Statistical Analysis Plan for Study 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

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Version 5.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for pancrelipase Study 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 (Protocol Amendment 6), in Subjects with EPI due to Cystic Fibrosis."

Study M16-111 examines the efficacy and safety of pancrelipase manufactured with a modernized process (MP) in subjects with Exocrine Pancreatic Insufficiency (EPI) due to Cystic Fibrosis (CF). This examination is being conducted in Part 1 of this study.

Study M16-111 also examines the efficacy and safety of pancrelipase manufactured with the approved process at an Alternate Active Pharmaceutical Ingredient Site (AAPIS) in subjects with EPI due to CF. This examination is being conducted in Part 2 of this study.

Unless otherwise specified, summaries and analyses will be performed within each study Part (Part 1 or Part 2), without integration of data between study Parts.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

2.0 Study Design and Objectives

2.1 Objectives and Hypotheses

The objective of Part 1 is to demonstrate non-inferiority of pancrelipase Delayed-Release (DR) capsules MP 24,000 USP Units (lipase) drug product 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 the coefficient of absorption (CFA).

The objective of Part 2 is to demonstrate non-inferiority of DR 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 for each study Part.

2.2 Study Design Overview

Part 1 is a Phase 4, double-blind, randomized, active-controlled, two-period, two-sequence crossover design that will test pancrelipase DR capsules MP for non-inferiority compared to the currently US marketed Creon® in subjects of 12 years or older with EPI due to CF, as measured by CFA. Part 2 is a Phase 4, double-blind, randomized, active-controlled, two-period, two-sequence crossover design that will test pancrelipase DR capsules AAPIS for non-inferiority compared to the currently US marketed Creon® in subjects of 12 years or older with EPI due to CF, as measured by CFA.

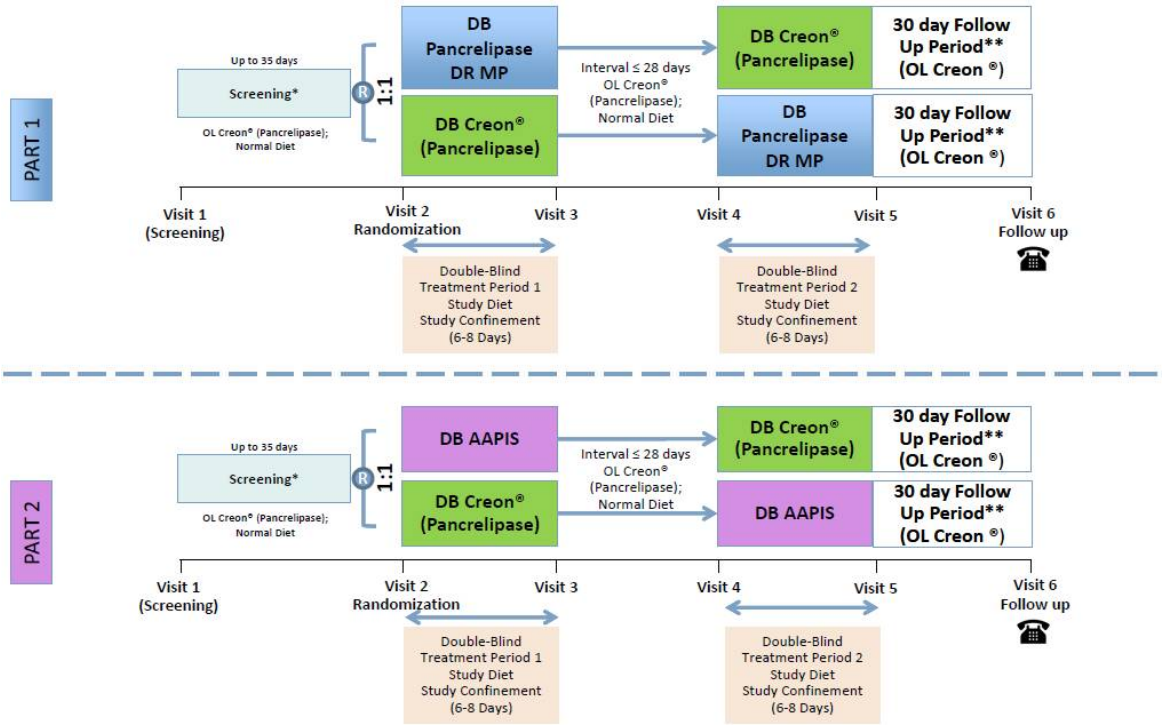
For study Part 1, the target number of evaluable subjects is 22, with a screening of approximately 36 subjects and enrollment/randomization of approximately 26 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects in Part 1 (22) has completed the study, there is a possibility that additional subjects in screening will not be enrolled in this 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 this Part. See Section 2.4 Sample size determination for details.

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.

2.3 Treatment Assignment and Blinding

Within each Part, subjects will be randomized in a 1:1 ratio to one of the 2 treatment sequence arms as shown below. The randomization is central without any stratification.

Part 1:

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

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

2.4 Sample Size Determination

The sample size determination consists of a power calculation for the total number of evaluable subjects needed and assumptions for percentage of drop-outs for the total number of subjects enrolled. A non-inferiority margin of 12% is chosen for the study. This non-inferiority margin for comparing Pancrelipase DR MP to Creon® (Part 1) or comparing Pancrelipase DR AAPIS to Creon® (Part 2) was derived based on Creon's effect in a more comparable subject population in the historical study with a similar study design as follows:

Based on historical data from 4 placebo-controlled studies (Studies S223.3.101[1], S223.3.102[2], S245.3.126[3], S245.3.127[4]), the effect in CFA is 36.8% (95% confidence interval: 32.6% – 41.0%) comparing Pancrelipase DR Capsules 24,000 with placebo.

Specifically, in the historical placebo-controlled Creon® Study S245.3.126[3], which had a similar study design as Study M16-111 (as a two-period, two-sequence cross-over study conducted in an adult population at the same dose strength as M16-111), the effect of Creon® compared to placebo in CFA was estimated as 39.02% (95% CI: 32.3% – 45.8%) based on 31 enrolled CF subjects with confirmed EPI based on the eligibility criteria of a historical CFA < 70%, or current or historical Fecal Elastase-1 (FE-1) < 50 µg/g. However, it is expected that the current Study M16-111 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 FE-1 less than 15 µg/g to be enrolled. At the time of the protocol amendment 6, all subjects enrolled (N=10) in Study M16-111 had a screening FE-1 of less than 15 µg/g and a screening CFA below 50%.

A subgroup analysis in Study S245.3.126 was 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%).

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 who complete the two crossover treatment periods and have valid CFA as the primary endpoint, the power of the study to claim non-inferiority by comparing the 99% confidence interval (CI; i.e., based on one-sided type I error of 0.005) with a margin of 12% is approximately 96%, 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 with a margin of 12%), assuming a standard deviation (SD) of 10% for the within-subject treatment difference (see Section 2.4.1 for justification of 10% SD based on BSSR).

Table 1. 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 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 with evaluable CFA in both 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 with evaluable CFA in both treatment periods.

2.4.1 Blinded Sample Size Re-Estimation (BSSR)

As of the date of the approval of SAP version 4.0, 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%.

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 the study 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 are available for approximately half of the planned subjects (i.e., 13 or 10 subjects for Part 1 or Part 2, respectively). It will be performed by the AbbVie study statistician. Since the study database will not be un-blinded to conduct the BSSR, AbbVie does not plan to put additional firewalls in place.

Detailed methodology of the BSSR

The initial sample size N_0 is determined by

$$N_0 = 2\frac{[\, t_{N_0-2}(1-\alpha) + t_{N_0-2}(1-\beta)]^2}{B^2}\hat{\sigma}_e^2$$

where α is the one-sided type I error, $1-\beta$ is the power, B is the non-inferiority margin, and $\hat{\sigma}_e^2$ is the within-subject variance estimate. When $\alpha = 0.005, 1-\beta = 0.96, B = -12$, SD of treatment difference = 12 (then $\hat{\sigma}_e^2 = \frac{12^2}{2} = 72$), then $N_0 = 22$. When $\alpha = 0.005, 1-\beta = 0.98, B = -12$, SD of treatment difference = 10 (then $\hat{\sigma}_e^2 = \frac{10^2}{2} = 50$), then $N_0 = 18$.

Interim BSSR will be conducted when CFA data for the first n_1 (e.g., $n_1 = 13$ or 10 for Part 1 or Part 2, respectively) subjects are available. Within-subject variance σ_e^2 will be estimated using the blinded estimate of the total variance $\hat{\sigma}_{os}^2$ based on n_1 subjects.[5] The total interim variance $\hat{\sigma}_{os}^2$ will be estimated with the formula below.

$$\hat{\sigma}_{os}^2 = \frac{1}{2(n_1 - 1)}\sum_{i=1}^{2}\sum_{j=1}^{n_1/2}(d_{ij} - \bar{d})^2$$

where d_{ij} is period difference (Period 2 – Period 1) for subject j in sequence i, $\bar{d}$ is the overall mean for all d_{ij}, which can be calculated without knowledge of the treatment allocation. $\hat{\sigma}_{os}^2$ is an unbiased estimate of σ_e^2 if there is no treatment difference. I.e.,

$$E(\hat{\sigma}_{os}^2) = \sigma_e^2 + \frac{n_1}{2(n_1 - 1)}(\tau_T - \tau_R)^2$$

where $\tau_T - \tau_R$ denotes the treatment difference.

Then the estimated sample size will be calculated as

$$\widehat{N} = 2\frac{[\, t_{\widehat{N}-2}(1-\alpha) + t_{\widehat{N}-2}(1-\beta)]^2}{B^2}\hat{\sigma}_{os}^2$$

with $\alpha = 0.005, 1 - \beta = 0.90,\ B = -12.$

In order to incorporate a cap on the sample size of 50 subjects (e.g., $N_{cap} = 50$), the final recalculated sample size will be

$$\widehat{N}_{recal} = \min(\max(N_0\ , \widehat{N}), N_{cap}\,)$$

Based on the formula above, the final recalculated sample size will be always greater than or equal to the initial sample size of evaluable subjects (22 or 18 for Part 1 or Part 2, respectively) and less than or equal to the limit of 50 evaluable subjects.

3.0 Endpoints

3.1 Primary Endpoint(s)

The primary efficacy endpoint is the CFA measured at the end of each treatment period.

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

Fat intake will be determined from fat content of food consumed on Day 3, 4, 5 of each treatment period. Fat excretion will be determined from the fat content in the stool(s) collected after the first blue dyed stool (exclusive) and until the second blue dyed stool (inclusive) during each treatment period.

3.2 Secondary Endpoint(s)

The secondary efficacy endpoints 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 on Day 3, 4, 5 of each treatment period. 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 after the first blue dyed stool (exclusive) and until the second blue dyed stool (inclusive) during each treatment period.
- Stool fat.

  Stool fat will be determined from the stool fat in the stool(s) collected after the first blue dyed stool (exclusive) and until the second blue dyed stool (inclusive) during each treatment period.
- Stool weight.

  Stool weight will be determined from the net weight of the stool samples collected after the first blue dyed stool (exclusive) and until the second blue dyed stool (inclusive) during each treatment period.

3.3 Additional Exploratory Endpoint(s)

To assess additional exploratory endpoints, subjects will complete an EPI Symptom Diary on a daily basis during each confinement treatment period. Additional exploratory efficacy endpoints include:

- Stool frequency

  Stool frequency will be determined by self-report on the EPI Symptom Diary (number of bowel movements over the last 24 hours).
- Stool consistency

  Stool consistency will be determined by self-report on the EPI Symptom Diary (No bowel movements over the last 24 hours, Hard/difficult to pass, Formed/normal, Loose/watery).
- Diarrhea

  Diarrhea will be determined by self-report on the EPI Symptom Diary (None, Mild, Moderate, Severe).
- Abdominal pain

  Abdominal pain will be determined by self-report on the EPI Symptom Diary (None, Mild, Moderate, Severe).
- Bloating

  Bloating will be determined by self-report on the EPI Symptom Diary (None, Mild, Moderate, Severe).
- Flatulence

  Flatulence will be determined by self-report on the EPI Symptom Diary (None, Mild, Moderate, Severe).

3.4 Safety Endpoint(s)

The safety variables include:

- Percentage of subjects reporting treatment-emergent adverse events (TEAEs).
- Analysis of laboratory data and vital signs.

4.0 Analysis Populations

The following population sets will be defined and used for the analyses for each study Part.

The Screening Confinement Set consists of all subjects who started screening confinement. The screening confinement period was removed from the study design in protocol amendment 6. Therefore, the Screening Confinement Set (denoted SC-P1) is only defined for Part 1 and includes subjects screened under protocol Amendment 5 or earlier.

The Intent-to-Treat (ITT) Population includes all randomized subjects in each study Part (denoted as ITT-P1 and ITT-P2 for Part 1 and Part 2, respectively). Subjects will be included in the analysis according to the treatment sequence to which they are randomized.

The Evaluable Set (ES) consists of all randomized subjects in each study Part who complete both double-blind (DB) treatment periods and have 100% of stool samples collected and analyzed by the laboratory and valid total fat intake value for both DB treatment periods. The ES for Part 1 and Part 2 will be denoted as ES-P1 and ES-P2, respectively. Subjects will be included in the analysis according to the study drug that they actually received.

The Safety Analysis Set consists of all randomized subjects who received at least 1 dose of study drug in the DB treatment periods in each study Part (denoted as SA-P1 and SA-P2 for Part 1 and Part 2, respectively). Subjects will be included in the analysis according to the regimen that they actually received.

The Open Label Safety Analysis Set in each study Part consists of all subjects who received at least 1 dose of open label Creon during any study period (denoted as OLSA-P1 and OLSA-P2 for Part 1 and Part 2, respectively). For Part 1, subjects who received open label Creon during the maintenance period (only applicable for subjects enrolled prior to protocol amendment 6) will also be included in OLSA-P1.

For Part 1, the population sets include: the Screening Confinement Set (SC-P1), Intent-to-Treat Population (ITT-P1), Evaluable Set (ES-P1), Safety Analysis Set (SA-P1) and Open Label Safety Analysis Set (OLSA-P1). For Part 2, the population sets include: the Intent-to-Treat Population (ITT-P2), Evaluable Set (ES-P2), Safety Analysis Set (SA-P2) and Open Label Safety Analysis Set (OLSA-P2).

5.0 Subject Disposition

The total number of subjects who started and completed screening confinement and the duration of screening confinement (days) will be summarized for the Screening Confinement Set for study Part 1 using SC-1. Reasons for exclusion, including screen failure, will be summarized.

The number and percentage of subjects who prematurely discontinued open-label Creon for study Part 1 and Part 2 will be summarized for all reasons and primary reason using OLSA-P1 and OLSA-P2, respectively.

A summary of subject accountability will be provided for the ITT Population for study Part 1 and Part 2 using ITT-P1 and ITT-P2, respectively. The number of subjects in each of the following categories will be summarized for each treatment sequence:

- Subjects randomized in the study
- Subjects who took at least one dose of study drug in DB Treatment Period 1
- Subjects who completed DB Treatment Period 1
- Subjects who took at least one dose of study drug in DB Treatment Period 2
- Subjects who completed DB Treatment Period 2
- Subjects who prematurely discontinued study drug in DB Treatment Period 1 (all reasons and primary reason)
- Subjects who prematurely discontinued study drug in DB Treatment Period 2 (all reasons and primary reason)
- Subjects who prematurely discontinued the study Part (all reasons and primary reason)

6.0 Study Drug Duration and Compliance

For the Safety Analysis Set, duration of double-blind treatment will be summarized per treatment period for each regimen using SA-P1 and SA-P2 for study Part 1 and Part 2, respectively. Duration of treatment is defined for each subject as last dose date of the corresponding DB treatment minus first dose date of the corresponding DB treatment + 1. Duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, minimum and maximum.

Descriptive statistics will also be provided for average lipase units/fat (g) intake in Days 3 - 5 and average lipase units/weight (kg) in Days 3 - 5 per regimen during the DB treatment periods for the Safety Analysis Set. In addition, the number and percentage of subjects will be summarized by categorized average lipase units/fat intake (g) in Days 3 - 5 for the following categories:

- < 2500
- 2500 - 3500
- 3500 - 4500
- 4500 – 5500
- > 5500

Treatment compliance in each DB treatment period will be summarized by regimen and overall for the Safety Analysis Set. Treatment compliance in each DB treatment period is defined as the number of capsules taken divided by the number of capsules that should have been taken in Days 3 - 5 of that treatment period.

The number and percentage of subjects who are at least 90% treatment compliant with study drug administration will be summarized for each DB treatment period. In addition, compliance rate will be summarized using the number of observations, mean, standard deviation, median, minimum and maximum for each DB treatment period.

In addition, duration of exposure to open-label (OL) Creon during the period prior to randomization (for subjects who are never randomized, this will be the screening period or maintenance period when OL Creon is administered), will be summarized for the Open Label Safety Analysis Set for study Part 1 and Part 2 using OLSA-1 and OLSA-2, respectively. For OLSA-1, this includes the Maintenance Period (for subjects screened before protocol amendment 6) and the Screening Period (for subjects screened after protocol amendment 6). Duration of treatment is defined for each subject as last dose date of OL Creon prior to Visit 2 minus first dose date of OL Creon + 1. Duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, minimum and maximum.

Duration of exposure to OL Creon between DB Treatment Period 1 (TP1) and DB Treatment Period 2 (TP2) and after TP2 will be summarized for the Safety Analysis Set for study Part 1 and Part 2 using SA-P1 or SA-P2, respectively. Duration of treatment is defined for each subject as last dose date of OL Creon prior to Visit 4 minus first dose date of OL Creon after Visit 3 + 1 plus last dose date of OL Creon after Visit 5 minus first dose date of OL Creon after Visit 5 + 1. In other words, the total duration for the interval between TP1 and TP2, and the period after TP2 will be summed to calculate the duration of open-label treatment following randomization. Duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, minimum and maximum.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized for the ITT Population for study Part 1 and Part 2 using ITT-P1 and ITT-P2, respectively. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized overall and by treatment sequence for the ITT Population by study Part.

Continuous demographic and baseline characteristics variables include age, weight, height, body mass index (BMI), systolic blood pressure, diastolic blood pressure, pulse rate, and FE-1, and for ITT-P1 only, CFA in Screening Confinement Period. Categorical demographic and baseline characteristics variables include sex, ethnicity, race, and age (12 - 18, > 18 years).

Safety related baseline characteristics including height, weight, body mass index, systolic blood pressure, diastolic blood pressure, and pulse rate will be summarized by treatment sequence for each DB treatment period for the ITT Population.

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized overall and by treatment sequence for the ITT Population by study Part. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms (PTs) will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or PT).

7.3 Prior and Concomitant Medications

A prior medication is defined as any medication taken prior to the date of the first dose of study drug in the DB treatment period. A concomitant medication for each DB treatment period is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug for that period or any medication that started on or after the date of the first dose of study drug but not after the date of the last dose of study drug for that period.

Medications will be summarized for the ITT Population for study Part 1 and Part 2 using ITT-P1 and ITT-P2, respectively. The number and percent of subjects who received a prior medication will be summarized overall and by treatment sequence by the generic name assigned by the most current version of the World Health Organization (WHO) Drug Dictionary in alphabetical order for prior medications. Also, the number and percentage of subjects who received a concomitant medication will be summarized by regimen per treatment sequence and overall by the generic name assigned by the most current version of the WHO Drug Dictionary in alphabetical order for concomitant medications.

8.0 Efficacy Analyses

8.1 General Considerations

All efficacy analyses will be conducted for the Evaluable Set for study Part 1 and Part 2 using ES-P1 and ES-P2, respectively, unless otherwise specified. Efficacy analyses based on the EPI Symptom Diary will be conducted for the ITT Population for study Part 1 and Part 2 using ITT-P1 and ITT-P2, respectively.

The number of observations, mean, standard deviation, median, minimum and maximum will be summarized.

8.2 Handling of Missing Data

For the primary efficacy endpoint, the Evaluable Set in each study Part is used which requires all subjects to have completed both DB treatment periods and have 100% of stool samples collected and analyzed by the laboratory and valid total fat intake value. Thus, there should be no missing data for the CFA calculation. Fat intake in the calculation will use the fat content data of recorded food consumed in Days 3 - 5 of the corresponding treatment period. No fat content will be imputed for missing records of food consumed. Similarly, for the secondary endpoint of CNA, there should be no missing data for the CNA calculation due to the definition of Evaluable Set. Nitrogen intake will be calculated from the protein content of recorded food consumed in Days 3 - 5 of the corresponding

treatment period. No protein content will be imputed for missing records of food consumed. There should also be no missing data for the secondary endpoints of stool fat or stool weight due to the definition of the Evaluable Set, so there will be no imputation of stool fat or stool weight for missing records. For the additional exploratory efficacy endpoints, non-missing data will be summarized and reported, with no imputation of missing records.

8.3 Primary Efficacy Endpoint(s) and Analyses

8.3.1 Primary Efficacy Analysis

The CFA will be analyzed using a mixed effects model including sequence, period and regimen as fixed effects and subjects within sequence as a random effect. From this model, an estimate of the treatment difference along with a 99% CI will be derived and used to compare with a non-inferiority margin of 12%. The 95% CI for the estimate of the treatment difference will also be provided.

8.3.2 Main Analysis of Primary Efficacy Endpoint

In each study Part, the primary efficacy endpoint of CFA (defined in Section 3.1) will be analyzed based on the Evaluable Set (ES-P1 and ES-P2 for study Part 1 and Part 2, respectively). The following methods will be used to address potential intercurrent events:

- Subjects with premature discontinuation of study drug in Part 1 or Part 2 or who did not receive any dose of study drug in both treatment periods for Part 1 or Part 2 will be excluded from ES-P1 or ES-P2, respectively
- Subjects without 100% of stool samples collected and analyzed by the laboratory in both treatment periods in Part 1 or Part 2 will be excluded from ES-P1 or ES-P2, respectively

The estimand corresponding to the primary efficacy endpoint for Part 1 is the mean CFA difference between Pancrelipase DR capsules MP and Creon® (pancrelipase) DR capsules among participants who complete both treatment periods and have 100% of stool

samples collected and analyzed by the laboratory in both treatment periods. The estimand corresponding to the primary efficacy endpoint for Part 2 is the mean CFA difference between Pancrelipase DR capsules AAPIS and Creon® (pancrelipase) DR capsules among participants who complete both treatment periods and have 100% of stool samples collected and analyzed by the laboratory in both treatment periods. The attributes of the estimands corresponding to the primary efficacy endpoint for each study Part are summarized in Table 2.

Table 2. Study M16-111 Estimand Attributes

	Attributes of the Estimand				
Estimand	**Population**	**Endpoint**	**Treatment**	**Handling of Intercurrent Events (IEs)**	**Population-Level Summary**
Part 1 Primary	Evaluable set in Part 1 (CF subjects who are randomized and complete both treatment periods and have 100% of stool samples collected and analyzed by the laboratory in Part 1)	CFA at treatment Periods 1 and 2	Pancrelipase DR capsules MP or Creon® (pancrelipase) DR capsules	IE1: Premature discontinuation from either of the treatment periods in Part 1 IE2: Subjects without 100% stool sample collected in Part 1 Subjects with IE1 or IE2 will be excluded from the analysis population.	Mean CFA difference between two treatment groups
Part 2 Primary	Evaluable set in Part 2 (CF subjects who were randomized and completed both treatment periods and have 100% of stool samples collected and analyzed by the laboratory in Part 2)	CFA at treatment Periods 1 and 2	Pancrelipase DR capsules AAPIS or Creon® (pancrelipase) DR capsules	IE1: Premature discontinuation from either of the treatment periods in Part 2 IE2: Subjects without 100% stool sample collected in Part 2 Subjects with IE1 or IE2 will be excluded from the analysis population.	Mean CFA difference between two treatment groups

AAPIS = alternate active pharmaceutical ingredient site; CF = cystic fibrosis; CFA = coefficient of fat absorption; DB = double-blind; DR = delayed-release; IE = intercurrent event; MP = modernized process

8.3.3 Supplementary Analyses of the Primary Efficacy Endpoint

The following supplementary analysis of the primary efficacy endpoint will be conducted. In each study Part, the primary analysis will be repeated using all randomized subjects

(ITT-P1 and ITT-P2 for Part 1 and Part 2, respectively). In this analysis, subjects will be included using their observed CFA measurements from each available treatment period.

8.4 Secondary Efficacy Endpoint(s) and Analyses

8.4.1 Secondary Efficacy Analyses

The secondary efficacy endpoints 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 regimen as fixed effects and subjects within sequence as a random effect. From this model, an estimate of the treatment difference along with a 95% CI will be derived. All comparisons for all secondary variables between the regimen will be descriptive.

8.5 Additional Exploratory Efficacy Endpoint(s) and Analyses

8.5.1 Additional Exploratory Efficacy Analyses

The additional exploratory efficacy endpoints will be stool frequency, stool consistency, diarrhea, abdominal pain, bloating, and flatulence. Stool frequency will be summarized for the ITT Population by regimen for each diary day for Days 1-6 and by regimen for average stool frequency, which is calculated as the mean stool frequency for each subject of all non-missing diary days for Days 1-6. Stool consistency, diarrhea, abdominal pain, bloating and flatulence will be summarized (number and percentage for each ordinal category) for each diary day by regimen. Diary Days 1-6 will be included in the summary table. All comparisons for all additional exploratory variables between the regimen will be descriptive.

The EPI Symptom Diary, which collects assessments for the additional exploratory variables, was added as a case report form (CRF) as part of protocol amendment 6 (after many Part 1 subjects were already enrolled). Summary tables for the additional exploratory efficacy endpoints will only be provided for Part 1 if 6 or more subjects in the ITT Population complete at least one diary day in each treatment period of Part 1.

9.0 Safety Analyses

9.1 General Considerations

Safety data will be summarized separately by study Part for the Screening Confinement Set, Safety Analysis Set, and the Open Label Safety Analysis Set. For the Safety Analysis Set, safety summaries will be presented by regimen and overall. Subjects are assigned to a regimen based on the treatment actually received on the first day of dosing of the corresponding treatment period, regardless of the treatment randomized. For Part 1, safety analyses will be conducted using SC-P1, SA-P1 and OLSA-P1. For Part 2, safety analyses will be conducted using SA-P2 and OLSA-P2.

9.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA SOCs and PTs according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

9.2.1 AEs During the Screening Confinement Period

AEs and SAEs that have a start date either on or after the first day of the Screening Confinement Period, and up to the end day of the Screening Confinement Period will be summarized by SOC and PT for the Screening Confinement Set for Part 1 using SC-P1. Listing of SAEs during the Screening Confinement Period will also be provided for the Screening Confinement Set.

9.2.2 AEs During the Open Label Period(s)

AEs and SAEs that have a start date during an Open Label Period will be summarized by SOC and PT for the Open Label Safety Analysis Set for study Part 1 and Part 2 using OLSA-P1 and OLSA-P2, respectively. These AEs and SAEs include the following:

- For Part 2 and for Part 1 subjects enrolled under protocol amendment 6 or later: AEs and SAEs that have a start date either on or after the first dose date of OL Creon in Screening Period, and before the first dose of the study drug in DB Treatment Period 1 (if the subject entered the DB treatment period), or on or after the first dose date of OL Creon in the Screening Period (if the subjects never entered the DB treatment period)
- For Part 1 subjects enrolled under protocol amendment 5 or earlier: AEs and SAEs that have a start date either on or after the first dose date of the Maintenance Period, and before the first dose of the study drug in DB Treatment Period 1 (if the subject entered the DB treatment period), or on or after the first dose date of the Maintenance Period (if the subject never entered the DB treatment period)
- For Part 1 and Part 2: AEs and SAEs that have a start date either on or after the first dose date of the Open Label Period after DB Treatment Period 1, and before the first dose of the study drug in DB Treatment Period 2 (if the subject entered DB Treatment Period 2), or on or after first dose date of the Open Label Period after DB Treatment Period 1 (if the subject never entered the DB treatment period)
- For Part 2 and for Part 1 subjects enrolled after protocol amendment 6: AEs and SAEs that have a start date either on or after the first dose date of OL Creon in the Follow Up Period after DB Treatment Period 2

Listing of SAEs during the Open Label Period(s) will also be provided for the Open Label Safety Analysis Set.

9.2.3 AEs During the Double-Blind Treatment Period

9.2.3.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs for the regimen administered in 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, defined as the earliest of: the first dose date of OL Creon after Visit 3, the start of the first dose of DB Treatment Period 2, or 30 days after the last dose of study drug during DB Treatment Period 1. For the regimen administered in 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, defined as the earlier of the first dose date of OL Creon after Visit 5 or 30 days after the last dose of study drug during DB Treatment Period 2.

9.2.3.2 Adverse Event Overview

An overview of AEs will be presented for the Safety Analysis Set for study Part 1 and Part 2 using SA-P1 and SA-P2, respectively. The overview will consist of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study drug according to the investigator
- Any severe treatment-emergent AE
- Any serious treatment-emergent AE
- Any treatment-emergent AE leading to discontinuation of study drug
- Any treatment-emergent AE leading to death
- All deaths

9.2.3.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent adverse events will be summarized by SOC and PT for the Safety Analysis Set for study Part 1 and Part 2 using SA-P1 and SA-P2, respectively; by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency overall.

9.2.3.4 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and in listing format for the Safety Analysis Set for study Part 1 and Part 2 using SA-P1 and SA-P2, respectively.

9.3 Analysis of Laboratory Data

The clinical laboratory tests defined in the protocol (e.g., hematology and clinical chemistry) will be summarized by regimen for the Safety Analysis Set for study Part 1 and Part 2 using SA-P1 and SA-P2, respectively.

Each laboratory variable will be summarized by visit with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from start to end of DB treatment period will be summarized for each laboratory variable by regimen, with the number of observations, mean at start of DB treatment period, and mean at end of DB treatment period. An ANOVA model with treatment as a factor will be used to compare change from start to end of DB treatment period between regimens. The LS mean, standard error, and 95% CI will be presented for the change

from start to end of DB treatment period within each regimen and between regimen difference.

Changes in laboratory parameters during treatment with each regimen will be tabulated using shift tables as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline to any post-baseline value during treatment with each regimen according to the normal range will be provided for each hematology and clinical chemistry parameter.

9.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, pulse rate, weight, and body temperature will be summarized by regimen for the Safety Analysis Set for study Part 1 and Part 2 using SA-P1 and SA-P2, respectively.

Each vital sign variable will be summarized by visit with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from start to end of DB treatment period will be summarized for each vital sign variable by regimen, with the number of observations, mean at start of DB treatment period, and mean at end of DB treatment period. An ANOVA model with treatment as a factor will be used to compare change from start to end of DB treatment period between regimens. The LS mean, standard error, and 95% CI will be presented for the change from start to end of DB treatment period within each regimen and between regimen difference.

Vital sign variables will be evaluated based on potentially clinically important (PCI) criteria (Appendix B). For each vital sign PCI criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized by regimen.

10.0 Interim Analyses

No formal interim analysis is planned.

As described in Section 2.4.1, a blinded sample size re-estimation will be conducted for each study Part when approximately half of the planned subjects in each Part (i.e., 13 subjects) have completed the two DB treatment periods and have the corresponding CFA data available for both periods.

10.1 Data Monitoring Committee

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 describes the roles and responsibilities of the DMC members, frequency of data reviews, relevant data to be assessed, and general operations.

Since there are no efficacy analyses for early stopping, no alpha adjustment is needed.

11.0 Overall Type-I Error Control

This study has one primary efficacy endpoint for which non-inferiority is tested at type I error of 0.01 by constructing two-sided 99% CI of the treatment difference for non-inferiority assessment. A unique non-inferiority assessment will be conducted separately for each study Part. Because each study Part will assess the non-inferiority of a different investigational product with separate randomization for populations in each study Part, adjustment for multiplicity is not planned.

For all the secondary endpoints, two-sided 95% CI will be calculated for the treatment difference estimate. Since all comparisons for all secondary variables will be descriptive, adjustment for multiplicity is not planned.

For BSSR (refer to Section 2.4.1), analytically and through simulations, it has been shown that the procedures do not meaningfully affect Type I error rate[6]. As such, no multiplicity adjustment is planned for the BSSR.

Since there are no efficacy analyses for early stopping planned for the DMC review, no alpha spending is needed due to the DMC review.

12.0 Version History

Table 3. SAP Version History Summary

Version	Date	Summary
1.0	26 Feb 2019	Original version
2.0	16 Jan 2020	• Added the Screening Confinement Set and the Maintenance Set, and updated the definition of the other analysis populations in Section 4.0; • Added the description of subject disposition, study drug duration and compliance, demographics, baseline characteristics, medical history, and prior/concomitant medications in Section 5.0, Section 6.0, and Section 7.0 due to SAP template change; • Added safety analyses of adverse events for the Screening Confinement Set and the Maintenance Set in Section 9.2; • Added description of data monitoring committee in Section 10.1.

Table 3. SAP Version History Summary (Continued)

3.0	05 Apr 2021	• Updated study title and Figure 1 to match protocol Amendment 6; • Added study Part 2 to Section 1.0, Section 2.0, Section 4.0, Section 5.0, Section 6.0, Section 7.0, Section 8.0, Section 9.0, Section 10.0, and Section 11.0; • Updated sample sizes and non-inferiority margin in Section 2.2 and Section 2.4; • Added Additional Exploratory Endpoints in Section 3.3, Section 8.2, and Section 8.5; • Added Open Label Safety Analysis Set to Section 4.0, Section 5.0, Section 6.0, Section 9.1 and Section 9.2.2; • Removed Maintenance Set from Section 4.0, Section 5.0, Section 6.0, Section 9.1 and Section 9.2.2; • Added clarification that Analysis Populations are defined by study Part in Section 4.0, Section 5.0, Section 6.0, Section 7.0, Section 8.0, Section 9.0, Section 10.0, and Section 11.0; • Added clarification that exposure to open label Creon will be reported separately for exposure before randomization and for exposure after randomization in Section 6.0; • Removed the AE summaries for maintenance period, added the AE summaries for open label Creon; • Updated the TEAE definition for double-blind treatment period in Section 9.2.3; • Added clarification that Safety Analysis Set will be population used in Section 9.3 and Section 9.4.
4.0	24 Sep 2021	• Updated sample sizes for study Part 2 in Section 2.2 and Section 2.4. • Added description of primary endpoint estimand and its attributes to Section 8.3. • Added supplementary analyses of the primary efficacy endpoint in Section 8.3.3.
5.0	21 Mar 2022	• Added clarification that Evaluable Set is defined based on 100% stool sample collection that is analyzable, ie, 100% of stool samples collected and analyzed by the laboratory. • Updated analysis population for EPI Symptom Diary efficacy endpoints to be the ITT population.

13.0 References

1. AbbVie. CR200.0126. A comparison of the efficacy and safety of Creon®20 and placebo in the treatment of steatorrhea in pediatric and adolescent cystic fibrosis patients with clinical exocrine pancreatic insufficiency. 1996.
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3. Trapnell BC, Maguiness K, Graff GR, et al. Efficacy and safety of Creon® 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros. 2009;8(6):370-7.
4. Graff GR, Maguiness K, McNarmara J, et al. Efficacy and tolerability of a new formulation of pancrelipase delayed-release capsules in children aged 7 to 11 years with exocrine pancreatic insufficiency and cystic fibrosis: a multicenter, randomized, double-blind, placebo-controlled, two-period crossover, superiority study. Clin Ther. 2010;32(1):89-103.
5. Golkowski D, Friede T, Kieser M. Blinded sample size re-estimation in crossover bioequivalence trials. Pharm Stat. 2014;13(3):157-62.
6. Kieser M, Friede T. Simple procedures for blinded sample size adjustment that do not affect the type I error rate. Stat Med. 2003;22(23):3571-81.

Appendix A. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered into the study even though s/he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study.
- Subject took prohibited concomitant medication.

Appendix B. Potentially Clinically Important Criteria for Safety Endpoints

The criteria for Potentially Clinically Important (PCI) vital sign findings are described in Table B.

Table B. Criteria for Potentially Clinically Important Vital Sign Values

Vital Signs Variables	Criterion	Definition of Potentially Clinically Important
Systolic Blood Pressure (mmHg)	Low	Value ≤ 90 and ≥ 20 decrease from Baseline
	High	Value ≥ 180 and ≥ 20 increase from Baseline
Diastolic Blood Pressure (mmHg)	Low	Value ≤ 50 and ≥ 15 decrease from Baseline
	High	Value ≥ 105 and ≥ 15 increase from Baseline
Pulse (bpm)	Low	Value ≤ 50 and ≥ 15 decrease from Baseline
	High	Value ≥ 120 and ≥ 15 increase from Baseline
Weight (kg)	Low	≥ 7% decrease from Baseline
	High	≥ 7% increase from Baseline
Temperature (°C)	High	Value ≥ 38.3 and ≥ 1.1 increase from Baseline