Statistical Analysis Plan for Study M21-432

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

Date: 20 July 2023

Version 2.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for CREON or ABT-SLV245 Study M21-432 titled "Exocrine Pancreatic Insufficiency (EPI): Phase 4 Study of Symptoms of EPI in Subjects Treated with CREON® (Pancrelipase) with an Alternate Source of Active Pharmaceutical Ingredient."

Study M21-432 evaluates the clinical symptoms of EPI in subjects diagnosed with Cystic Fibrosis (CF) or Chronic Pancreatitis (CP) treated with CREON-SPL.

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, Hypotheses, and Estimands

The objective of this study is to evaluate the clinical symptoms of EPI in subjects diagnosed with Cystic Fibrosis (CF) or Chronic Pancreatitis (CP) treated with CREON-SPL.

This is a descriptive and exploratory study. No formal statistical hypothesis is being tested. The estimands corresponding to the study objective are the descriptive statistics for the difference in the pharmacodynamic endpoints (see Section 3.1) of **CREON-SPL** between Baseline and each of the post-Baseline visit in the PP population (see Section 4.0).

For each subject, the Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q) score is collected at Screening, Baseline (Day 1), Day 8, Day 15, Day 29 and Day 85. The score for Abdominal Symptom Domain Score (ASDS) [A] and Bowel Movement Symptom Score (BMSS) [B] are averaged to get the Total Symptom Score (TSS) [T = (A+B)/2] at

each visit. The difference between Baseline and each of the post-Baseline visit will be calculated.

2.2 Study Design Overview

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

This study will consist of 4 periods as follows:

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

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

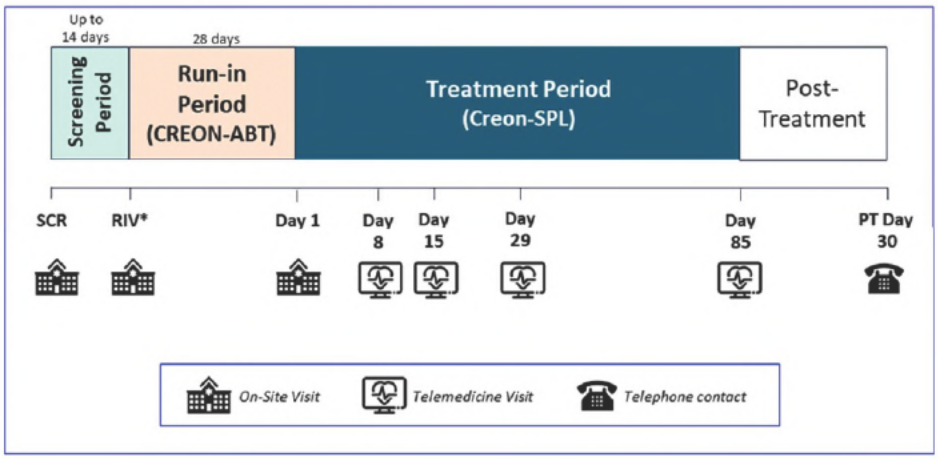
Treatment Period: Subjects who complete the Run-in Period will be assessed for the continuation criteria at Day 1. Only subjects who meet all continuation criteria will be dispensed additional study drug. Blinded **CREON-ABT** study drug from the Run-in Period will be returned, and the subject will be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

15, 29, and 85). Study procedures, including assessment of EPI symptoms and adverse events (AEs), will be conducted at each visit.

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

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



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

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

2.3 Treatment Assignment and Blinding

This is a single-arm, single-blinded study (subject will not be aware of the sequence of order in which study drugs CREON-ABT and CREON-SPL are dispensed) with no stratification. The subjects will be receiving blinded CREON-ABT for 28 days in the Run-in Period. The subjects, after completing the Run-in Period will be enrolled in the Treatment Period. In this period, the subjects will be receiving blinded CREON-SPL for

85 days. The investigators will know the sequence of assignment of study drug but must not inform the subject of this assignment.

2.4 Sample Size Determination

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

Based on Johnson CD, et al,[1] the average TSS from PEI-Q was estimated to be 1.4 (SD = 0.7) for CP and CF subjects with EPI symptoms. Assuming the covariance between the TSS at Baseline and post-Baseline after switching to **CREON-SPL** to be 0.365, the SD for the change of the TSS between Baseline and post-Baseline is estimated to be 0.5. A sample size of 24 evaluable subjects will provide a precision of ± 0.2 in terms of half-length of the 95% confidence interval for the estimate of change in TSS based on PEI-Q.

3.0 Endpoints

3.1 Pharmacodynamic Endpoint(s)

The pharmacodynamic endpoints include:

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

3.2 Safety Endpoint(s)

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

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

4.0 Analysis Populations

The following population sets will be used for the analyses.

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

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

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

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

5.0 Subject Disposition

The number of subjects in each of the following categories will be summarized by investigator and overall, for the following group:

- Subjects who were screened;
- Subjects who took at least one dose of CREON-ABT;
- Subjects who prematurely discontinued study drug CREON-ABT;
- Subjects who completed protocol-specified Run-in-Period;

- Subjects who failed the continuation criteria;
- Subjects who took at least one dose of CREON-SPL;
- Subjects who prematurely discontinued study drug CREON-SPL;
- Subjects who completed protocol-specified Treatment Period;
- Subjects who prematurely discontinued study
- Subjects who completed study (completed the Follow-Up period after the Treatment Period);
- Subjects in the PP Population.

The number and percentage of subjects who prematurely discontinued CREON-ABT and CREON-SPL will be summarized by each primary reason. The denominator will be SAS-CREON-ABT and SAS-CREON-SPL, respectively. Similar summaries will be provided for the premature discontinuation of study. The denominator will be the total number of subjects who took at least one dose of CREON-ABT or CREON-SPL.

The number and percentage of subjects who failed the continuation criteria will be summarized by each criterion. The denominator will be the total number of subjects who completed CREON-ABT.

6.0 Study Drug Duration

The overall treatment duration will be summarized separately for Run-in-Period and Treatment Period. Duration of treatment is defined for each subject as (last dose date - first dose date + 1). Duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, minimum and maximum.

1. Summary of Duration of treatment in Run-in Period using FAS and SAS-CREON-ABT population separately. In addition, the number and percentage of subjects in each treatment duration interval 1 to <8 days of treatment, 8 to <15 days of treatment and >=15 days treatment will be summarized.
2. Summary of Duration of treatment in the Treatment Period using FAS population. In addition, the number and percentage of subjects in each treatment duration

interval (, 1 to <8 days, 8 to < 15 days, 15 to < 29 days, 29 to < 85 days, ≥85 days) will be summarized.

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 FAS population. 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

Continuous demographic variables include age, weight, height, body mass index (BMI), and TSS both at the start of the Run-in Period and at Baseline (Day 1), and prior Creon total daily dose. Categorical demographic variables include sex (male, female), ethnicity (Hispanic or Latino, Not Hispanic or Latino), race (White, Black, American Indian/Alaska Native, native Hawaiian or Other Pacific Islander, Asian, Multi, or Other), study population (CF only, CP only, or CF and CP), weight (< 60 or ≥ 60 kg), BMI (< 25 or ≥ 25 kg/m^2), tobacco user (current, former, never, unknown), and alcohol user (current, former, never, unknown).

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. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms 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 preferred term).

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name. The number and percentage of medications will be summarized per subject for both prior and concomitant medications.

A prior medication and procedure are defined as any medication and procedure performed prior to the date of the first dose of CREON-ABT. This includes medications and procedures with a start date before the first dose of CREON-ABT. In cases where incomplete or missing medication and procedure dates are collected, a conservative approach will be taken and it will be counted as a prior medication and procedure.

A concomitant medication for CREON-ABT is defined as any medication that started prior to the date of the first dose of CREON-ABT and continued to be taken after the first dose of CREON-ABT or any medication that started on or after the date of the first dose of CREON-ABT, but not after the date of the last dose of CREON-ABT.

A concomitant medication for CREON-SPL is defined as any medication that started prior to the date of the first dose of CREON-SPL and continued to be taken after the first dose of CREON-SPL or any medication that started on or after the date of the first dose of CREON-SPL, but not after the date of the last dose of CREON-SPL.

In the situation where an incomplete or missing medication date is collected, a conservative approach will be taken and it will be counted as a concomitant medication unless there is evidence that the medication was not taken during the study drug treatment (e.g., an end date before the first dose of study drug (CREON-ABT or CREON-SPL, where applicable).

A concomitant procedure for CREON-ABT is defined as any procedure that started prior to the date of the first dose of CREON-ABT and continued after the first dose of CREON-

ABT or any procedure that started on or after the date of the first dose of CREON-ABT, but not after the date of the last dose of CREON-ABT.

A concomitant procedure for CREON-SPL is defined as any procedure that started prior to the date of the first dose of CREON-SPL and continued after the first dose of CREON-SPL or any procedure that started on or after the date of the first dose of CREON-SPL, but not after the date of the last dose of CREON-SPL.

In the situation where an incomplete or missing procedure date is collected, a conservative approach will be taken and it will be counted as a concomitant procedure unless there is evidence that the procedure was performed before the study drug treatment (e.g., an end date before the first dose of study drug (CREON-ABT or CREON-SPL, where applicable).

Note that a medication or a procedure can be considered both a prior and concomitant medication or procedure if it started prior to the first dose of study drug (CREON-ABT or CREON-SPL, where applicable) and continued after the first dose of study drug.

Prior procedures and concomitant procedures will be listed by subject numbers.

8.0 Handling of Potential Intercurrent Events for the Primary and Key Secondary endpoints

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

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

Subjects who have missing PEI-Q data for a particular visit (besides Day 1) will be excluded from the analysis of that visit.

9.0 Pharmacodynamic Endpoint Analyses

9.1 General Considerations

All pharmacodynamic analyses will be conducted in the PP population.

This is a descriptive and exploratory study. No formal statistical hypothesis is being tested.

All the analyses will be performed after all ongoing subjects have completed the Treatment Period and the database has been locked. This will be the final analysis for the pharmacodynamic endpoints.

"Baseline" refers to the last non-missing observation before the first administration of CREON-SPL, unless otherwise specified in the individual analysis section.

9.2 Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q) Domain Scores

The Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q) is provided in Appendix C. It is comprised of three domains: abdominal symptoms, bowel movements, and impacts. Assessment of EPI symptoms will be done using abdominal symptoms domain, bowel movement symptoms domain, and the Total Symptom Score.

9.2.1 Abdominal Symptoms Domain Score (ASDS)

The Abdominal Symptoms Domain (ASD) consists of 7 questions, each with 5 answer choices. A score of 0 - 4 will be assigned to each answer as specified in the Table 1. The Mean Abdominal Symptoms Domain Score (A) is the average of the total score. The mean score for this domain can range from 0 to 4.

Table 1. PEI-Q Score Assignment

ANSWER	SCORE
NO NOT AT ALL	0
YES, A LITTLE BIT	1
YES, SOME	2
YES, QUITE A BIT	3
YES, A LOT	4

9.2.2 Bowel Movement Symptoms Score (BMSS)

The Bowel Movement Symptoms (BMS) consists of 6 questions, each with 5 answer choices. A score of 0 - 4 will be assigned as specified in the Table 1. The Mean Bowel Movement Symptoms Score (B) is the average of the total score for this domain. The mean score for this domain can range from 0 to 4.

9.2.3 Total Symptom Score (TSS)

The Total Symptom Score will be calculated as the average of the Mean Abdominal Symptoms Domain Score (A) and Mean Bowel Movement Symptoms Score (B). It can range from 0 to 4.

9.3 Handling of Missing Data in PEI-Q

The PEI-Q data are designed to be collected when all questions are answered, so there will be no missing data. Subjects who have missing PEI-Q data for a particular visit (besides Day 1) will be excluded from the analysis of that visit.

9.4 Pharmacodynamic Endpoints and Analyses

9.4.1 Pharmacodynamic Endpoints

The pharmacodynamic endpoints include the TSS, ASDS and BMSS at Baseline (Day 1), each of the post-Baseline visits (Day 8, 15, 29 and 85) and change from Baseline to each of the post-Baseline visits.

9.4.2 Main Analysis of Pharmacodynamic Endpoints

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

The same descriptive statistics will also be produced for the scores at the Screening Visit because change from Screening to Baseline will be used as the context for the main efficacy analysis.

In addition, a sensitivity analysis for TSS, ASDS and BMSS will be provided by excluding subject 1401 as this subject may have been accidentally unblinded by the site during the Creon-SPL treatment period.

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the SAS-CREON-ABT and SAS-CREON-SPL population separately. Safety summaries will be presented by treatment periods using the respective population groups.

10.2 Adverse Events

Per the study protocol, all AEs (non-serious and serious) reported from the time of study drug administration until 30 days post discontinuation of study drug administration will be

collected. In addition, AEs related to study procedures (non-serious and serious) will be collected from the time the subject signed the study-specific informed consent.

All Adverse events (AEs) and Serious Adverse events (SAEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) coded 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.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs (TEAE) for the SAS-CREON-ABT are defined as any AE with the onset date on or after the first dose of the CREON-ABT until 30 days after the last dose of CREON-ABT or until the initiation of CREON-SPL, whichever is earlier. Similarly, TEAEs for SAS-CREON-SPL are defined as any AE with the onset date on or after the first dose of CREON-SPL until 30 days after the last dose of CREON-SPL. In the cases that an AE happens in a day that a subject takes both CREON-ABT and CREON-SPL, such AE will be counted under CREON-SPL. This definition will be used for all summaries except the one additional AE overview summaries in Section 10.2.2. If an incomplete onset date was collected for an AE, the AE will be assumed to be treatment-emergent unless there is evidence that confirms that the AE was not treatment-emergent (e.g., the AE end date was prior to the date of the first dose of study drug).

All TEAEs will be summarized overall, as well as by primary MedDRA SOC and Preferred Term. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The number and percentage of subjects experiencing TEAEs will be summarized.

10.2.2 Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories for the SAS-CREON-ABT and SAS-CREON-SPL:

- Any TEAE
- TEAEs with a "reasonable possibility" of being related to study drug according to the investigator
- Severe TEAEs
- Serious TEAEs
- Serious TEAEs with a "reasonable possibility" of being related to study drug according to the investigator
- TEAEs leading to discontinuation of study drug
- TEAEs leading to death
- TEAEs of Special Interest
- TEAEs of Special Interest with a "reasonable possibility" of being related to study drug according to the investigator
- All deaths

The same summaries will be repeated by restricting the analysis period of SAS-CREON-ABT and SAS-CREON-SPL to 28 days after the first dose of CREON-ABT and CREON-SPL, respectively. For SAS-CREON-ABT, the analysis period will not include days on or after the first dose of SAS-CREON-SPL.

The same summaries will also be repeated by using AE rates per 100 patient years of exposure, instead of number and percentage of AEs. For this summary, the definitions of SAS-CREON-ABT and SAS-CREON-SPL in Section 10.2.1 will apply.

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

Treatment-emergent adverse events will be summarized by SOC and PT for the SAS-CREON-ABT and SAS-CREON-SPL; 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.

If a subject has an AE with unknown severity or relationship to study drug, the subject will be counted in the severity/relationship level category of "unknown" even if the subject has another occurrence of the same AE with a known severity/relationship. The only exception is if the subject has another occurrence of the same AE with the highest level of severity or a relationship assessment of "Reasonable possibility." In this case, the subject will be counted under the most extreme severity/relationship category.

In addition, treatment-emergent adverse events will be summarized by PT for the SAS-CREON-ABT and SAS-CREON-SPL, sorted by decreasing frequency in SAS-CREON-SPL

10.2.4 Treatment-Emergent Adverse Events per Patient-Years of Exposure

Treatment-emergent adverse events will also be summarized by PT using AE rates per 100 patient years for the SAS-CREON-ABT and SAS-CREON-SPL, sorted by decreasing rates in SAS-CREON-SPL. AE rates per 100 patient-years of exposure are defined as the number of AEs divided by the total exposure in 100 patient-years. Exposure period for CREON-ABT and CREON-SPL is the same as the reporting period for treatment-emergent AE defined in Section 10.2.1. Different occurrence of the same TEAE in a single subject will all be counted.

10.2.5 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 SAS-CREON-ABT and SAS-CREON-SPL.

10.2.6 Adverse Events of Special Interest

Adverse events of special interest will be summarized by SOC and PT. The following TEAEs compatible with clinical symptoms of EPI will be considered as Adverse Events of Special Interest (AESI) for this study:

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

Detailed information about the search criteria is in Appendix B.
Tabular listings of adverse events of special interest will be provided.

10.3 Analysis of Laboratory Data

Laboratory data are not collected prospectively during the treatment period. No laboratory analysis is planned.

10.4 Analysis of Vital Signs

Vital sign data are not collected prospectively during the treatment period. No vital sign analysis is planned.

11.0 Interim Analysis

No formal interim analysis is planned.

11.1 Data Monitoring Committee

An external data monitoring committee (DMC) composed of persons independent of AbbVie and with relevant expertise in their field will review 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.

12.0 Overall Type-I Error Control

Since there are no efficacy analyses for early stopping planned for the DMC review, or formal statistical hypothesis testing, alpha spending is not applicable.

There are pharmacodynamic endpoints analyzed descriptively. Multiplicity adjustment is not planned for analyses.

13.0 Version History

Table 2. SAP Version History Summary

Version	Date	Summary
1.0	07 Dec 2021	Original version
2.0	20 Jul 2023	Major updates: 1. Section 9.4.2 - Sensitivity analysis for events of accidentally breaking blindness. 2. Section 10.2.1 - In the cases that an AE happens in a day that a subject takes both CREON-ABT and CREON-SPL, such AE will be counted under CREON-SPL.

14.0 References

1. Johnson CD, Williamson N, Janssen-van Solingen G, et al. Psychometric evaluation of a patient-reported outcome measure in pancreatic exocrine insufficiency (PEI). Pancreatology. 2019;19(1):182-90.

Appendix A. Protocol Deviations

The number and percentage of subjects for each category in the collected data for protocol deviation will be summarized.

Appendix B. Definition of Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) will be identified using the following search criteria:

Adverse Event of Special Interest	Preferred Terms
Diarrhea	• Diarrhoea • Diarrhoea haemorrhagic • Diarrhoea infectious • Defaecation urgency • Frequent bowel movements • Gastrointestinal hypermotility • Faecal volume increased • Overflow diarrhoea
Abdominal pain	• Abdominal discomfort • Abdominal Pain • Abdominal pain lower • Abdominal pain upper • Gastrointestinal pain
Abdominal bloating	• Abdominal distension • Gastrointestinal sounds abnormal
Flatulence	• Flatulence
Steatorrhea	• Faeces pale • Faecal fat increased • Faeces discoloured

Appendix C. Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q)

This questionnaire asks about problems you may experience if you do not produce enough enzymes to digest your food.

ABDOMINAL SYMPTOMS	NO NOT AT ALL	YES, A LITTLE BIT	YES, SOME	YES, QUITE A BIT	YES, A LOT	SCORE
1. In the past 7 days, did you have **stomach pain?**	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
2. In the past 7 days, did you **feel** bloated (your stomach feeling **tight** and **full**)?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
3. In the past 7 days, did your **stomach make noises?**	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
4. In the past 7 days, did you **pass gas**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
5. In the past 7 days, when you **passed gas** did it **smell bad**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
6. In the past 7 days, did you **feel sick** (but didn't actually vomit/throw up)?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
7. In the past 7 days, did you have a **lack of appetite?**	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
					Sum of abdominal symptom scores:	☐
					Mean abdominal symptom domain score (A):	☐

BOWEL MOVEMENT SYMPTOMS	NO NOT AT ALL	YES, A LITTLE BIT	YES, SOME	YES, QUITE A BIT	YES, A LOT	SCORE
8. In the past 7 days, did you have **diarrhea (watery poo)**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
9. In the past 7 days, did you feel the need to **rush to the toilet** to have a **bowel movement (have a poo)**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
10. In the past 7 days, did your **poo** look **lighter** or **orange** in color?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
11. In the past 7 days, when you had a **poo** did it **smell bad**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
12. In the past 7 days, did you see or have **fat or oil** in your **poo** or on the **toilet paper**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
	NO NOT AT ALL	YES, A LITTLE BIT	YES, MODERATELY	YES, QUITE A BIT	YES, EXTREMELY	SCORE
13. In the past 7 days, did you feel you needed to be **close to a toilet** because of your **enzyme problems**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐

Sum of bowel movement symptom scores:	☐
Mean bowel movement symptom score (B):	☐
MEAN TOTAL SYMPTOM SCORE ([A+B]/2):	☐

Only complete if you have been diagnosed with Pancreatic Exocrine Insufficiency (PEI)

IMPACTS	NO NOT AT ALL	YES, A LITTLE OF THE TIME	YES, SOMETIMES	YES, MOST OF THE TIME	YES, ALL OF THE TIME	SCORE
14. In the past 7 days, did you avoid **fatty food**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
15. In the past 7 days, did your **enzyme problems** affect your ability to **concentrate**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
	NO NOT AT ALL	YES, A LITTLE BIT	YES, MODERATELY	YES, QUITE A BIT	YES, EXTREMELY	SCORE
16. In the past 7 days, did you feel **embarrassed going to the toilet** because of your **enzyme problems**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
17. In the past 7 days, did you feel **worried, anxious** or **stressed** because of your **enzyme problems**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
	NO NOT AT ALL	YES, A LITTLE OF THE TIME	YES, SOMETIMES	YES, MOST OF THE TIME	YES, ALL OF THE TIME	SCORE
18. In the past 7 days, did your **enzyme problems** affect your **social activities**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐
Sum of impact scores:						☐
Mean impact domain score (C):						☐
MEAN TOTAL SUMMARY SCORE (PEI PATIENTS) ([A+B+C]/3):						☐