creon® (pancrelipase) Delayed Release capsules 24,000 USP Units (lipase). Each subject is able to serve as his/her own control, thus minimizing the number of subjects exposed to meet the primary objective.

The study Part 2 utilizes a cross-over as the optimal design to demonstrate non-inferiority for pancrelipase formulated as Pancrelipase DR capsules manufactured with AAPIS, 24,000 USP Units (Lipase) as compared to Creon® (pancrelipase) DR capsules 24,000 USP Units (lipase). Each subject is able to serve as his/her own control, thus minimizing the number of subjects exposed to meet the primary objective.

For both study Parts, due to the nature of the effects of pancrelipase on fat absorption, and the lack of absorption of pancrelipase, there is no concern related to any carry over effect with immediate rollover between DB Treatment Period 1 and DB Treatment Period 2. This interval is not intended as a washout period and any imbalance in this period length would not lead to any difference on study endpoints. The flexibility in the duration of the interval between the DB treatment period is intended to allow subjects to deal with logistical aspects (such as school and work schedules) related to the need for hospitalization/confinement during DB treatment, and to allow sites to more effectively manage their staffing and occupancy. The same applies to the interval between Parts, for subjects who elect to participate on both Parts.

The active control used in this study is commercially available Creon® (pancrelipase) Delayed Release capsules 24,000 USP Units (lipase) with previously demonstrated safety and efficacy.

DB treatment is chosen for this study to enhance scientific rigor in the study, and to eliminate any possibility of subjects biasing the results by altering diet consumption or stool collection during the study.

5.6.2 Appropriateness of Measurements

The measurements included in this study are standard measurements used in studies assessing the pharmacodynamics and safety of pancreatic enzyme replacement therapies.

In studies investigating the efficacy of pancreatic enzyme supplementation, the commonly employed and scientifically accepted primary endpoint to determine efficacy is the CFA. The CFA reflects fat absorption and is a gauge for the lipase activity in pancreatic enzyme supplements on the digestion of dietary fat. The CFA endpoint is also appropriate for studies that assess pharmacodynamics endpoints but are not designed to determine efficacy of a compound versus placebo. The effects on the CFA can be observed even after a short treatment period of 3 – 7 days. Thus, 5 days of study drug treatment is generally accepted and sufficient in trials using the CFA as the endpoint.

The CNA reflects protein absorption and is a gauge for the protease activity in pancreatic enzyme supplements on the digestion of dietary protein.

5.6.3 Suitability of Subject Population

Patients aged 12 years or older with CF were selected for this study because they represent a commonly diagnosed and investigated population in terms of maldigestion and secondary malabsorption due to EPI. The clinical symptoms, the need for enzyme supplementation and the therapeutic objectives for treating maldigestion are well defined in these patients.

Patients with pancreatic insufficiency often have a variable dosing regimen highly dependent on food intake and pattern. Even though patients may be well controlled by their PERT prior to study participation, there is a risk that participation in the study with a diet that contains different amounts of fat and protein than their usual pre-study diet may

result in some gastrointestinal symptoms. However, considering the short duration of the study periods with study drug intake, and the fact that subjects will be carefully observed during confinement/hospitalization, and return immediately to their usual diet, and the fact that the PERT dose during confinement will be adjusted to the new fat content of the diet, the risk of destabilizing their underlying condition is considered minimal.

It has been previously shown that an inverse linear correlation exists between the level of the remaining endogenous lipase activity and the improvement in CFA induced by PERTs.[7] The enrollment of subjects with low endogenous lipase activity (more severe disease) may improve the interpretability and clinical relevance of on-treatment CFA values in PERT trials.

Therefore, in order to select a more severe patient population, the most conservative cutoff for fecal elastase-1 of < 15 µg/g was chosen to select subjects with EPI. Removing the requirement for a screening off-PERT CFA < 70% is particularly relevant, given the challenges elicited by the ongoing COVID-19 pandemic.

5.6.4 Selection of Doses in the Study

The maximum labeled dose of Creon® (4,000 LU/g fat intake/day) has been selected for this study, and is also applied to the pancrelipase DR MP drug product and the pancrelipase DR AAPIS drug product, as the effect of the MP drug product and AAPIS drug product is believed to be non-inferior to that of Creon®. The maximum labeled dose is chosen to provide sufficient lipase to adequately digest the dietary fat required in the study without exceeding the maximum recommended dose of pancrelipase contained in the Cystic Fibrosis Foundation guidelines.

5.6.5 Assessments for COVID-19 Infection

In the setting of the COVID-19 pandemic, assessments for COVID-19 infection in this study are being conducted to:

- Protect subjects from potentially worse outcomes associated with COVID-19 infection due to study related procedures in the setting of the confinement periods.

General screening for COVID-19 infection (e.g., temperature checks, symptoms, exposures to COVID-19 infected person[s]) prior to a study visit will be conducted per local standard of care.

Study-required assessments will include COVID-19 testing (done locally or via central laboratory) prior to each Double-Blind Treatment Period confinement. COVID-19 test results must be available and reviewed prior to the subject entering each confinement period.

Additional COVID-19 testing outside of study-required testing may be done per the discretion of the investigator.

6.0 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 after it is released for distribution.

Complaints associated with any component of the investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Section 6.1 through Section 6.1.6. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events

considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide another cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject, will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event 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 accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event 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 adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

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. 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.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.2 Adverse Event Severity

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

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.

6.1.3 Relationship to Study Drug

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

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

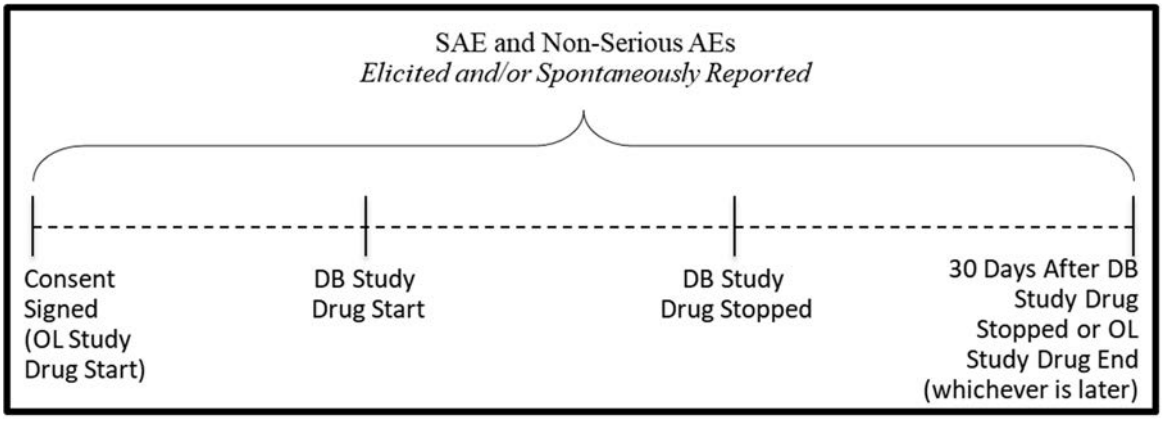
If an investigator's opinion of no reasonable possibility of being related to study drug is given, another cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration (starting at the time the subject is dispensed OL drug at the screening period of the first study part) until 30 days following discontinuation of DB study drug administration of the last study part have elapsed will be collected, whether solicited or spontaneously reported by the subject.

Adverse event information will be collected in each Part as shown in Figure 2.

Figure 2. Adverse Event Collection for each Study Part



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE® is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

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

For safety concerns, contact the Specialty Development Safety Team at:

Specialty Development Safety Team
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Telephone Contact Information:
Phone: +1 (833) 942-2226
Email: SafetyManagement_Hormones@abbvie.com

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

Therapeutic Area MD:

[redacted] MD
Medical Director
Specialty Development, AbbVie
1 N. Waukegan Road
North Chicago, IL 60064

Telephone Contact Information:
Office: [redacted]
Mobile: [redacted]
Fax: [redacted]
Email: [redacted]

In emergency situations involving study subjects when the TA MD 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 MD:

Phone: +1 (973) 784-6402

AbbVie will be responsible for Serious Unexpected Suspected Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product(s) (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the

Reference Safety Information (RSI). The RSI in effect at the start of the IND Annual reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

6.1.6 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 5.3.1.1). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected. In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained before collection of any such information. A separate consent will be provided by AbbVie for this purpose. Pregnancies in study subject's partners will be collected from the date of the first dose through 30 days following the last dose of study drug.

While pregnancy in a study subject is not considered an adverse event, the medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 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 TA MD 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.).

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

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 (example: printing illegible), missing components/product, or packaging issues.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form available in the electronic data capture (EDC) system used to collect information during the study. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified), it should be reported as soon as possible using the following contact information to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study:

Primary Contact:

[redacted]
Study Project Manager
Specialty Development, AbbVie
1 N. Waukegan Road
North Chicago, IL 60064, USA

Office: [redacted]
Fax:
Email:

Alternate Contact:

[redacted]
Study Management Associate
Specialty Development, AbbVie
1 N. Waukegan Road
North Chicago, IL 60064, USA

Office: [redacted]
Email:

If a protocol deviation occurs (or is identified) that is likely to have a significant effect on subject safety or study data, it should be reported to AbbVie within 1 business day. The principal investigator is responsible for notifying the IEC/IRB, the regulatory authorities (as applicable).

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). These will include analysis populations, hypotheses to be tested, methods for summarizing the data, statistical tests to be performed, missing data handling, analysis conventions, and primary estimand attributes. The analysis will be performed using SAS (SAS Institute Inc., Cary, NC, USA).

The number of observations, mean, standard deviation, median, minimum and maximum will be summarized for continuous variables. Discrete variables will be summarized by counts and percentages. Medical History will be presented by count and percentage of subjects broken down by Body System and Diagnosis.

All the analyses will be performed separately for Part 1 and Part 2.

8.1.1 Definition for Analysis Populations

The analysis populations will be defined separately for Part 1 and Part 2.

The Intent-to-Treat (ITT) Population includes all randomized subjects. Subjects will be included in the analysis according to the treatment sequence that they are randomized to. ITT population will be used for summaries of subjects' disposition and baseline characteristics.

The Evaluable Set consists of all randomized subjects who complete both treatment periods and have 100% stool samples collected for both treatment periods. Subjects will be included in the analysis according to the study drug that they actually received. The Evaluable Set will be used for the efficacy analysis for the primary and secondary endpoints.

The Safety Analysis Set consists of all randomized subjects who received at least 1 dose of double-blind study drug. Subjects will be included in the analysis according to the study drug that they actually received.

8.1.2 Primary and Secondary Endpoint Analyses

Non-inferiority assessments will be performed based on subjects who complete both treatment periods. The primary pharmacodynamic variable will be the CFA. The CFA values, measured at the end of the two cross-over periods, will be analyzed using a mixed effects model including sequence, period and treatment group as fixed effects and subjects within sequence as a random effect. From this model, the mean CFA difference between two treatment groups will be estimated, along with its two-sided 99% confidence interval (CI) that will be compared with a non-inferiority margin of 12%. If the upper bound of the 99% CI of CFA difference (Creon® - Pancrelipase DR MP in Part 1, or Creon® - Pancrelipase DR AAPIS in Part 2) rules out the margin, the non-inferiority of the Pancrelipase product investigated in that Part to Creon® will be declared.

The two-sided 95% CI for the estimate of the mean CFA difference will also be provided. The primary estimand and specified estimand attributes for each study Part will be described in the SAP. Supplementary analyses for the primary endpoint will be described in the SAP.

The secondary pharmacodynamic variables will be the CNA, stool fat, and stool weight. These variables will also be analyzed separately using a mixed effects model including sequence, period and treatment group as fixed effects and subjects within sequence as a random effect. From this model, an estimate of the treatment difference along with its two-sided 95% CI will be derived. All comparisons for all secondary pharmacodynamic variables between the treatment groups will be descriptive.

Additional exploratory pharmacodynamic variables include stool frequency, stool consistency, diarrhea, abdominal pain, bloating, and flatulence. These variables will be summarized by treatment group using descriptive statistics.

8.1.3 Safety Analysis

Safety analyses will be carried out using the Safety Analysis Set. Treatment-emergent AEs and SAEs, will be summarized and reported. Treatment-emergent AEs for DB Treatment Period 1 are defined as reported AEs that have a start date either on or after the first dose of the study drug during DB Treatment Period 1 and up to the end of DB Treatment Period 1. For DB Treatment Period 2, treatment emergent AEs are defined as reported AEs that have a start date either on or after the first dose of study drug during DB Treatment Period 2 and up to the end of DB Treatment Period 2. Adverse Events that occur during the administration of OL Creon® will be summarized separately for events that happen during the screening period and after randomization. The number and percent of subjects experiencing AEs will be tabulated by system organ class (SOC) and Medical Dictionary for Drug Regulatory Activities (MedDRA®) preferred term. In addition, summary of AEs by severity and relationship to study drug will be presented. Serious AEs, or AEs that lead to premature study discontinuation will be listed and described in detail. All these summaries will be done by treatment group. Mean change in vital signs and laboratory variables at each visit will be summarized. The last evaluation prior to the first dose of DB study drug in the corresponding treatment period will be used as baseline for the analysis in that treatment period. A frequency table will be presented for Potentially Clinically Important (PCI) vital sign findings. Shift tables for laboratory variables will be presented according to the reference ranges (low, normal or high).

Due to the small number of subjects per treatment group, only summary statistics will be applied to all the safety parameters.

8.2 Determination of Sample Size

8.2.1 Non-inferiority Margin Justification

The selection of a non-inferiority margin of 12% for the CFA is based on historical placebo-controlled Creon® Study S245.3.126, which had a similar study design (two-period, two-sequence cross-over) as Study M16-111, and enrolled 31 CF subjects with confirmed EPI based on the eligibility criteria of a historical CFA < 70%, or current

or historical fecal elastase-1 < 50 µg/g. The effect of Creon® compared to placebo in CFA was estimated as 39.02% (95% CI: 32.3% – 45.8%). However, it is expected that the current study will enroll subjects with more severe EPI than the subjects in Study S245.3.126, as the enrollment criteria for EPI in the current study is more stringent: subjects need to have a baseline fecal elastase less than 15 µg/g to be enrolled. Therefore, the non-inferiority margin for comparing Pancrelipase DR MP to Creon® (Part 1) or comparing Pancrelipase DR AAPIS to Creon® (Part 2) should be derived based on Creon's effect in a more comparable subject population in the historical study. At the time of the writing of this amendment, all subjects enrolled in Study M16-111 had a screening FE-1 of less than 15 µg/g and a screening CFA below 50%.

A subgroup analyses in Study S245.3.126 has been performed to estimate the Creon effect in subjects with a more severe EPI, defined as having a CFA of 50% or less during the placebo treatment period (since the screening FE-1 value was not collected in Study S245.3.126). The Creon effect compared to placebo in CFA was estimated as 52.25% (95% CI: 47.0% – 57.5%) in this subject population. Based on the lower bound of the 95% CI for the estimate of Creon effect, a non-inferiority margin of 12% would preserve over 70% of that effect ((47-12)/47=74%).

8.2.2 Sample Size Determination

For each study Part, it is assumed that the expected difference in means of CFA between Creon® and Pancrelipase DR MP (Part 1) or between Creon® and Pancrelipase DR AAPIS (Part 2) is 0. For Part 1, with 22 subjects completing the 2 crossover treatment periods and having valid CFA in both periods, the power to claim non-inferiority is approximately 96% based on one-sided type I error of 0.005 (i.e., based on two-sided 99% CI for non-inferiority assessment), assuming a standard deviation (SD) of 12% for the within-subject treatment difference.

For Part 2, with 18 subjects completing the 2 crossover treatment periods and having valid CFA in both periods, the power to claim non-inferiority is approximately 98% based on one-sided type I error of 0.005 (i.e., based on two-sided 99% CI for non-inferiority

assessment), assuming a standard deviation (SD) of 10% for the within-subject treatment difference (see Section 8.2.3).

Table 3. Study Power for Non-Inferiority in Primary Endpoint of CFA

SD of Treatment Difference	Power (N=22)	Power (N=18)
8%	99%	99%
10%	99%	98%
12%	96%	89%
14%	87%	75%

Note: Power for non-inferiority in primary endpoint by evaluable sample size, if true CFA difference is 0.

It is expected that a screening failure rate of about 30% will be observed and that approximately 10-15% of the subjects will drop out during the crossover treatment periods. Based on these assumptions, approximately 36 subjects will be screened and approximately 26 subjects will be randomized in Part 1 to expect 22 subjects to complete the crossover treatment periods, and approximately 30 subjects will be screened and approximately 20 subjects will be randomized in Part 2 to expect 18 subjects to complete the crossover treatment periods.

8.2.3 Blinded Sample Size Re-Estimation (BSSR)

For Part 1, with a sample size of 22 evaluable subjects, the study Part is sufficiently powered if the SD of the within-subject treatment difference in CFA is 12%. For Part 2, with a sample size of 18 evaluable subjects, the study Part is sufficiently powered if the SD of the within-subject treatment difference in CFA is 10%. However, if the actual SD for a respective study Part is larger than the assumed SD (12% or 10% for Part 1 or Part 2, respectively), the power for that study Part may be insufficient. In order to ensure the assumption of SD holds for the study, a **blinded** review and estimate of the SD will be conducted for each study Part when the CFA data from the two treatment periods for approximately half of the planned subjects are available. If the estimate of the SD is much different from the assumed SD, the sample size of the study may be adjusted based

on the estimated SD from the blinded data. The detailed BSSR plan is documented in the SAP.

As of the date of the approval of protocol amendment 7, Part 1 BSSR has been completed. The blinded estimate of the SD for the within-subject treatment difference in CFA from Part 1 was approximately 7%. Per the BSSR plan specified in the SAP, the Part 1 sample size remains the same as 22 evaluable subjects. However, the assumption of the SD used in the Part 2 sample size determination has been adjusted to 10%.

8.3 Study Data Reporting

If one study Part (Part 1 or Part 2) is completed earlier than the other study Part, the database lock and formal unblinded analysis for the completed study Part will be performed. Analysis of one Part will not unblind the other. The AbbVie study team will review the efficacy and safety results from the unblinded analysis of the completed Part and an interim study report for the corresponding study Part may be prepared for regulatory submission.

8.4 Randomization Methods

For Part 1 at Visit 2 (DB Treatment Period 1 Day 1), eligible subjects will be randomized in a 1:1 ratio, to one of the 2 treatment sequence arms as shown below:

Sequence Arm	Treatment Period 1	Treatment Period 2
A	Pancrelipase DR capsules **MP**	Creon® (Pancrelipase) DR capsules
B	Creon® (Pancrelipase) DR capsules	Pancrelipase DR capsules **MP**

MP = modernized process uniform coated pellets, large scale

Subjects randomized to Sequence Arm A will take pancrelipase DR 24,000 MP drug product during DB Treatment Period 1 and then take Creon® during DB Treatment Period 2. Subjects randomized to Sequence Arm B will take Creon® during DB Treatment Period 1 and then take pancrelipase DR MP-drug product during DB Treatment Period 2.

For Part 2 at Visit 2 (DB Treatment Period 1 Day 1), eligible subjects will be randomized in a 1:1 ratio, to one of the 2 treatment sequence arms as shown below:

Sequence Arm	Treatment Period 1	Treatment Period 2
C	Pancrelipase DR capsules **AAPIS**	Creon® (Pancrelipase) DR capsules
D	Creon® (Pancrelipase) DR capsules	Pancrelipase DR **AAPIS**

AAPIS = Delayed-release capsules of pancrelipase manufactured at an Alternate Active Pharmaceutical Ingredient Site; DR = Delayed release

Subjects randomized to Sequence Arm C will take Pancrelipase DR capsules AAPIS drug product during DB Treatment Period 1 and then take Creon® during DB Treatment Period 2. Subjects randomized to Sequence Arm B will take Creon® during DB Treatment Period 1 and then take Pancrelipase DR capsules AAPIS drug product during DB Treatment Period 2.

The randomization is central without any stratification. Randomization schedules for Part 1 and Part 2 are independent from each other. The randomization schedule will be prepared by the Randomization Personnel of AbbVie.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, USPI, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. When deemed necessary by the IRB/IEC, the documented assent of subjects who are minor children must be obtained. If a subject reaches 18 years of age prior to completion of study participation, the investigator will obtain a new Informed Consent from the subject before further study participation.

A copy of the informed consent and the subject assent will be given to the subject/subject's representative (in case of a minor child) 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 and assent, if applicable, were obtained prior to any study-related procedures and that the subject/subject's representative received a signed copy of each document.

Information regarding incentives 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 ICF.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents. The printed report from ABVDiet will serve as source document for the fat and protein consumption and will be maintained by the clinical site.

The investigator/institution will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available

through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The EPI Symptom Diary must be completed for each subject enrolled in this study using a paper questionnaire. The questionnaire will serve as source data for the study.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

Site Training

Prior to the first site activation, an investigators' meeting will be held to ensure the study is conducted according to GCP and regulatory guidelines and that all participating sites are trained on the study in accordance to the protocol. This will support consistency and compliance to the protocol procedures that are critical to the success and validity of the clinical trial data. In addition to protocol training, Investigators and site staff will be trained on diet planning and compliance, stool collection procedures, dispensation and handling of the study drug and expectations regarding ABVDiet completion. Details regarding potential side effects and permissible/prohibited concomitant treatments will be discussed. Procedures for defining, monitoring and reporting AEs and SAEs will be outlined. Clearly defined roles and responsibility of the clinical investigators as well as study team contacts will be presented during the investigators' meeting. Breakout sessions involving the site dietitian and central dietitian will occur to allow for training on the ABVDiet tool and diet requirements.

Prior to enrolling any subject in the study, a Site Initiation Visit will be held at each clinical site with AbbVie personnel (and/or their representatives), the investigators, and the appropriate site personnel. The visit's agenda will include a detailed discussion and review of the protocol and essential documents, performance of study procedures, eCRF completion, AE monitoring and reporting and specimen collection methods. The personnel at the study site will be trained on the study procedures, when applicable, by an AbbVie monitor or designee.

Manuals pertaining to the use of all relevant systems (EDC, central lab, ABVDiet, etc.) will be made available to sites at the time of the site initiation visit.

Monitoring

The AbbVie monitor will monitor the study site throughout the study. A source document review will be performed against entries on the eCRFs and a quality assurance check will

be performed to ensure that the investigator is complying with the protocol and regulations.

Monitoring visits will be scheduled at mutually agreeable times periodically throughout the study and at a frequency deemed appropriate for the study. Monitoring visits will be conducted to evaluate the progress of the study, ensure the rights and wellbeing of subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from available source documents and the conduct of the study is in compliance with the approved protocol and applicable amendments, GCPs and applicable national regulatory requirements. A monitoring visit will include a review of the essential clinical study documents (regulatory documents, CRFs, source documents. Drug disposition records, subject ICFs, etc.) as well as discussion on the conduct of the study with the Investigator and site study staff. The investigator and site study staff should be available during these to facilitate the review of the clinical study record and resolve/document any discrepancies found during the monitoring visit.

In addition, ongoing Medical Safety monitoring of the data will be conducted by a physician or representative at AbbVie.

Data Quality Assurance

Data entered into eCRFs will be electronically transferred to AbbVie and imported into the database using validated software throughout the study. Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

Routine hematology, serum chemistry, stools weight and content, pregnancy testing will be analyzed using a central laboratory. The data from these analyses will be electronically transferred from the central laboratory to the study database using validated software. A review of all laboratory results will be conducted by the Investigator, the AbbVie monitor, a physician, and other appropriate personnel at AbbVie.

The consumed amounts of fat, protein and calories will be calculated by ABVDiet. The applicable endpoint data will be electronically transferred from ABVDiet to the EDC system and will be reviewed by the central dietitian, the AbbVie monitor and other appropriate personnel at AbbVie. ABVDiet will be accessible to the AbbVie monitor and AbbVie study team to allow review of diet compliance throughout the course of the study.

12.0 Use of Information

All information concerning pancrelipase and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of pancrelipase. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for trial-related monitoring, audits, IEC/IRB review and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study and will forward a copy of this report to AbbVie or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end of study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for pancrelipase.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Phase 4 Study to Compare US Marketed Creon® Drug Product with Drug Product Manufactured with a Modernized Process at an Alternate Manufacturing Site and with Drug Product manufactured with the approved manufacturing process at an alternate **A**ctive **P**harmaceutical **I**ngredient Site, in Subjects with EPI due to Cystic Fibrosis
Protocol Date:	15 September 2021

Signature of Principal Investigator Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
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., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
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 investigation and all 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. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	Therapeutic Area MD	Development
[redacted]	Therapeutic Area Associate VP	Development
[redacted]	Program Lead	Development Operations
[redacted]	Study Project Manager	Development Operations
[redacted]	Director	Statistics
[redacted]	Senior Director	Statistics

Appendix C. Study Activities

a. Overall Study Activities for Study Part 1 and Study Part 2

Activity	Screening	Double-Blind Treatment Period					Follow-Up Period
		DB Treatment Period 1		Interval	DB Treatment Period 2		Visit 6
	Visit 1[o]	Visit 2 Day 1	Visit 3 Day 6, 7 or 8[b]	Up to 28 Days[c]	Visit 4 Day 1	Visit 5[a] Day 6, 7 or 8[b]	30 Days Post Hospital Discharge
Informed Consent[p]	X						
Medical History	X	X[d]			X[f]		
Previous dose of PERT	X				X[f]		
Concomitant Medication Review	X	X	X		X	X	X
Physical Examination	X[r]	X	X		X[f]	X	
Height	X						
Body weight	X	X[e]	X[e]		X[e]	X[e]	
Vital Signs	X[r]	X	X		X	X	
Clinical Laboratory Tests	X[r]	X	X		X[f]	X	
Stool Collection for Fecal Elastase Testing	X[s]						
Pregnancy Testing[g]	X	X			X		
Diet Plan Design	X[h]						
Start hospitalization/confinement		X			X		
IRT system contact	X[i]	X[j]	X[l]		X[k]	X[q]	

Activity	Screening	Double-Blind Treatment Period					Follow-Up Period
		DB Treatment Period 1		Interval	DB Treatment Period 2		Visit 6
	Visit 1[o]	Visit 2	Visit 3	Up to 28 Days[c]	Visit 4	Visit 5[a]	30 Days Post Hospital Discharge
		Day 1	Day 6, 7 or 8[b]		Day 1	Day 6, 7 or 8[b]	
Adverse Events Review		See Table b. "Treatment Periods Activities"			See Table b. "Treatment Periods Activities"		X
Study Drug Administration	X						
Treatment Compliance Check							
Diet Administration							
Dietary Records							
Stool Collection							
EPI Symptom Diary							
Hospital/Confinement site discharge			X[f]			X	
COVID-19 Testing		X[m]			X[m,n]		
COVID-19 signs and symptoms screening		X			X		

a. Or early termination visit (except hospitalization and stool collection/dietary record).

b. Days 6, 7 or 8 depending on the first appearance of the 2nd dyed stool after the 2nd stool dye marker is administered.

c. In exceptional circumstances, this period may be extended upon consultation with the sponsor.

d. To be updated only if there is new historical information available since Visit 1.

e. Done in the morning prior to any food intake and prior to any blood sampling.

f. If subject elects to enter directly into DB Treatment Period 2 from DB Treatment Period 1, this is not required.

g. For females with child-bearing potential: serum pregnancy test at the Screening Visit (Visit 1) and urine pregnancy test for other visits specified above.

h. Diet plans both the treatment periods for each study Part should be done prior to V2.

i. Unique subject number assignment. Subjects who are participating in both study Parts will only be assigned a subject number at the start of the first study Part they participate in and will use this number throughout the study.

j. Randomization and study drug kit number allocation for DB Treatment Period 1.

k. Study drug kit number allocation for DB Treatment Period 2.

l. At discharge to assign drug for interval between Treatment Period 1 and Treatment Period 2.

m. Subjects must have a negative viral COVID-19 test result, from a COVID-19 test done within 7 days prior to entering the DB treatment Period confinements (Visit 2 and Visit 4).

n. Subjects who choose to go directly from DB Treatment Period 1 confinement to DB Treatment Period 2 confinement do not need to perform a COVID-19 test unless otherwise directed by the investigator.

o. Subjects participating in both Parts and ≤ 30 days have occurred since Visit 5 of the previous Part, will not need screening repeated, but eligibility needs to be confirmed at Visit 2 of the second study Part.

p. Subjects who have already completed one study part prior to this amendment approval, and want to participate in the second part must sign the amended consent. Also, subjects who have agreed to participate in both study parts and it has been greater than 30 days between parts must resign the consent.

q. For the follow up period, the subject will be dispensed a 30 day supply of open label Creon®, at the dose they received during the screening period, to be taken during the follow up period.

r. This does not need to be repeated if subject is participating in both parts and < 30 days between Visit 5 and Visit 1 of the next study part.

s. A pre-screening consent may also be obtained from the subject prior to the screening visit so a stool sample can be collected and brought to the study site at the Screening Visit.

b. Treatment Periods (Hospitalization/Confinement) Activities for Study Part 1 and Study Part 2

Activity	Treatment Periods (DB 1 and DB 2)					
	Visits 2 and 4					Visits 3 and 5
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6, 7 or 8[a]
Hospitalization/Confinement	X	X	X	X	X	X[a]
Study Drug Administration	X	X	X	X	X	X[b,e,f]
Treatment Compliance Check	X	X	X	X	X	X
Stool marker (blue dye) to be taken after last food intake (bedtime)		X			X	
Diet	X	X	X	X	X	X
Dietary Records			X[c]	X	X[c]	
Stool Collection			X[d]	X[d]	X[d]	X[a]
EPI Symptom Diary[g]	X	X	X	X	X	X[h]
Concomitant Medication Review	X	X	X	X	X	X[a]
Adverse Events Review	X	X	X	X	X	X[a]

a. Days 6, 7 or 8 depending on the appearance of the 1st blue dyed stool after the intake of the 2nd stool dye marker on Treatment Period Day 5 evening.

b. Until 2nd stool marker is passed on Day 6, 7 or 8.

c. Dietary record starts with Day 3 breakfast (1st meal following 1st stool dye marker intake on Day 2), and ends with Day 5 dinner or 2nd snack (last meal prior to 2nd stool dye marker intake on Day 5).

d. Stool collection starts after the subject passes the first stool dye marker (excluding the first blue dyed stool), and ends with the first blue dyed stool (including the blue dyed stool) after the second stool dye marker administration.

e. Study drug for the interval between Treatment Period 1 and Treatment Period 2 will be dispensed at discharge from confinement/hospitalization at Visit 3.

f. For the follow up period, the subject will be dispensed a supply of open label Creon®, at the dose they received during the screening period, to be taken during the follow up period.

g. Completed prior to the administration of study drug, prior to breakfast on each day of study confinement.

h. Completed by the subject each day until subject is discharged.