Statistical Analysis Plan for Study M16-142

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

Date: 13 December 2020

Version 1.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for CREON or ABT-SLV245 Study M16-142 titled "Creon® (pancrelipase) therapy for subjects with exocrine pancreatic insufficiency (EPI) due to pancreatic cancer: A double-blind, randomized, parallel design with 2 dose cohorts of pancrelipase in resected pancreatic cancer subjects and an open-label single dose cohort in non-resected pancreatic cancer subjects".

Study M16-142 examines the effects of Creon in subjects with resected pancreatic cancer receiving 2 dosing cohorts, and one dosing cohort in non-resected pancreatic cancer subjects.

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.

This SAP includes changes to analyses described in the protocol version 3.0 dated 22 November 2019. Details are outlined in Section 12.0.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses, and Estimands

The objective of this study is to evaluate the effects of Creon® (pancrelipase) on stool fat and EPI symptoms in subjects with resected pancreatic cancer receiving 2 dosing cohorts, and one dosing cohort in non-resected pancreatic cancer subjects.

The hypothesis for the primary objective of a significant change in stool fat from Baseline to Week 1 will be tested at 2-sided 5% α-level for each dose cohort in the resected pancreatic cancer population and for the non-resected population as well.

For each subject, the average stool fat per day (grams/day) from the stools collected in last 48 hours prior to the baseline visit and prior to the Week 1 visit will be calculated and the difference between those 2 visits will be calculated.

The estimand corresponding to the primary objective is:

Mean change in stool fat from baseline to Week 1 will be calculated in subjects treated with either high dose of CREON (72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks) or low dose of CREON (12,000 USP units (Lipase) with meals/6,000 USP units (Lipase) with snacks) in the Evaluable Analysis Set for stool fat in the Resected Pancreatic Cancer regimen. Subjects who do not have an evaluable stool sample (described in Section 9.2.3) at both Baseline and Week 1 will be excluded from the analysis.

2.2 Study Design Overview

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

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

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

At Day 1, eligible resected subjects will be randomized in 1:1 ratio to one of following dose cohorts, and will remain on blinded therapy for 13 weeks:

1. Low dose (cohort of 12,000 USP units (Lipase) with meals/6,000 USP units (Lipase) with snacks)

2. High dose (cohort of 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks)

At Weeks 1, 5, or 9, subjects who meet dose modification criteria described in Section 2.4 will be titrated once by the IRT to the following dose cohorts in a blinded fashion:

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

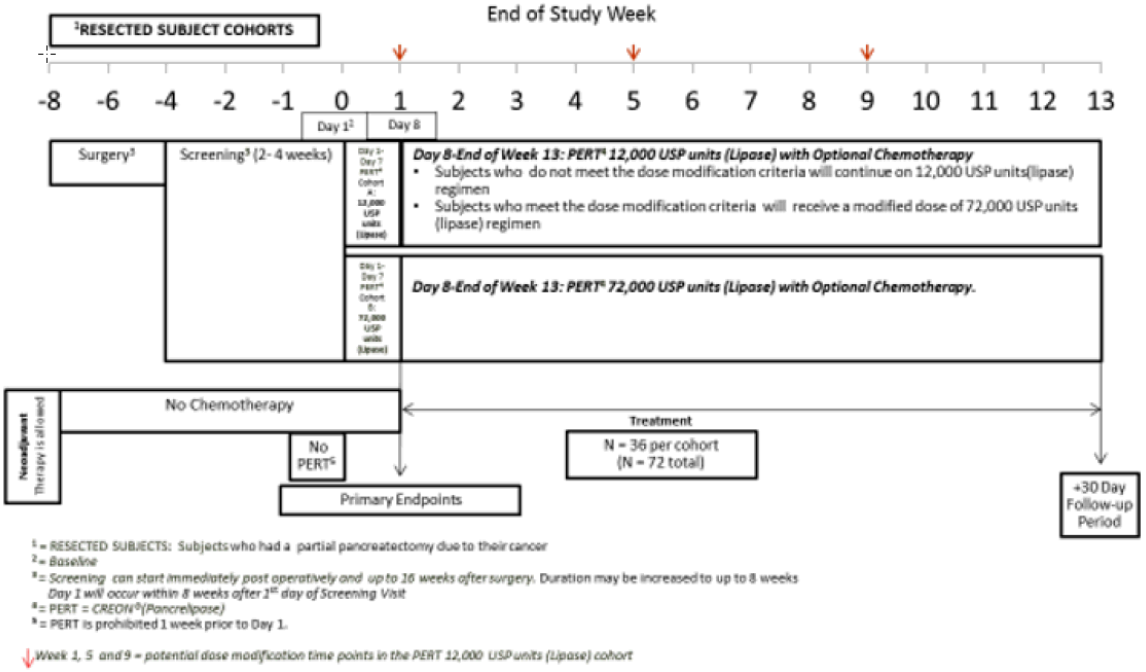
Non-resected subjects in the open-label dose cohort will receive pancrelipase at a dose of 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks during the entire duration of the study.

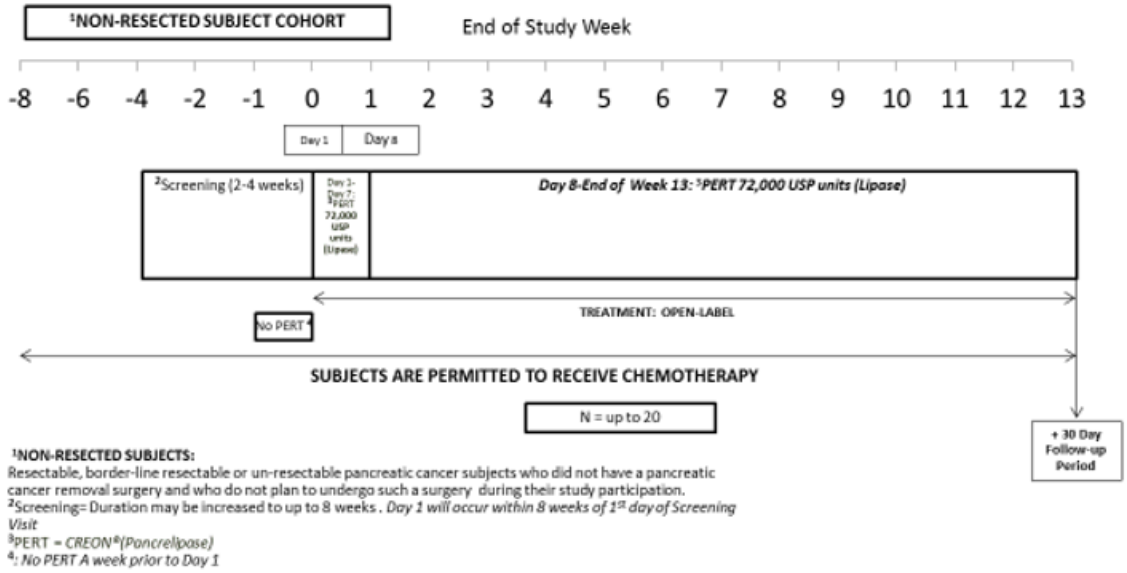
No interim analyses are currently planned. Study sites and resected subjects in the double-blind cohorts will remain blinded for the treatment period of the study.

In support of the primary endpoints, it is critical for subjects, who were on PERT before the start of the study, to stop PERT a week prior to Day 1 and to initiate stool collection 48 hours prior to Day 1 and Week 1 visits. The schematic of the study is shown in Figure 1.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic





2.3 Treatment Assignment and Blinding

Eligible resected subjects will be randomized in 1:1 ratio to one of following dose cohorts, and will remain on blinded therapy throughout the study treatment period (13 weeks):

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

Subjects in the non-resected population will receive open-label Creon (cohort of 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks) for 13 weeks (n = 20).

The randomization is central with no stratification.

2.4 Sample Size Determination

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

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

Non-Resected Subjects: Up to 20 subjects will be enrolled. This is an exploratory cohort and no formal statistical tests are planned for this cohort.

2.5 Dose Modification

Dose modifications will be determined by a "dispensation score" calculated in EDC based on the responses to Questions 7, 8 and 10 from the EPI Symptom Questionnaire (Appendix D). The "dispensation score" will be then entered in IRT by the sites. Whether the subject needs dose modification will be determined by the "dispensation score" and IRT will then dispense the corresponding drug accordingly. The process will keep the site staff and the subjects blinded on whether the subject will be dose modified or not. The dose modification process including the details of the IRT dispensation score derivations are documented in the Study M16-142 Documentation of Key Decision dated 09 February 2020. The general dose modification rules are described as below.

Calculation of Total Score for Dose Modification:

The score for dose modification will be calculated by assigning the following values to each one of the responses to Questions 7, 8, and 10 in the EPI symptom questionnaire: none = 0, mild = 1, moderate = 2, severe = 3, very severe = 4. The total score for dose modification will be calculated as the sum of the responses to Questions 7, 8, and 10 within each visit. If none of the three questions are answered, the score will be noted as NULL.

The criteria for dose modification are described below:

a. If current score = NULL, then maintain dose.
b. If the previous score is NULL and the score for the current visit is available, then replace the previous score with the last available visit score as the previous score and follow the dose escalation criteria d) e) or f).
c. If the Baseline visit score and all other visit scores prior to the present visit are NULL but the present visit score is available, then maintain dose.
d. If current score <= 2, then maintain dose.
e. If current score > 2 and there is less than 30% improvement from the previous score, i.e., current score > (0.7 × previous score), then increase dose.

f. If current score > 2 and there is 30% or more improvement from the previous score i.e., current score <= (0.7 × previous score), then maintain dose.

The subjects, site staffs and Abbvie site monitors will be blinded to the detailed dose modification criteria as well as the subject's dose medication status.

Resected Subjects

The dose for resected subjects in the low dose cohort (12,000 USP units (Lipase) with meals/6,000 USP units (Lipase) with snacks) will be modified to the high dose (72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks) at Week 1, 5, or 9 if the dose modification criteria defined above are met. Subjects randomized to the high dose cohort are not dose modified.

Only one dose modification will be permitted throughout the study. For subjects who have already experienced dose escalation, they will remain on the high dose level for the rest of the treatment duration, even if they continue to meet the dose escalation criteria in the subsequent visit(s). No further dose escalation is allowed.

Non-Resected Subjects

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

3.0 Endpoints

3.1 Primary Endpoint(s)

Resected Pancreatic Cancer Subjects

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

3.2 Secondary Endpoint(s)

Resected Pancreatic Cancer Subjects

- Change from Baseline to Week 1 in average daily stool frequency. The average daily stool frequency is calculated from the last 3 days prior to each of Baseline and Week 1 visit.
- Change from Baseline to Week 1 in stool consistency, based on the proportion of days having watery stool consistency in the last 7 days prior to each of Baseline and Week 1 visit.
- Change from Baseline to Week 1 in the total EPI Symptoms Score.

3.3 Additional Endpoint(s)

Resected Pancreatic Cancer Subjects

- Average daily stool frequency for 7 days prior to each of Weeks 5, 9 and 13 visits compared to Baseline visit.
- Stool consistency in the 7 days prior to each of Weeks 5, 9 and 13 visits compared to Baseline visit.
- Total EPI Symptom Score at Weeks 5, 9 and 13 visits compared to Baseline visit.
- The scaled total score for each scale/item as described below of Quality of life (QoL) (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLQ]-C30 and QLQ PAN26) at Weeks 1, 5, 9, and 13 visits compared to Baseline visit.

QLQ-C30:

  - Global health status/QoL.
  - Functional scales (Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning).
  - Symptom scales/items (Fatigue, Nausea and vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties).

QLQ-PAN26:

- Pancreatic Pain.
- Digestive symptoms (Gastrointestinal).
- Hepatic (Jaundice).
- Altered bowel habit.
- Poor body image.
- Satisfaction with health care.
- Sexuality (Sexual dissatisfaction).

- Body weight and body mass index (BMI) at Weeks 1, 5, 9 and 13 visits compared to Baseline visit.
- Chemotherapy tolerability (as defined in Section 9.4.6).
  - Difference in expected or planned chemotherapy from the last scheduled visit (Yes / No / Not Applicable, no chemotherapy planned) at Week 1, 5, 9 and 13 visits.
  - Proportion of expected or planned chemotherapy due to chemotherapy tolerability.
  - Proportion of different types of changes due to chemotherapy tolerability (entire regimen permanently discontinued / one or multiple agents permanently discontinued / dose held / dose interrupted / dose reduced / change in treatment administration schedule).
  - Diagnosis of changes due to chemotherapy tolerability (Adverse events / Medical history).
- Serum albumin and pre-albumin level at Weeks 1, 5, 9 and 13 compared to Baseline.

Non-Resected Pancreatic Cancer Subjects

- Change in stool fat from Baseline (Day 1) to Week 1 (Day 8).
- Change from Baseline to Week 1, 5, 9 and 13 in average daily stool frequency. The average daily stool frequency is calculated from the last 7 days prior to each of Baseline and Weeks 1, 5, 9, and 13 visits.

- Change from Baseline to Week 1, 5, 9, and 13 in stool consistency, based on the proportion of days having watery stool consistency in the last 7 days prior to each of Baseline and Week 1 visit.
- Change in the total EPI Symptoms Score from Baseline to Weeks 1, 5, 9, and 13.
- Change in scaled total score for each domain as described below of QoL (EORTC QLQ-C30 and QLQ-PAN26) from Baseline to Weeks 1, 5, 9, and 13.

QLQ-C30:

  - Global health status/QoL.
  - Functional scales (Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning).
  - Symptom scales/items (Fatigue, Nausea and vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties).

QLQ-PAN26:

  - Pancreatic Pain.
  - Digestive symptoms (Gastrointestinal).
  - Hepatic (Jaundice).
  - Altered bowel habit.
  - Poor body image.
  - Satisfaction with health care.
  - Sexuality (Sexual dissatisfaction).

- Chemotherapy tolerability (as defined in Section 9.4.6).
  - Difference in expected or planned Chemotherapy from the last scheduled visit (Yes / No / Not Applicable, no chemotherapy planned) at Week 1,5,9 and 13 visits.
  - Proportion of expected or planned Chemotherapy due to chemotherapy tolerability.
  - Proportion of different types of changes due to chemotherapy tolerability (entire regimen permanently discontinued / one or multiple agents permanently discontinued / dose held / dose interrupted / dose reduced / change in treatment administration schedule).

- Diagnosis of changes due to chemotherapy tolerability (Adverse events / Medical history).

- Change in the following measurements from Baseline to Weeks 1, 5, 9, and 13: Body weight, and BMI.
- Change in the following measurements from Baseline to Week 5, 9, and 13 for serum albumin and serum pre-albumin level.

3.4 Safety Endpoint(s)

Safety endpoints will be based on evaluations including adverse events (AE) monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology, chemistry, and urinalysis). This information will be copied from the protocol.

4.0 Analysis Populations

The following population sets will be used for the analyses.

1. **Intention to Treat (ITT)**

The Intention to Treat (ITT) Set consists of all randomized subjects in the resected regimen and all enrolled subjects in the non-resected regimen. Subjects will be analyzed as randomized or enrolled. This population will be used to summarize subject disposition only.

The randomized treatment group in the resected regimen consists of the following groups:

a. **High Dose:** Subjects randomized to Creon 72,000 dose cohort (72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks)
b. **Low Dose:** Subjects randomized to Creon 12,000 dose cohort (12,000 USP units (Lipase) with meals/6,000 USP units (Lipase) with snacks)

The treatment group in the non-resected regimen consists of all the subjects enrolled. All the subjects in this group will be receiving the High Dose of Creon 72,000 dose cohort (72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks).

2. **Full Analysis Set (FAS)**

Resected and Non-Resected Subjects

The Full Analysis Set (FAS) includes all randomized or enrolled subjects who received at least one dose of study drug in the resected or the non-resected regimens, respectively. FAS will be used to summarize baseline characteristics unless it is specified otherwise.

3. **Evaluable Analysis Set for Stool Fat Analysis (EAS-SF)**

Resected and Non-Resected Subjects

The Evaluable Analysis Set for Stool Fat Analysis includes subjects from the FAS who have evaluable stool fat (see Section 9.3.2.1) at both Baseline and Week 1 visits.

4. **Supplementary Analysis Set for Stool Fat Analysis (EAS-SF-SUPP)**

The Supplementary Analysis Set for the Stool Fat Analysis includes subjects from the FAS in the resected regimen who have 100% stool sample collected for the 48 hour collection period at both Baseline (Day 1) and Week 1 visits (see Section 9.2.1).

5. **Safety Analysis Set (Safety)**

Resected and Non-Resected Subjects

The Safety Analysis Set will include all randomized/enrolled subjects who received at least one dose of study drug.

4.1 Analysis Treatment Groups

The following analysis treatment groups will be used in different analyses:

1. **Analysis Treatment Group Per Day 1 Dispensing (ATG-Day 1, Resected and Non-Resected Regimen):** These treatment groups will be determined by the actual study drug the subjects were dispensed at Day 1 visit.
    a. **High Dose Group:** Subjects who were dispensed the high dose (72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks) at the Day 1 visit.
    b. **Low Dose Group:** Subjects who were dispensed the low dose (12,000 USP units (Lipase) with meals/6,000 USP units (Lipase) with snacks) at the Day 1 visit.
2. **Analysis Treatment Group Per All Dispensing (ATG-All Dispensing, Resected regimen only):** The following treatment groups will be determined by the actual study drug the subjects were dispensed throughout the study.
    a. **High Dose:** Subjects who were dispensed the high dose (72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks) at the Day 1 visit.
    b. **Low Dose:** Subjects who were dispensed the low dose (12,000 USP units (Lipase) with meals/6,000 USP units (Lipase) with snacks) at the Day 1visit.
    c. **All low Dose:** Subjects who were dispensed the low dose (12,000 USP units (Lipase) with meals/6,000 USP units (Lipase) with snacks) at all visits.
    d. **Any High Dose:** Subjects who was dispensed the high dose (72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks) at any of the visits.
3. **Analysis Treatment Group - Dynamic (ATG-Dynamic) per visit (Week 1, Week 5, Week 9, Week 13, Resected regimen only):** These treatment group will be defined based on study drug dispensed to the subjects at the prior visit. For example, the dynamic treatment group at Week 1 visit would be based on the study drug dispensed to the subjects at Day 1 visit, which can be identified after unblinding by the kit number that had been dispensed to the subjects at Day 1 visit.

a. **High Dose Group:** Subjects who was dispensed the high dose (72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks) at the prior visit.

b. **Low Dose Group:** Subjects who was dispensed the low dose (12,000 USP units (Lipase) with meals/6,000 USP units (Lipase) with snacks) at the prior visit.

4.2 Analysis Treatment Groups for Various Analyses

Table 1. Analysis Population and Analysis Treatment Groups for Various Analyses

Analysis	Analysis Set	Resected		Non-Resected (All High Dose)
		Analysis Treatment Groups	Treat Group Category	Analysis Treatment Groups
Disposition	ITT	As randomized	High Dose, Low Dose, Overall	As enrolled
Baseline Characteristics, Medical History, Prior and Concomitant Medications	FAS	ATG-Day 1	High Dose, Low Dose, Overall	ATG-Day 1
Drug Exposure	Safety	ATG-All Dispensing	High Dose, Low Dose, All Low Dose, Any High Dose, Overall	ATG-Day 1

Table 1. SA Analysis Treatment Groups for Various Analyses P Version Summary History (Continued)

Analysis			Analysis Set	Resected		Non-Resected (All High Dose)
				Analysis Treatment Groups	Treat Group Category	Analysis Treatment Groups
Drug Compliance (week 1)			Safety	ATG-Day 1	High Dose, Low Dose, Overall	ATG-Day 1
Efficacy	Primary	stool fat (Week 1 within group)	EAS-SF, EAS-SF-SUPP	ATG-Day 1	High Dose, Low Dose	ATG-Day 1
	Secondary	stool fat (Week 1 between group)	EAS-SF, EAS-SF-SUPP	ATG-Day 1	High Dose, Low Dose	NA
		Stool Frequency/Stool Consistency/EPI Symptom Week 1	FAS	ATG-Day 1	High Dose, Low Dose	ATG-Day 1
	Additional	Stool Frequency/Stool Consistency by visit	FAS	ATG-Dynamic	High Dose, Low Dose, Overall	ATG-Day 1
		PRO by visit (EPI/PAN 26/C30)	FAS	ATG-Dynamic	High Dose, Low Dose, Overall	ATG-Day 1
		BMI/Weight by visit	FAS	ATG-All Dispensing	High Dose, Low Dose, All Low Dose, Any High Dose, Overall	ATG-Day 1

Table 1. SA Analysis Treatment Groups for Various Analyses P Version Summary History (Continued)

Analysis			Analysis Set	Resected		Non-Resected (All High Dose)
				Analysis Treatment Groups	Treat Group Category	Analysis Treatment Groups
Efficacy	Additional	Albumin and pre-albumin by visit	FAS	ATG-All Dispensing	High Dose, Low Dose, All Low Dose, Any High Dose, Overall	ATG-Day 1
		Chemotherapy tolerability by visit	FAS	ATG-All Dispensing	High Dose, Low Dose, All Low Dose, Any High Dose, Overall	ATG-Day 1
Safety		AE/SAE in Week 1	Safety	ATG-Day 1	High Dose, Low Dose, Overall	ATG-Day 1
		AE/SAE analyses (entire treatment period)	Safety	ATG-Dynamic	High Dose, Low Dose, Overall	NA
		All other AE/SAE analysis	Safety	ATG-All Dispensing	High Dose, Low Dose, All Low Dose, Any High Dose	ATG-Day 1
		Lab / Vital Signs	Safety	ATG-All Dispensing	High Dose, Low Dose, All Low Dose, Any High Dose	ATG-Day 1

5.0 Subject Disposition

The total number of subjects who were screened, randomized or enrolled, and treated will be summarized.

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized for high or low dose cohort at

randomization in the resected regimen and for subjects enrolled in the non-resected regimen:

- Subjects randomized or enrolled in the study;
- Subjects who took at least one dose of study drug;
- Subjects who completed protocol-specified treatment;
- Subjects who completed the study;
- Subjects who prematurely discontinued study drug (all reasons and primary reason);
- Subjects who prematurely discontinued study (all reasons and primary reason).

6.0 Study Drug Duration and Compliance

The overall treatment duration (irrespective of whether the subjects are receiving high dose or low dose of the study drug) will be summarized. 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. In addition, the number and percentage of subjects in each treatment duration interval (< 1 Week, 1 to < 5 weeks, 5 to < 9 weeks, 9 to < 13 weeks, ≥ 13 weeks) will be summarized.

The number of capsules taken per day for the first week of treatment will be summarized for all subjects in the Safety Analysis Set. The number of meals and snacks per day reported in the dosing diary for the first week of treatment will also be tabulated.

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 and Disease Characteristics

Continuous demographic variables include baseline age, weight, height, body mass index (BMI), hip and waist circumference, and Fecal elastase-1 (FE-1). Categorical demographic variables include sex, ethnicity, race, weight (< 60 or ≥ 60 kg), BMI (< 25 or ≥ 25 kg/m^2), tobacco user (current, former, never, unknown), alcohol user (current, former, never, unknown) and ECOG performance status.

Cancer history data will also be summarized categorically according to their histologic type, overall staging at the initial diagnosis, overall staging at study entry, anatomical location of the cancer involvement in the pancreas (head, neck, body, tail or multiple), the presence of metastatic disease at study entry (Yes or No), completion of neo-adjuvant chemotherapy or neo-adjuvant radiotherapy (Yes or No), history of resection of their primary pancreatic cancer (Yes/No).

Pancreatic Cancer resection history will also be summarized according to what procedure they went through (pancreaticoduodenectomy, polyrus preserving whipple, distal pancreatectomy, total pancreatectomy, or other).

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 by high or low dose cohort as the study drug is dispensed to the subjects at randomization (Day 1) in the resected population and for subjects enrolled in the non-resected populations. 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 study drug. This includes medications and procedures with a start date before the first study drug administration date. 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. Prior radiation therapies will be summarized according to the relative location category (primary, regional, distant, unknown and multiple).

A concomitant medication 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 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.

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 before the study drug treatment (e.g., an end date before study drug start date).

A concomitant procedure is defined as any procedure that started prior to the date of the first dose of study drug and continued after the first dose of study drug or any procedure 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.

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 study drug start date). A procedure will be considered a concomitant procedure where one of the following three cases occurs (1) the start date is missing and the end date is either after or on the first study drug dose date; (2) the start date is prior to or on the last dose of study drug and the end date is missing; (3) both the start date and the end date are missing.

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 and continued after the first dose of study drug.

Prior procedures (excluding pancreatic resection), concomitant procedures and study cancer concomitant radiation therapies will be listed by subjects numbers.

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

The primary efficacy endpoint of change in stool fat from Baseline to Week 1 (defined in Section 3.1) will be analyzed based on the EAS-SF and EAS-SF-SUPP population and the following methods will be used to address potential intercurrent events:

- Subjects with missing or incomplete (not evaluable) stool fat sample at either Baseline or Week 1 will be excluded from the analysis.

9.0 Efficacy Analyses

9.1 General Considerations

The primary efficacy analyses will be conducted in the EAS-SF and EAS-SF-SUPP for the supplementary analysis of the stool fat. All other efficacy analyses will be conducted

in the FAS population, considering different groups for different analysis as tabulated in Table 2 in Section 4.2. All tests will be 2-sided at an alpha level of 0.05.

The Primary Analysis and other analyses will be performed after all subjects in the resected and non-resected population have completed the study and the database has been locked. This will be the only and final analysis for the primary and secondary efficacy endpoints as well as all other efficacy endpoints in the study.

"Baseline" refers to the last non-missing observation before the first administration of study drug or randomization if no study drug is given, unless otherwise specified in the individual analysis section.

9.2 Handling of Missing Data

Missing data will be imputed using the following methods for the efficacy analyses.

9.2.1 Adjustment for Missing Stool Fat Samples in Stool Fat per Day

The stool fat (g) will be reported for each subject per 24 hours period for 2 consecutive 24-hour collection periods (total 48-hour period) separately, prior to both Baseline (Day 1) visit and Week 1 (Day 8) visit. The average daily stool fat (g/day) at both Baseline and Week 1 visit will be calculated from these two reported 24-hour stool fat for each subject.

Step 1: The two reported 24-hour stool fat value will be assessed to see whether they are evaluable values at both Baseline and Week 1 based on the stool frequency and number of stool sample missed to be collected for the corresponding 24-hour period, following the rules in Section 9.3.2.1.

Step 2: If the reported 24-hour stool fat value is deemed to be evaluable but there are missing stools in that 24-hour collection period, the adjusted 24-hour stool fat will be calculated as following:

$$x = \frac{y}{p} * 100$$

where,

x : Calculated adjusted stool fat for a 24 hour period

p : Percentage of stool sample collected in a 24 hour period

y : Laboratory reported 24-hour stool fat from the stool samples collected in a 24 hour period

If a subject has evaluable 24-hour stool fat value for both days for a visit, then the stool fat for that visit will be determined based on the average of the two evaluable value (with adjustment if needed as described in Step 2 above). If subject has only one evaluable 24-hour stool fat value for a visit, then the stool fat for that visit will be determined based on that evaluable value (with adjustment if needed as described in Step 2 above). If both 24-hour stool fat values for that visit are not evaluable, then subject is considered having no evaluable stool fat data for that visit with no imputation.

9.2.2 Missing EPI Symptoms Score

The EPI Symptoms Questionnaire data will be used to compute the EPI Symptom score. Each of the 12 questions is scored as described in Dose modification, Section 2.5. The missing answers to any of the 12 questions of the EPI questionnaire will not be possible unless the subject did not complete the EPI questionnaire at all. The questionnaire can be submitted only when all the questions in the questionnaire have been answered. No questions can be skipped before submitting. Missing EPI questionnaire will not be imputed.

9.2.3 Missing Stool Frequency

Daily stool frequency will be collected from Day –7 through Day –1, Day 1 through Day 7 and for 7 days prior to each subsequent visit. For the stool frequency analysis, the mean frequency for 3 days prior to each visit (for example, Day –3, –2, –1 will be

considered for Baseline, and Day 5, 6, 7 for Week 1) is considered. If stool frequency data for any of the 3 days prior to each visit is not available, then the missing value is estimated using the following criteria.

- If data for none or only 1 day is available for a visit, then the mean stool frequency for the visit will be considered as missing.
- If data for 2 days of the 3 required days are available, then the mean stool frequency for the visit will be calculated based on the data from the 2 available days.

For the supplementary analysis of the stool frequency, the mean stool frequency for each week is considered. If stool frequency data for all 7 days in a week is not available, then the missing value is estimated using the following criteria.

- If data for 50% or less i.e., three or less days are available for each week, then the mean stool frequency for the week will be considered missing for the analysis.
- If data for more than 50% i.e., 4 or more days are available, then the stool frequency for the missing days will be imputed using the mean value of the available data. Finally, the mean stool frequency for the week will be calculated.

9.2.4 Missing Stool Consistency

Daily stool consistency will be collected once daily from Day –7 through Day –1, Day 1 through Day 7 and for 7 days prior to each subsequent visit. For the stool consistency analysis, the proportion of watery stool consistency among the 7 days prior to each visit (for example, Day –7 to –1 will be considered for Baseline, and Day 1 to Day 7 for Week 1) is considered. For example, among the 7 days for a visit if 6 of those days have watery consistency, then the proportion of days with watery stool consistency will be 6/7. If stool consistency data for any of the seven days prior to each visit is not available, then the proportion of days with watery stool consistency will be estimated using the following criteria.

- If data for 50% or less i.e., 3 or less days are available for each week, then the mean stool consistency for the week will be considered missing for the analysis.
- If data for more than 50% i.e., 4 or more days are available, then the proportion of days with watery stool consistency will be determined based on the available data. For example, if 5 days data is available for a visit and 3 of those days have watery consistency, then the proportion of days with watery stool consistency will be 3/5.

9.2.5 Missing QoL Score (EORTC QLQ-C30 and QLQ-PAN26)

Refer to the score manual for the EORTC QLQ-C30 for imputing missing items (Appendix B).

9.3 Primary Efficacy Endpoint(s) and Analyses

9.3.1 Primary Efficacy Endpoint(s)

Resected Pancreatic Cancer Subjects

The primary endpoint is change in stool fat from Baseline (Day 1) to Week 1 (Day 8) for each dose cohort. Stool fat is collected during the 48 hours prior to the Day 1 (Day –2 and Day –1) and Week 1 (Day 6 and Day 7) visits.

9.3.2 Main Analysis of Primary Efficacy Endpoint (s)

The stool fat (g) for each subject for the 48 period prior both Baseline (Day 1) visit and Week 1 (Day 8) visit will be calculated according to Section 9.2.1. The change in stool fat from Baseline to Week 1 will be analyzed using an analysis of covariance (ANCOVA) model including treatment as a fixed effect and Baseline stool fat as the covariate. The least square mean estimates for change in stool fat along with its two-sided 95% CI will be provided for each treatment group. The hypothesis testing for a difference from baseline to Week 1 in stool fat will be tested at 2-sided 5% α-level for each treatment group in EAS-SF separately.

The attributes of the estimands corresponding to the primary efficacy endpoint are summarized in Table 2.

Table 2. Summary of the Estimand Attributes of the Primary Efficacy Endpoint

Estimand	Attributes of the Estimand				
	Population	**Endpoint**	**Treatment**	**Intercurrent Events**	**Statistical Summary**
Primary	Evaluable Analysis Set for Stool Fat (EAS-SF) in the Resected Pancreatic Cancer cohort.	Change in Stool Fat from Baseline (Day 1) to Week 1 (Day 8).	CREON (*High Dose*: 72,000 USP units (Lipase) with meals/36,000 USP units (Lipase) with snacks, *Low Dose*: 12,000 USP units (Lipase) with meals/ 6,000 USP units (Lipase) with snacks).	IE: Subjects with missing or incomplete (not evaluable) stool fat sample at either Baseline or Week 1 will be excluded from the analysis.	Mean Change in stool fat from Baseline to Week 1 for each dose cohort separately.

9.3.2.1 Criteria for Evaluable Stool Fat Sample

The laboratory reported 24-hour stool fat value will be evaluable for analysis if the following condition is true.

- Stool collection in the corresponding 24-hour period is at least 67%. If stool collection data is missing or less than 67% of stool sample is collected, then the corresponding 24-hour stool fat value is not evaluable.

The stool fat (g) will be reported by lab for each subject per 24 hours period for 2 consecutive 24-hour collection periods (total 48-hour period) separately, prior to both Baseline (Day 1) visit and Week 1 (Day 8) visit. The average daily stool fat (g/day) at

both Baseline and Week 1 visit will be calculated from these two reported 24-hour stool fat for each subject. If the stool collection for a 24-hour period is evaluable with missing stool samples, then the total stool fat for that period will be adjusted following the imputation rule in Section 9.2.1. The average daily stool fat (g/day) at both Baseline and Week 1 visit will be calculated from the adjusted stool fat values for the analysis.

If the data on the "total bowel movements" and the "bowel movements not collected" is missing on any of the 4 days, then the stool fat will be regarded as missing for that day.

9.3.3 Supplementary Analyses of the Primary Efficacy Endpoint(s)

A supplementary analysis will be performed for the primary efficacy endpoint on the subjects included in the EAS-SF-SUPP (subjects with 100% stool sample collected for the 48 hour collection period at both Baseline (Day 1) and Week 1 visits) using the ATG-Day 1 group (High Dose and Low Dose) for the resected population. The change in stool fat from Baseline to Week 1 for each treatment group will be analyzed using the ANCOVA model described in Section 9.3.2.

9.4 Secondary and Additional Efficacy Analyses

9.4.1 Stool Fat

Resected Subjects

For comparison between dose cohorts for change in stool fat from Baseline to Week 1, the ANCOVA model including treatment as fixed effect and baseline stool fat as the covariate as described for the primary analysis will be used. The least square mean estimate of the difference between two treatment groups in change from baseline in stool fat will be provided along with the 95% CI and P value. The analysis will be performed using the EAS-SF and EAS-SF-SUPP set for the resected population only.

Non-Resected Subjects

The change in stool fat from Baseline to Week 1 will be analyzed using an analysis of covariance (ANCOVA) model including Baseline stool fat as the covariate. The least square mean estimates for change in stool fat along with its two-sided 95% CI will be provided. The null hypothesis of no change in mean stool fat from Baseline to Week 1 will be tested at 2- sided 5% α – level in EAS-SF.

9.4.2 Stool Frequency

Stool frequency is collected each day for 7 days prior to each visit during the study period. For the analysis, the average number of stool frequency per day is considered for the last 3 days prior to each visit (Day –3 to Day –1 for Baseline and Day 5 to Day 7 for Week 1 visit). The average stool frequency per day for a visit is defined as total number of stools in the last 3 days divided by 3 for that visit.

The analyses will be performed using the population and treatment groups as described in Table 1 in Section 4.2.

- For analysis of change in stool frequency from Baseline to Week 1, both within dose cohort and for comparison between dose cohorts (resected regimen only), an ANCOVA model including treatment as a fixed effect (resected population only) and Baseline stool frequency as the covariate will be used. Day –3, Day –2 and Day –1 would be considered for Baseline and Day 5, Day 6 and Day 7 would be considered for Week 1 visit.
- Descriptive summary statistics will be provided for change in stool frequency from Baseline to Week 1, 5, 9 and 13. For the summary, the average stool frequency per day for the Baseline and Week 1 is defined as total number of stool frequency in the last 3 days divided by 3 for that visit for comparison to Week 1. However, the average stool frequency per day for the Baseline and Week 5, 9 and 13 is defined as total number of stool frequency in the last 7 days divided by 7 for that visit for comparison to all other post-baseline visits.

- Descriptive statistics per day for stool frequency are presented specifying the mean, standard deviation, median, minimum and maximum of stool frequency for 7 days prior to Baseline and Week 1.

Sensitivity Analysis for Stool Frequency:

- For the sensitivity analysis, the average number of stool frequency per day is considered for the last 7 days prior to each visit. The average stool frequency per day for a visit is defined as total number of stool frequency in the last 7 days divided by 7 for that visit. Day –7 to Day –1 would be considered for Baseline and Day 1 to Day 7 would be considered for Week 1 visit.
- The 7-day mean will be analyzed similar to the primary analysis of the stool frequency using an ANCOVA model including treatment as a fixed effect (resected population only) and Baseline stool frequency as the covariate. Summary statistics and comparing the change in stool frequency from Baseline to Week 1 will also be summarized.

9.4.3 Stool Consistency

Stool consistency will be collected once a day for 7 days prior to each visit using the Bristol Stool Chart and will be characterized based on the typology below for the analysis. The proportion of days with watery consistency during 7-day period prior to each visit will be calculated at each visit for each subject. The analyses will be performed using the population and treatment groups as described in Table 1 in Section 4.2.

- A Wilcoxon paired signed rank test will be performed for comparison of the proportion of days with watery stool consistency of Week 1 to that at Baseline within each dose cohort in the resected population. Similar test will be performed in the non-resected population as well.
- For comparison of change in the proportion of days with watery stool consistency from Baseline to Week 1 between two dose cohorts will be assessed through the non-parametric Wilcoxon Rank-Sum test in the resected population.

- Descriptive statistics will be provided for proportion of days with watery stool consistency at Week 1 (Day 8), 5, 9 and 13 as well as change from Baseline for each visit in both the resected and non-resected population.
- The number and percentages of subjects with 7 different types of stool consistency reported and 2 different types of characterization of stool consistency as described in Table 3 will be summarized per day for 7 days prior to Baseline (Day 1) and 7 days prior to Week 1 (Day 8) visit for the non-resected population and for each analysis treatment group in the resected population.

Table 3. Characterization of Bristol Stool Chart for Analysis

Stool Type (Score)	Characterization
Type 1 (1), Type 2 (2), Type 3 (3), Type 4 (4), Type 5 (5)	Hard/Normal
Type 6 (6), Type 7 (7)	Watery

9.4.4 EPI Symptom Score

EPI symptom score for the efficacy analysis will be calculated at each visit as the total score for the responses to all the 12 questions in the EPI Symptoms Questionnaire. The response score will range from 0 to 4 for each question (0 corresponding to None to 4 corresponding to Very Severe). Therefore, the total score will range from 0 to 48.

The analyses will be performed using the population and treatment groups as described in Table 1 in Section 4.2.

- Change in EPI Symptom Score from baseline to Week 1 will be analyzed similarly to the stool frequency analyses using an ANCOVA model including treatment as a fixed effect (resected population only) and Baseline EPI Symptom score as the covariate for both within dose cohort and for comparison between dose cohorts (resected population only).
- Similar analyses will also be provided for the subset of questions (Question 7, 8 and 10) used for dose modification criteria (resected population only).

- Descriptive summary statistics will be provided for change in EPI Symptom score from Baseline to Week 1, 5, 9 and 13 in both the resected and non-resected population.
- Descriptive statistics per day for EPI Symptom score are presented specifying the mean, standard deviation, median, minimum and maximum of stool frequency for 7 days prior to Baseline (Day 1) and Week 1 (Day 8).

9.4.5 QoL (EORTC QLQ-C30 Score and QLQ-PAN26 Score)

The score calculations are described in Appendix B. The total scaled score for each domain in both the Questionnaires will range from 0 to 100. The analyses will be performed using the population and treatment groups as described in Table 1 in Section 4.2.

QLQ-C30:

There are 3 scales/domains described in the QLQ-C30 questionnaire. The global health status/QoL scale, functional scale (Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning), and symptom scale/items (Fatigue, Nausea and vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties) will be analyzed separately.

- Descriptive statistics will be provided for each scaled score and change from baseline for each visit.

QLQ-PAN-26:

There are several domains described in the QLQ-PAN-26 questionnaire. The score in the Pancreatic pain, Digestive symptoms (Gastrointestinal), Hepatic (Jaundice), Altered bowel habit, Poor body image, Satisfaction with the Health Care and Sexuality (Sexual dissatisfaction) domains will be analyzed.

Similar analyses as QLQ-C30 will be performed.

9.4.6 Chemotherapy Tolerability

The following analysis for chemotherapy tolerability will be provided using descriptive statistics for each visit:

- Number and percentage of subjects with change in expected/planned chemotherapy from the last scheduled visit (Yes / No / Not Applicable, no chemotherapy planned)
- For change in expected/planned chemotherapy = yes, the number and percent of subjects that had this change due to chemotherapy tolerability (Yes / No)
- For both change in expected/planned chemotherapy = yes and change in chemotherapy due to tolerability = yes, number and percent of subjects with each type of changes due to chemotherapy tolerability (entire regiment permanently discontinued / one or multiple agents permanently discontinued / dose held / dose interrupted / dose reduced / change in treatment administration schedule)
- For both change in expected/planned chemotherapy = yes and change in chemotherapy due to tolerability=yes, number and percent of subjects with changes due to Adverse events or Medical history.
- The analyses will be performed in both the resected and non-resected population using the population and treatment groups as described in Table 1 in Section 4.2.

9.4.7 BMI, Body Weight

The change from baseline to each visit in body weight, BMI, hip and waist circumference, will be summarized from Baseline (Day 1) to each post baseline visit using descriptive statistics.

The number and percentage of subjects who had more than 10% (≥ 10%) reduction in their body weight and for subjects who had more than 10% (≥ 10%) increment in their body weight for each visit will also be summarized.

Body Mass Index (BMI) is calculated as follows at each visit:

BMI (kg/m^2) = Body Weight (kg) / Body Height2 (m^2):

The analyses will be performed in both the resected and non-resected population using the population and treatment groups as described in Table 1 in Section 4.2.

9.4.8 Serum Albumin, Pre-Albumin

The analyses will be performed in both the resected and non-resected population using the population and treatment groups as described in Table 1 in Section 4.2.

For all the laboratory parameters of serum albumin and pre-albumin, the change from baseline to each of the post baseline visit (Week 5, 9 and 13), and from baseline to the final post-baseline values will be summarized using descriptive statistics.

9.4.9 Exploratory Analysis for Dietary Intake

The fat intake data will be summarized using descriptive statistics including the average fat intake per day (gram/day) by week and by treatment group. The fat intake data for each subject will be included in a listing as well. Similar descriptive summary and listings will also be developed for protein, carbohydrate and calorie intake data.

Additional exploratory analyses may be performed.

9.5 Efficacy Subgroup Analyses

There is no subgroup analysis planned.

10.0 Safety Analyses

10.1 General Considerations

The analyses will be performed in both the resected and non-resected population using the population and treatment groups as described in Table 1 in Section 4.2.

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, SAEs will be collected from the time the subject signed the study-specific informed consent.

All AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Organ Classes (SOCs) and preferred terms (PTs), Version 21.0 or higher. 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) is defined as AEs that first occur or worsen on or after the first dose of study treatment in until the last study drug treatment. Pancrelipase acts locally in the gastrointestinal tract and is not absorbed in the body thus the effect of the study drug will disappear right after the drug discontinuation. Therefore, the AEs occurring after the study drug treatment period is not considered to be TEAE. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. 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).

Three main analyses for TEAE will be provided:

- Incidence rate of TEAE in the first week of study treatment
- Exposure-adjusted incidence rate for TEAE during the entire treatment period
- Incidence rate of TEAE leading to study drug discontinuation

10.2.1.1 Incidence Rate of TEAE in the First Week of Study Treatment

Number and percent of subjects experiencing TEAEs will be summarized for the first week of study treatment (Day 1 to Week 1 visit, inclusive), for resected population and non-resected population. Specifically, TEAEs will be summarized by treatment group as described below:

1. An overview of the number and percentage of subjects with TEAEs in the first week
2. A summary of the number and percentage of subjects with TEAEs in descending order of overall incidence frequency by MedDRA PT in the first week
3. A summary of the number and percentage of subjects with TEAEs by primary MedDRA SOC and PT in the first week
4. A summary of the number and percentage of subjects with serious TEAEs in descending order of overall incidence frequency by MedDRA PT in the first week
5. A summary of the number and percentage of subjects with serious TEAEs by primary MedDRA SOC and PT TEAEs in the first week
6. A summary of the number and percentage of subjects with TEAEs leading to discontinuation of study drug by primary MedDRA SOC and PT in the first week
7. A summary of the number and percentage of subjects with drug-related (i.e., with reasonable possibility to be related to study drug) TEAEs by primary MedDRA SOC and PT in the first week
8. A summary of the number and percentage of subjects with TEAEs by primary MedDRA SOC, PT and maximum severity in the first week

10.2.1.2 Exposure-Adjusted Incidence Rate (EAIR) for TEAE During the Entire Treatment Period

Dose escalation is allowed for subjects in resected population who meet dose escalation criteria on or after Week 1 visit. To adjust for potentially different exposure times between treatment groups, exposure-adjusted incidence rates will be provided based on ATG-Dynamic treatment group for resected population, and for Creon high dose cohort for non-resected population.

The exposure-adjusted incidence rate (EAIR) for a treatment group is defined as the number of subjects with a particular TEAE under that treatment group divided by the total exposure-time to that treatment group among subjects who had received that treatment. More specifically,

$$EAIR_i = \frac{n_i}{T_i} = {}^{n_i}/_{\sum t_{ij}},$$

where,

i = high dose, low dose;

j = 1, number of subjects who received treatment *i,*

n_i : the number of subjects with the event when subject is under treatment *i,*

t_{ij} : subject *j's* total exposure under treatment *i*, and

T_i : the total exposure time for treatment *i.*

For subjects in resected population, to determine whether subject has the event under treatment *i*, ATG-dynamic group will be used. Namely, the treatment group will be determined based on the drug dispensed at prior study visit before the event occur. To calculate the total exposure time under treatment *i* for a subject, the drug dispensed at each dispensing visit will be considered, the total exposure time under high dose and/or

low dose will be calculated for each subject. E.g., if a subject has Day 1 dispensing = low dose, and Week 1 and subsequent visits dispensing = high dose, then for this subject:

- Low dose exposure time for this subject = date of Week 1 visit – date of Day
- High dose exposure time for this subject = last date of study drug – date of Week 1 visit +1.

Specifically, EAIR for TEAE during the entire treatment period will be summarized by treatment group as described below:

1. EAIR of TEAEs in descending order of overall incidence frequency by MedDRA PT in the entire treatment period
2. EAIR of serious TEAEs in descending order of overall incidence frequency by MedDRA PT in the entire treatment period
3. EAIR with drug-related (i.e., with reasonable possibility to be related to study drug) TEAEs by primary MedDRA SOC and PT
4. EAIR with drug-related (i.e., with reasonable possibility to be related to study drug) serious TEAEs by primary MedDRA SOC and PT

10.2.1.3 Incidence Rate of TEAE Leading to Study Drug Discontinuation During the Entire Treatment Period

A summary of the number and percentage of subjects with TEAEs leading to discontinuation of study drug by primary MedDRA SOC and PT will be provided by treatment group (ATG-All dispensing) for resected population, and for high dose cohort in non-resected populations.

10.2.2 Listing of AEs

The following additional listings will be prepared. Both ATG-Day 1 treatment group and ATG-Dynamic treatment group prior to AE start date will be included in the listing.

- List of all TEAEs by resection cohort, ATG-Day 1 treatment group and subject ID
- Listing of all serious TEAEs by resection cohort, ATG-Day 1 treatment group and subject ID
- Listing of all TEAEs that led to discontinuation of study drug by resection cohort, ATG-Day 1 treatment group and subject ID
- Listing of all fatal TEAEs
- Listing of all AEs in the safety follow-up period, by resection cohort, ATG-Day 1 treatment group and subject ID
- Listing of all deaths by resection cohort, ATG-Day 1 treatment group and subject ID
- List of subject numbers associated with each PT for all AEs assessed by the investigator as having a reasonable possibility of being related to study drug by resection cohort, ATG-Day 1 treatment group.

10.3 Analysis of Laboratory Data

Laboratory test variables as well as their statistical analysis methods including hematology, chemistry, urinalysis, and additional test variables are specified in Table 4. The analyses will be performed in both the resected and non-resected population using the population and treatment groups as described in Table 1 in Section 4.2.

Table 4. Laboratory Variable and Corresponding Statistical Analyses

Laboratory Test Variables	
Hematology	Hematocrit
	Hemoglobin
	Red blood cell (RBC) count
	White blood cell (WBC) count
	Neutrophils
	Bands
	Lymphocytes
	Monocytes
	Basophils
	Eosinophils
	Platelet count (estimate not acceptable)
Urinalysis	Specific gravity
	Ketones
	pH
	Protein
	Blood
	Glucose
Clinical Chemistry	Blood urea nitrogen (BUN)
	Creatinine
	Total bilirubin
	Pre-albumin
	Albumin
	Alanine transaminase (ALT)
	Aspartate transaminase (AST)
	Alkaline phosphatase
	Sodium
	Potassium
	Calcium

Table 4. Laboratory Variable and Corresponding Statistical Analyses (Continued)

Laboratory Test Variables	
Clinical Chemistry (continued)	Inorganic phosphorus
	Uric acid
	Cholesterol
	Total protein
	Glucose
	Triglycerides
	Bicarbonate/CO2
	Chloride
Other Tests	Nutritional Biomarkers

For all the laboratory parameters, the mean change from baseline to Week 13 visit (the final post-baseline) will be summarized with descriptive statistics.

Where it is applicable to categorize a laboratory assessment by Normal, High, or Low according to the normal range provided by the central laboratory, changes in laboratory parameters will be tabulated using shift tables categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline to the minimum and maximum value during treatment will be created by the analysis treatment groups described above.

10.4 Analysis of Vital Signs and Weights

The mean change from baseline to Week 13/EOT visit in vital signs, will be summarized for both resected and non-resected population. Vital sign variables include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature.

11.0 Interim Analyses

No Interim analysis is planned.

12.0 Overall Type-I Error Control

The primary endpoint will be tested for each treatment group (high dose, low dose) in resected population separately at 2-sided alpha level of 0.05. Multiplicity adjustment is not planned for the primary endpoint analysis, as well not planned for any secondary endpoint analysis, as this study is not intent for registrational purpose or drug label enhancement.

13.0 Version History

Table 5. SAP Version History Summary

Version	Date	Summary
1.0	13 December 2020	Original version

14.0 References

1. Christopher HN, Mukherjee S, Bridgewater J,et al. Health-Related Quality of Life in SCALOP, a Randomized Phase 2 Trial Comparing Chemoradiation Therapy Regimens in Locally Advanced Pancreatic Cancer. Int J Radit Oncol Biol Phy. 2015;93(4):810-18.
2. MedDRA – Medical Dictionary for Regulated Activities. International Federation of Pharmaceutical Manufacturers Associations (IFPMA), c/o TRW, VAR1/8A/MSSO, 12011 Sunset Hills Road, Reston, VA 20190-3285, USA, Version 8.1.
3. Kim MK, Kim SB, Ahn JH, et al. Gemcitabine Single or Combination Chemotherapy in Post Anthracycline and Taxane Salvage Treatment of Metastatic Breast Cancer: Retrospective Analysis of 124 Patients. Cancer Res Treat. 2006;38(4):206-13.
4. https://www.cancercareontario.ca/sites/ccocancercare/files/gemcitabine.pdf

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. Quality of Life (QoL) (EORTC QLQ-C30 and QLQ PAN 26)

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.

Thus, a **high raw score for a functional scale** represents a *high / healthy level of functioning*, a **high score for the global health status / QoL** represents a *high QoL*, but a **high score for a symptom scale / item** represents a *high level of symptomatology / problems.*

The principle for scoring these scales is the same in all cases:

- To estimate the average of the items that contribute to the scale; this is the raw score.
- To use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

In practical terms, if items I_1, I_2, In are included in a scale, the procedure is as follows.

Raw Score

We calculate the raw score as follows:

Raw Score = RS = *(I1 + I2 + ... + In)/n*

Linear Transformation

Then linear transformation is applied to 0-100 to obtain the score S.

Functional Scales:

$$S = \left\{\frac{RS - 1}{range}\right\} * 100$$

Symptom Scales / items:

$$S = \left\{1 - \frac{RS - 1}{range}\right\} * 100$$

Global health status / QoL:

$$S = \left\{\frac{RS - 1}{range}\right\} * 100$$

Range is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6.

Table 6. Scoring the QLQ-C30

	Scale	Number of items	Item Range	Version 3.0 Item numbers
Global health status / QoL				
Global health status / QoL	QL2	2	6	29,30
Functional Scales				
Physical Functioning	PF2	5	3	1 to 5
Role Functioning	RF2	2	3	6,7
Emotional Functioning	EF	4	3	21 to 24
Cognitive Functioning	CF	2	3	20,25
Social Functioning	SF	2	3	26,27
Symptom Scales / items				
Fatigue	FA	3	3	10,12,18
Nausea and vomiting	NV	2	3	14,15
Pain	PA	2	3	9,19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhea	DI	1	3	17
Financial Difficulties	FI	1	3	28

QLQ-PAN-26, the pancreatic cancer module, is designed for patients at all disease stages undergoing surgical resection, palliative surgical intervention, endoscopic palliation or palliative chemotherapy (Fitzsimmons *et al*., 1999a,b). The module comprises 26 questions hypothesized as 17 scales and single items specifically related to pancreatic disease symptoms, treatment side-effects, and emotional issues. The scores for QLQ-PAN-26 are calculated in the same way as QLQ-C30.

Score after Linear transformation for each scale:

$$S = \left\{\frac{RS - 1}{range}\right\} * 100$$

where, RS is the Raw Score as described above.

A high score will represent a high level of disease symptoms/problems. The QLQ-PAN-26 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. All items are scored 1 to 4, giving *range* = 3.

Table 7. Scoring the QLQ-PAN-26

	Scale	Number of items	Item Range	Item numbers
Pancreatic Pain	PP	4	3	31,33 to 35
Bloating	BO	1	3	32
Gastrointestinal	GA	2	3	36,37
Taste Loss	TL	1	3	38
Indigestion	IN	1	3	39
Flatulence	FL	1	3	40
Weight	WE	1	3	41
Weak Limbs	WL	1	3	42
Dry Mouth	DM	1	3	43
Jaundice	JA	2	3	44,45
Altered Bowel Habit	AB	2	3	46,47
Poor Body Image	PB	2	3	48,49
Side Effects of Treatment	SI	1	3	50
Future Health Concern	FH	1	3	51
Forward Planning limited	FP	1	3	52
Satisfaction with Health Care	SA	2	3	53,54
Sexual dissatisfaction	SX	2	3	55,56

Appendix C. Missing Data Imputation of Quality of Life (QoL) (EORTC QLQ-C30 and QLQ PAN 26

If 50% or less are unanswered for each functioning, assume that the missing items have values equal to the average of those items which are present for that functioning. The missing items are simply ignored when making the calculations. For example, if a functioning (i^{th} functioning with scores Q_{ij} to the j^{th} question) has range 4 and one of the item (I_{i3}) is missing. Then, following the rule, the raw score for that function will be calculated as:

$$\text{Raw score } (RS) = (I_{11} + I_{12} + I_{14})/3$$

$$\text{Functioning Scale Score (S)} = \left\{1 - \frac{RS - 1}{3}\right\} * 100$$

However, if more than 50% of the questions are unanswered, the score for that functioning will be left missing. The single item measures, if missing, cannot be imputed as well.

Appendix D. Questions from the EPI Questionnaire Considered for Dose Modification

Exocrine Pancreatic Insufficiency (EPI) Symptom Questionnaire

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

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

   ☐**None**

   ☐**Mild**

   ☐**Moderate**

   ☐**Severe**

   ☐**Very Severe**

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

   ☐**None**

   ☐**Mild**

   ☐**Moderate**

   ☐**Severe**

   ☐**Very Severe**

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

   ☐**None**

   ☐**Mild**

   ☐**Moderate**

☐**Severe**

☐**Very Severe**