Study Title:	A Randomized, Parallel Group Study to Evaluate the Safety, Pharmacokinetics, and Dose Response of Paltusotine Treatment in Subjects with Carcinoid Syndrome
Protocol Number:	CRN00808-11
Investigational Product:	Paltusotine
Product Phase:	2
Sponsor:	Crinetics Pharmaceuticals, Inc. 6055 Lusk Blvd San Diego, CA 92121
Statistical Analysis Plan Date:	19 January 2024
Statistical Analysis Plan Version:	V1.0

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SAP Approval

Authored and approved by:

See last page for electronic signature manifestation

[redacted] Biometrics
Crinetics Pharmaceuticals

Reviewed and approved by:

See last page for electronic signature manifestation

Signature & Date
[redacted] Biometrics
Crinetics Pharmaceuticals

See last page for electronic signature manifestation

Signature & Date
[redacted]
Crinetics Pharmaceuticals

Revisions to the Statistical Analysis Plan described herein must be approved through a formal written amendment except for minor editorial changes to tables, figures, or listing shells, and any necessary textual clarifications for programmers that do not affect the stated analysis variables, study endpoints, or statistical methods.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE(s)	Adverse Event(s)
[redacted]	[redacted]
ATC	Anatomical Therapeutic Chemical
BLQ	below the limit of quantification
BMI	body mass index
BM	bowel movement
C	Celsius
CI(s)	confidence interval(s)
COVID-19	coronavirus disease 2019
CRF(s)	case report form(s)
CS	Carcinoid Syndrome
CSR	clinical study report
CV	coefficient of variance
DMC	data monitoring committee
EDC	electronic data capture
ECG	electrocardiogram
EOR	End of Randomized Treatment Phase
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ-GI.NET21	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire - Gastrointestinal Neuroendocrine Tumor Module
EOS	End of Study
EQ VAS	EQ Visual Analogue Scale
EQ-5D-5L	EQ-5-Dimension 5-Level
FACT-CSI	Functional Assessment of Cancer Therapy – Carcinoid Syndrome Symptom Index
5-HIAA	5-hydroxyindolacetic acid
ICH	International Council on Harmonisation
INR	International normalized ratio
IRT	Interactive Response Technology
IWRS	Interactive Web-based Randomization System
kg	kilograms
MedDRA	Medical Dictionary for Regulatory Activities
max	maximum
mg	milligram

Abbreviation	Definition
AE(s)	Adverse Event(s)
min	minimum
n	number of observations
NET	neuroendocrine tumor
NRS	numeric rating scale
OLE	Open-label Extension
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Status
PK	pharmacokinetics
PKS	pharmacokinetic set
PT	preferred term
QD	once a day
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula
RTP	Randomized Treatment Phase
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System (SAS® Institute Inc., Cary, NC)
SD	standard deviation
SI	International System of Units
SOC	system organ class
TEAE(s)	treatment-emergent adverse event(s)
TLF	tables, figures, and listings
ULN	upper limit normal
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods to be implemented for the analyses of Study CRN00808-11 (protocol version v6.0, dated 20 NOV 2023). The purpose of SAP is to provide details on analysis populations, variable derivation, missing data handling, as well as details on statistical methods to analyze safety and efficacy data. If there are any deviations from protocol planned analyses that are documented in protocol Section 8, the SAP takes precedence. Descriptive PK results will be presented.

The SAP will be finalized prior to the study database lock. Any deviations from this SAP will be documented in the clinical study report (CSR).

This SAP is written with consideration of the recommendations outlined in the International Council on Harmonisation (ICH) E9[1], ICH E9 (R1)[2] guidelines, and ICH E3[3].

2. STUDY DESIGN

This is a Phase 2, randomized, open-label, parallel-group, multi-center study designed to evaluate the safety, pharmacokinetic, and dose response of paltusotine in participants with carcinoid syndrome.

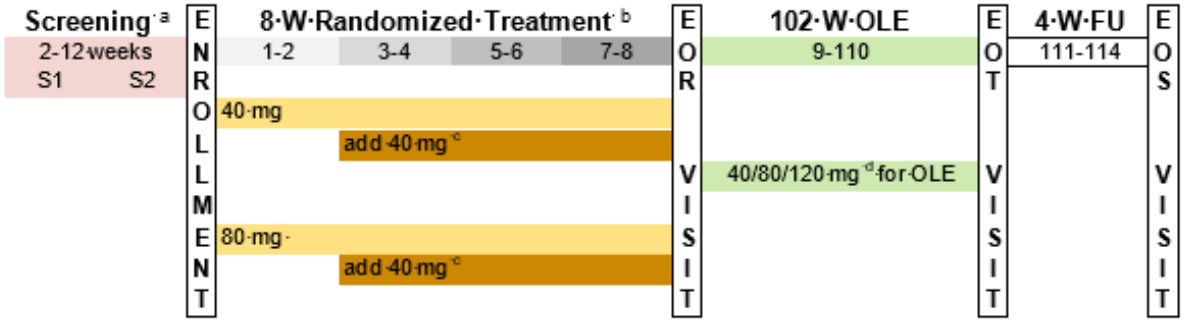
2.1. OVERALL STUDY DESIGN

The study includes a Screening Period of up to 12 weeks. After completion of Screening, participants will be randomly assigned to 40 mg QD or 80 mg QD paltusotine open-label dose groups for 8 weeks in a 1:1 ratio, referred to as the randomized treatment phase (RTP). A dose up-titration by 40 mg QD is an option based on symptomatology during the first 4 weeks of the RTP. Participants completing the 8-week RTP may begin the Open Label Extension (OLE) Phase of the study, in which participants will receive paltusotine for 102 weeks.

For all participants, there will be a Safety Follow-up 4-weeks after the last dose of paltusotine. Participants who participate in the RTP only will complete the study in up to 12 weeks. Participants who continue in the OLE Phase will complete the study in up to 110 weeks or 28 months.

The study design is summarized and presented in Figure 1 below. Refer to protocol Section 1.2 (Schedule of Activities) for the schedule of assessments.

Figure 1: Study Design



EOR = End of Randomized Treatment; EOS = End of Study; EOT = End of Treatment; OLE = Open-label Extension; w = week; FU = follow-up;
Note: An EOS visit will be 28 days after last dose of study drug.
[a] S1, S2 are Screening Visits 1 and 2, graph is not proportional to duration; last injection of lanreotide or octreotide long-acting release and the expected visit S2 is not longer than the usual interval between injections for the participant.
[b] It is anticipated that participants will complete the 8 weeks of RTP. Participants who complete the RTP, and for whom the Investigator recommends continuation of treatment on paltusotine, may be eligible to participate in the OLE Phase.
[c] If participants have recurrent carcinoid symptoms that require short-acting octreotide, the dose will be up-titrated once by 40 mg of paltusotine QD at the Day 14 or Day 28 (Section 4.1 of the protocol).
[d] Dose of paltusotine during OLE Phase is determined by Investigator based on the frequency of rescue treatment and of study drug tolerability and will start on Day 56 (Section 4.1.3 of the protocol).

2.2. Symptom Eligibility

Participant symptom qualifying eligibilities are based on the history use of somatostatin receptor ligand (SRL) treatment in the past 12 weeks and the frequency of bowel movement and/or flushing episodes as shown below.

Symptom Qualifying Eligibility Criteria	**Not currently treated with SRL agonists**	**SRL Treated Symptom Controlled**
BM Criteria Only	Average of ≥4 BM/day over the period of 2 weeks between S1 and S2	An average increase of ≥1 BM/day during a 7-day period after S2 compared with period between S1 and S2; **AND** An absolute frequency of ≥3 daily BMs, in at least 4 days within the 7-day period after S2
Flushing Episode Criteria Only	>2 flushing episodes/day in at least 2 days over the period of 2 weeks between S1 and S2	An increase in daily average flushing episodes during a 7-day period after S2 compared with period between S1 and S2; **AND** At least 3 flushing episodes on at least 1 day within the 7-day period after S2
Both BM and Flushing Criteria	Both	Both

2.3. Blinding and Randomization Methods

The study is an open label study.

At Baseline/Day 1 visit, qualified participants will be randomized to treatment, using an interactive web response system (IWRS). The randomization number will be recorded in the electronic data capture (EDC) system. A total of 30 participants will be randomized to 40 mg or 80 mg of paltusotine active treatment in 1:1 ratio.

3. STUDY OBJECTIVE(S) AND ENDPOINT(S)

Objectives and Endpoints

Objectives	Endpoints
Safety	
To evaluate the safety and tolerability of paltusotine at 40, 80, and 120 mg QD doses	Incidence of TEAEs, including serious TEAEs and TEAEs leading to discontinuation; change from Baseline to the EOR in safety parameters: clinical laboratory tests, physical exam findings, vital signs, 12lead ECG, and 24-hour continuous cardiac monitoring (only for participants on 120 mg dose)
Pharmacokinetics	
To assess the PK of 40, 80, and 120 mg paltusotine	Steady state trough levels at each dose at EOR
Exploratory Efficacy for Randomized Treatment Phase	
To derive responder rates for the different dose arms	Proportion of clinical responders by dose during the last week of the Randomized Treatment Phase: <u>In participants who meet diarrhea entry criteria only</u>: • Have fewer than 4 mean bowel movements daily • Have a >20% reduction in the mean daily number of bowel movements compared with Baseline <u>In participants who meet flushing entry criteria only:</u> • Have a >30% reduction compared with Baseline in the mean daily number of flushing episodes. <u>In participants who meet both diarrhea and flushing entry criteria:</u> • Have less than 4 mean bowel movements daily • Have a >20% reduction in the mean daily number of bowel movements compared with Baseline • Have any reduction from Baseline in the mean daily number of flushing episodes.
To derive target symptom responder rates for participants in the different dose arms	Proportion of target symptom responders by dose during the last week of the Randomized Treatment Phase: • Participants with at least 20% decline in the number of target symptom episodes compared to Baseline. (Target symptom is the symptom [either BM or flushing] that troubled the participant the most at Baseline.
To evaluate the effect of paltusotine treatment on frequency of BMs/day	Change in mean daily BMs: • From the Baseline Period of Screening to the last week of the Randomized Treatment Phase

Objectives	Endpoints
To evaluate the effect of paltusotine treatment on frequency of flushing episodes/day	Change in mean daily number of flushing episodes: • From the Baseline Period of Screening to the last week of the Randomized Treatment Phase
To evaluate the effect of paltusotine treatment on severity of flushing episodes/day	Change in worst flushing in last 24 hours (using a 0 to 10 NRS): • From the mean Baseline Period of Screening to the mean in the last week of the Randomized Treatment Phase • From the highest score during Baseline Period in Screening to the highest score during the last week of the Randomized Treatment Phase
To evaluate the effect of paltusotine treatment on the frequency of daily target symptom episodes	Change in mean daily target symptom episodes: • From the Baseline Period of Screening to the last week of the Randomized Treatment Phase
To evaluate the effect of paltusotine treatment on biochemical markers of carcinoid syndrome	Change from Baseline to EOR in: • Plasma 5-HIAA • Plasma pancreastatin • Serum chromogranin A • Serum serotonin
To evaluate the effect of paltusotine treatment on the use of protocol defined rescue with short-acting octreotide injections	Change in use of short-acting octreotide: • Change in the proportion of days on short-acting octreotide in Screening, after participant has met entry criteria, to the proportion of days on short-acting octreotide of the last week of the Randomized Treatment Phase • Change in mean daily dose of octreotide in Screening, after participant has met entry criteria to the mean daily dose of short-acting octreotide during the last week of the Randomized Treatment Phase
To evaluate the effect of paltusotine treatment on incontinence	Change in the mean daily fecal incontinence episodes (defined as accidental passing of bowel movements including solid stools, liquid stools, or mucus): • From the Baseline Period of Screening to the last week of the Randomized Treatment Phase
To evaluate the effect of paltusotine treatment on abdominal pain severity	Change in worst abdominal pain in last 24 hours (using a 0 to 10 NRS): • From the mean Baseline Period of Screening to the mean in the last week of the Randomized Treatment Phase • From the highest score during Baseline Period in Screening to the highest score during the last week of the Randomized Treatment Phase
To evaluate the effect of paltusotine treatment on stool consistency	Change in “worst” (highest) stool score in last 24 hours (Bristol scale): • From the mean Baseline Period of Screening to the mean in the last week of the Randomized Treatment Phase • From the highest score during Baseline Period in Screening to the highest score during the last week of the Randomized Treatment Phase

Objectives	Endpoints
To evaluate the effect of paltusotine treatment on health-related quality of life	Change from Baseline to EOR in: • EORTC QLQ-C30 • EORTC QLQ-GI.NET21 scores • EQ-5D-5L • FACT-CSI
To evaluate participant-perceived carcinoid symptom severity and change	Change from Baseline to EOR in PGI-S (Patient Global Impression of Status) PGI-C (Patient Global Impression of Change) at EOR
To evaluate treatment preference	Change in Treatment preference from Baseline (pretrial treatment) to EOR
To evaluate the effect of paltusotine treatment on urgency to defecate	Change in mean daily urgency episodes (defined as BMs that make participants rush to the bathroom): From the Baseline Period of Screening to the last week of the Randomized Treatment Phase
Open-label Extension (OLE) Phase	
To evaluate the safety and tolerability of paltusotine	Incidence of TEAEs, including serious TEAEs and TEAEs leading to discontinuation; change from EOR to EOT in safety parameters: clinical laboratory tests, physical exam findings, vital signs, and 12-lead ECG
Pharmacokinetics	
To assess the PK of 40, 80, and 120 mg paltusotine	Steady state trough levels at each dose at EOT
Exploratory Efficacy for OLE Phase	
To evaluate the effect of paltusotine on tumor progression	Incidence of NET progression at EOT using 6-month interval imaging assessment while on paltusotine
To evaluate the persistence of effect of paltusotine	Proportion of clinical responders during the last week of the OLE phase by dose: <u>In participants who meet diarrhea entry criteria only</u>: • Have less than four mean bowel movements daily, and have a >20% reduction in the mean daily number of bowel movements compared with Baseline <u>In participants who meet flushing entry criteria only:</u> • Have a >30% reduction compared with Baseline in the mean daily number of flushing episodes <u>In participant who meet both diarrhea and flushing entry criteria:</u> • Have less than four mean bowel movements daily, and • have a >20% reduction in the mean daily number of bowel movements compared with Baseline, and • have any reduction from Baseline in the mean daily number of flushing episodes
	Proportion of target symptom responders during the last week of the OLE phase by dose
	Change in the mean from mean of the last week prior to Baseline to the mean of the last week of participation in the OLE Phase in daily BM frequency

Objectives	Endpoints
	Change from the mean of the last week prior to Baseline to the mean of the last week of participation in the OLE Phase in daily flushing episode frequency
	Change from Baseline to EOT in biomarkers of carcinoid syndrome (listed in Randomized Treatment Phase)
	Mean change from the last week prior to Baseline to the last week of participation in the OLE Phase in daily target symptom frequency
	• Change from Baseline to EOT • EORTC QLQ-C30 • EORTC QLQ-GI.NET21 scores • EQ-5D-5L • FACT-CSI
To evaluate the effect of paltusotine treatment on the use of protocol defined rescue with short-acting octreotide injections	Change in number of days treated with short-acting octreotide: • Change in the days on short-acting octreotide in last week prior to Baseline compared to the last week of EOT • Change in mean daily dose of octreotide during the last week prior to Baseline to the last week of EOT
To evaluate the effect of paltusotine treatment on incontinence	Change in mean daily fecal incontinence episodes (defined as accidental passing of bowel movements including solid stools, liquid stools, or mucus): • From the last week prior to Baseline to the last week prior to EOT
To evaluate the effect of paltusotine treatment on abdominal pain severity	Change in worst abdominal pain in the last 24 hours (using a 0 to 10 NRS): • From the mean in the last week prior to Baseline to the last week of OLE • From the highest score during last week prior to Baseline to the last week of OLE
To evaluate the effect of paltusotine treatment on urgency to defecate	Change in mean daily urgency episodes (defined as BMs that make participants rush to the bathroom): • From the last week prior to Baseline to the last week prior to EOT

BM=bowel movement; ECG=electrocardiogram; EOR=end of randomized Treatment Phase; EOS=End of Study; EOT=end of treatment; OLE=Open-Label Extension; PK=pharmacokinetic; TEAE=treatment-emergent adverse events; QD=once a day; EORTC QLQ-C30=EORTC Quality of Life questionnaire; EORTC QLQ-GI.NET21=EORTC Quality of Life questionnaire in GI NET; EQ-5D-5L=EuroQoL-5 Dimensions 5-Level; FACT-CSI=Functional Assessment of Cancer Therapy – Carcinoid Syndrome Symptom Index; 5-HIAA=5-hydroxyindoleacetic acid; NET=neuroendocrine tumors; NRS=numeric rating scale; PGI-C=Patient Global Impression - Change; PGI-S=Patient Global Impression of Status.

4. SAMPLE SIZE CONSIDERATIONS

Formal sample size calculations were not performed due to the exploratory nature of the study design. A total of 30 participants are considered suitable to assess the study objectives for safety, pharmacokinetics, and dose response in participants with carcinoid syndrome.

5. INTERIM ANALYSIS

No formal interim analysis is planned for this study. Periodic review of the data may be conducted at different study milestones.

6. SAFETY MONITORING COMMITTEE

A Safety Monitoring Committee (SMC), comprising independent subject matter experts, will be established to assess the risk versus benefit of the interventions during the trial. The SMC will meet at intervals as specified in the SMC charter and may convene for ad hoc meetings if there are immediate safety concerns identified during the study.

7. DEFINITIONS

7.1. Baseline

In general, Baseline is defined as the last non-missing assessment on or prior to the start of first dose of paltusotine (Day 1), with the following exceptions:

Baseline Period is defined as the last 7 consecutive days prior to Study Day 1 (first dose of paltusotine) without recorded short acting octreotide use from Diary for the following efficacy endpoints:

- Clinical responder and target symptom responder.
- Parameters that related to carcinoid syndrome symptoms (mean daily bowel movements, mean daily flushing episodes, mean daily fecal incontinence episodes, worst flushing episode in the last 24 hours, worst abdominal pain in the last 24 hours, "worst" stool score in the last 24 hours, and mean daily urgency episodes).

Baseline is the mean value of parameters that related to carcinoid syndrome symptoms during the Baseline Period. [redacted]

For efficacy endpoint of duration of short-acting octreotide use, Baseline is defined as the days taking short-acting octreotide between the date after participant has met symptom entry criteria (S2 for naïve or previously SRL-treated participants, and 7 days after S2 for SRL washout participants) to the day prior to the first dose of paltusotine (Study Day 1). [redacted]

Unless otherwise specified, missing data for baseline will not be imputed.

7.2. Study Day

If the visit date is on or after the first dose of paltusotine:

Study day = visit date – date of first dose of paltusotine + 1

If the visit date is prior the first dose of paltusotine:

Study day = visit date – date of first dose of paltusotine

8. ANALYSIS POPULATIONS

8.1. Safety Set

The Safety Set consists of all randomized participants who received at least 1 dose of paltusotine. This set will be used for all safety and exploratory efficacy analyses for RTP phase. Participants will be analyzed by the randomized dose group.

8.2. Pharmacokinetic Set

The pharmacokinetic (PK) set includes all participants who have received any amount of study drug and have at least one valid plasma concentration result. This set will be used for all analyses of paltusotine, octreotide, or lanreotide plasma concentrations collected during the study.

8.3. OLE Set

The OLE Set consists of all randomized participants who completed RTP phase of the study, eligible to participate OLE phase, and receive at least 1 dose of paltusotine in OLE phase. This set will be used for all safety and exploratory efficacy analyses in OLE period.

9. DATA CONSIDERATIONS

9.1. Handling of Missing and Incomplete Data

In general, missing data will not be imputed unless otherwise specified.

In general, only the observed data (not imputed data) will be presented in listings.

9.1.1. Missing Date for Adverse Events and Concomitant Medications

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications.

Missing Start Dates

- If the day is unknown, then:
  - If the month and year match the first dose of paltusotine start date month and year in this study, then impute the day of the first dose date.
  - Otherwise, assign the first day of the month.
- If the month is unknown, then:
  - If the year matches the year of the first dose of paltusotine date in this study, then impute the month of the first dose date in this study.
  - Otherwise, assign 'January'
- If the year is unknown, then the date will not be imputed and will remain missing.

If the imputed date is earlier than the birth date, then the birth date will be used. If the imputed start date is later than the end date, then the start date will be set as the same date as the end date.

9.1.2. Missing Efficacy Endpoints

Missing efficacy endpoint will not be imputed, unless otherwise specified.

9.2. Visit Time Windows

Data will be summarized based on nominal visit indications except for data captured at early termination and unscheduled visits. Data from early termination and unscheduled visits will be summarized based on mapped visit values. The analysis windows for early termination and unscheduled visits are presented in Table 1. Analysis windows will be similarly computed, using the midpoint method, for variables where data are not scheduled to be collected at every visit per the Schedule of Assessments (Section 1.2 of the protocol).

Table 1: Analysis Windows Mapping for Early Termination and Unscheduled Visits

Scheduled Visit	Target Study Day	Analysis Window (Days)*
Baseline (Day 1)	1	1
Week 2	15	2 to 22
Week 4	29	23 to 36
Week 6	43	37 to 50
Week 8	57	51 to 64
Week 10**	71	65 to 78
Week 12 ***	85	79 to 87
Week 24	169	88 to 211
Week 36	253	212 to 277
Week 48	337	278 to 372
Week 58	406	373 to 420
Week 70	490	421 to 532
Week 82	574	533 to 623
Week 96	672	624 to 723
Week 110	770	724 to 784
Week 114****	798	785 - 812

*Windows are determined by midpoints between visits.
** Week 10 is not required for participants who complete RTP but do not continue to OLE.
***Windows for Week 12 are from Days 79-87 for participants continue to OLE and Days 65-87 for participants exit after RTP. Visit 12 data from participants who complete RTP but not continue to OLE are safety follow-up and will not be mapped to scheduled visit.
**** Windows for Week 114 are safety follow-up and will not be mapped to scheduled visit.
Data collected at early termination and unscheduled visits prior to Study Day 1 are not eligible to be mapped to a scheduled visit, except for those identified as baseline values.
Note: algorithm for ECG windowing of Baseline and Week1/Day1. Baseline: the ECG before the first dose of paltusotine or the ECG closest to Day 1 if multiple ECGs were taken during the screening. Week 1/Day1: ECG after the first dose of paltusotine. All the other windows mapping will be based on table above.
Note: any questionnaire data after the date of early termination will not be included in the analysis.

If an assessment's mapped visit is a visit at which the participant has data from a scheduled visit present, or if no analyses are planned for the assessment at the mapped visit, the data collected at the early termination or unscheduled visit will not be included in summary analyses but will be included in participant listing.

In the event of multiple values from unscheduled or early termination assessments within an analysis window, the value closest to the scheduled visit target study day will be used for analyses. If two values tie as closest to the time point (for example, one value is before and the other value is after the time point), then the later value will be selected. If two measurements on a continuous scale have the same date and time, then the mean of these two values will be used, unless the value is a laboratory retest. In the case of a retest, the retest value will overwrite the original instead of taking an average. Data collected at all visits will be included in the data listings with visit presented as reported by the site.

Events of adverse events (AEs), protocol deviations (PDs), or new concomitant medications occurring on or after the first administration of study drug and prior to the first administration of study drug in the OLE Phase (Week 8 Visit) will be summarized in RTP phase. Those events occurring on or after the first administration of study drug in the OLE Phase will be considered as those in the OLE Phase. If time of the events is available, time will be included for the determination. If it cannot be determined whether the events occurred in RTP or OLE Phase, then such events will be counted as events or medications in RTP Phase.

9.3. Examination of Subgroup

Participants are enrolled with different symptom criteria based on SRL status (not currently treated with SRL therapy for at least 12 weeks prior to screening and are actively symptomatic [naïve or previously treated] and SRL-treated symptom controlled [SRL Washout]). SRL status will be used for the subgroup analysis of the baseline demographic and disease characteristic information, exploratory efficacy endpoints and TEAEs.

[redacted]

10. STATISTICAL METHODS OF ANALYSES

10.1. General Principles

All statistical processing will be performed using SAS® software version 9.4 or higher unless otherwise stated.

Where applicable confidence intervals will be 2-sided 90% CIs due to exploratory nature, unless stated otherwise.

No formal hypothesis testing is planned for this study. No multiplicity adjustments or adjustments for multiple comparisons will be applied.

[redacted]

Descriptive statistics will be used to provide an overview of the PK, efficacy and safety results. For categorical parameters, the number and percentage of participants in each category will be presented. For continuous parameters, descriptive summary will include n (number of participants), mean, standard deviation (SD), standard error (SE), median, minimum, and maximum.

The precision of original measurements will be maintained in listings and used in calculations. Derived values greater than three decimal places will be rounded to three decimal places for display in listings.

10.2. Disposition and Participant Accountability

Participant disposition will be summarized. The number and percentage of screen-failure participants (ie, participants screened but not randomized) and the associated reasons for screen

failure will be tabulated for all screened failed participants. For summary table, the most screen fail recent reason will be used if a participant screen failed multiple times.

The number and percentage of participants will be summarized by randomized dose group and in overall as:

- Randomized
- Randomized but not treated, with reasons
- Safety Set
- Discontinued during RTP (with reasons for discontinuation)
- Completed RTP
- Not continue to OLE, with reason
- OLE Set
- Discontinued during OLE, with reasons
- Completed OLE

By-participant data listings for all the above study disposition data including study completion and any reasons for premature study withdrawal will be presented. Also, by-subject listings of informed consent, re-consent, and eligibility criteria details will be presented. For participants who discontinued treatment, the detailed reason will be presented in a listing.

10.3. Protocol Deviations

Protocol deviations (PDs) are defined as any failure to comply with the study protocol as approved by the Institutional Review Board/Independent Ethics Committee, whether planned or unplanned. Important protocol deviations are a subset of all protocol deviations, which may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. Important protocol deviations are described in the Protocol Deviation Plan for CRN00808-11 which will be finalized prior to database lock.

All PDs will be presented separately for RTP phase and for OLE phase.

Important protocol deviations will be summarized by deviation category and randomized dose group and overall. PDs specific to coronavirus disease 2019 (COVID-19) will also be summarized in the same manner. A high-level summary will show any important PD and any COVID-19 PD by randomized dose group.

All PDs including important, non-important, and COVID-19 PDs will be presented in a by-participant data listing.

10.4. Demographic and Baseline Characteristics

All Baseline summaries will be presented on Safety Set and OLE Set. The following demographic variables will be summarized by randomized dose group and overall.

- Age at informed consent: as continuous and categorical (<65, ≥65 years) variable

- Sex
- Race
- Ethnicity
- Geographic region
- Weight (kg)
- Height (cm)
- BMI (kg/m^2): as continuous and categorical (<30, ≥ 30 kg/m^2) variable
- Baseline HbA1c (%): as continuous and categorical ($\geq 6.0\%$ vs $< 6.0\%$) variable
- Baseline Vital signs: diastolic and systolic blood pressure (mmHg), pulse rate (beats/min), and respiratory rate (breaths/min)
- Mean daily bowel movement at Baseline Period
- Mean daily flushing episodes at Baseline Period
- Entry criteria (diarrhea criteria only; flushing criteria only; diarrhea and flushing criteria, refer Section 2.1 for criteria detail)
- Baseline target symptom

All demographic and baseline characteristics data will be presented in by-participant data listings.

10.5. History of Carcinoid Syndrome

The following will be summarized by randomized dose group and overall for the Safety Set and OLE Set.

- Duration (months) since diagnosis of carcinoid syndrome
- Screening Group: Not currently on SRLs or Naïve to SRLs vs. SRL-Treated
- History of SRL-therapy (Yes/No)
- WHO Neuroendocrine Neoplasm Classification: NET Grade 1/2
- Tumor confirmation method (CT/MRI)

A by-participant listing of history of carcinoid syndrome will be provided.

10.6. Medical History

Reported medical history terms will be classified based on the MedDRA terminology, version 25.0 or higher. Medical history summarized by system organ class (SOC) and prefer term (PT) will be presented by randomized dose group and in overall for the Safety Set and OLE Set.

10.7. Prior and Concomitant Medication

Concomitant medications will be coded to preferred name and Anatomical Therapeutic Chemical (ATC) classification of ingredients using the WHO Drug Global terminology, Format GLOBALB3, Version March 2022, or newer.

Prior medication is defined as any medication that started before the date of the first dose of paltusotine (medication start date prior to the first dose date).

Pretreatment medication is defined as any medication that started and ended before the date of the first dose of paltusotine.

Concomitant medication is defined as any medication taken on or after the date of the first dose of paltusotine (medication end date on or after first dose date [or ongoing], and medication start date prior or on the last dose date). Any concomitant medications started after the date of the last dose of paltusotine will not be presented in the summary tables but will be included in the participant data listings.

If it cannot be determined whether the medication/treatment was a concomitant medication due to a partial start or stop date or if the medication/treatment is taken on the same date as the first administration of study drug, then it will be counted as a concomitant medication. Dates will not be imputed for by-participant listings.

If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant will be counted only once for the coded drug name or therapeutic class in summary.

Pretreatment, prior and concomitant medications will be summarized by ATC Level 4 and Preferred Name for randomized dose group and overall. Pretreatment and prior medications will be summarized for the Safety Set. Concomitant medications will be summarized for both the RTP phase and OLE Phase.

10.8. Exploratory Efficacy Analysis

[redacted]

10.8.1. General Analysis Methods

Descriptive statistics will be used to summary all exploratory efficacy endpoints by scheduled (assessment) visit.

The change from baseline will be considered as missing and not be imputed if either baseline or post-baseline results are missing.

10.8.2. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints for the RTP and OLE are as follows:

- Changes from Baseline to Week 8 (the last week of RTP, ie, 7 days prior Week 8 Visit) and to Week 110 (ie, 7 days prior Week 110 Visit) in
  - mean daily BMs

  - mean daily number of flushing episodes
  - mean daily fecal incontinence episodes
  - mean daily worst flushing score
  - highest of the worst flushing score
  - mean worst abdominal pain score in the last 24 hours
  - highest worst abdominal pain score
  - mean worst stool score in last 24 hours (Bristol scale)
  - highest worst stool score in last 24 hours (Bristol scale)
  - mean daily urgency episodes
  - proportion of days on short-acting octreotide
- Proportion of clinical responders by dose at Week 8 and Week 110
- Proportion of target symptom responders by dose at Week 8 and Week 110
- Change in biomarkers of Carcinoid Syndrome (plasma 5-HIAA, plasma pancreastatin, serum chromogranin A, and serum serotonin) from baseline to Week 8 and Week 110
- Change of following QoL measurements from baseline to Week 8 and to Week 110:
  - EORTC QLQ-C30
  - EORTC QLQ-GI.NET21
  - EQ-5D-5L
  - FACT-CSI
  - PGI-S
- Treatment preference at Week 8

10.8.3. Exploratory Efficacy Endpoints Related to CS Symptoms

All efficacy endpoints will be presented in by-participant data listings. Summary tables will include descriptive statistics by randomized dose group and overall. The data may be graphicly presented by randomized dose and scheduled visit.

[redacted]

The analysis of RTP phase and OLE phase will be performed separately.

10.8.3.1. Estimands

The following estimands will be applied to the summary of the efficacy endpoints related to Carcinoid Syndrome symptoms.

10.8.3.1.1. Estimand 1: Responder at Week 8 and Week 110

The Estimand 1 is to be used to analyze the binary responder endpoints at Week 8 and Week 110. It includes the following 4 attributes:

Population: Safety Set and OLE Set

Variable: proportion of participants as responder at Week 8 and Week 110

Inter-current event(s): Participants who receive prohibited medication or early withdrawal prior to scheduled Week 8 visit will be considered non-responders for RTP phase. Participant who consented to participate OLE receive prohibited medication or early withdrawal on or after Week 8 visit and prior to Week 110 will be considered non-responders for OLE phase.

Population-level summary: The number and proportion of responders will be presented by randomized dose groups and overall.

10.8.3.1.2. Estimand 2: Change from Baseline to Scheduled Visits

The Estimand 2 is to be used to analyze continuous efficacy endpoints. It includes the following 4 attributes:

Population: Safety Set and OLE Set;

Variable: Change from Baseline Period to each scheduled post baseline visits, including Week 8 (last week of RTP, 7 days prior to Week 8 visit) and Week 110 (last week of OLE, 7 days prior to Week 110 visit).

Inter-current event(s): all measurements *after* the participants receive prohibited medication post randomization and within the treatment period will be treated as missing and not be used in the analysis. Missing data will not be imputed.

Population-level summary: Descriptive statistics will be provided for change from Baseline Period by randomized dose groups and overall.

[redacted]

10.8.3.2. Change from Baseline in Mean Daily BMs/Flushing Episodes

10.8.3.2.1. Change from Baseline Period in Mean Daily Bowel Movements

The mean daily BMs for Baseline Period is defined as the sum of the non-missing BMs recorded in the symptoms diary for each day of the Baseline Period divided by the corresponding number of days with non-missing results.

The mean daily BMs for each scheduled visit is the sum of the non-missing BMs results for 7 days prior to the date of scheduled visit divided by the corresponding number of days with non-missing results.

Change and percent change in mean daily BMs from Baseline Period to the week of each scheduled visit (including Week 8 and Week 110) will be summarized using Estimand 2 as described in Section 10.8.3.1.2. The percent change from baseline will also be summarized as proportion of participants with >20%, >30%, and >40% reduction from baseline for each visit.

10.8.3.2.2. Change from Baseline Period in Mean Daily Flushing Episodes

The same analysis will be performed as described above in Section 10.8.3.2.1 for the number of flushing episodes.

10.8.3.2.3. Clinical Responder at Week 8 and Week 110

The number and proportion of clinical responders at Week 8 and at Week 110 will be summarized separately using Estimand 1 as described in Section 10.8.3.1.1.

Clinical Responders are defined as follows for participants with different entry criteria (refer Section 2.2 for detail) for both Week 8 (7 days prior to Week 8 visit) and Week 110 (7 days prior to Week 110 visit):

In participants who meet diarrhea entry criteria only:

- Have less than four mean BMs daily, and
- Have a > 20% reduction in the mean daily BMs compared with baseline period.

In participants who meet flushing entry criteria only:

- Have a > 30% reduction compared with baseline period in the mean daily number of flushing episodes.

In participants who meet both diarrhea and flushing entry criteria:

- Have less than four mean BMs daily; and
- Have a > 20% reduction in mean daily BMs compared with baseline period; and
- Have any reduction from baseline period in the mean daily number of flushing episodes.

Non-response is defined as failing to meet at least one criterion listed above per entry criteria group. [redacted]

[redacted]

For calculating the mean daily BMs and mean daily flushing episodes see Sections 10.8.3.2.1 and 10.8.3.2.2.

10.8.3.2.4. [redacted]

[redacted]

10.8.3.3. Change from Baseline Period in Worst Flushing Score

The WORST flushing score in the last 24 hours is recorded using numeric rating scale (NRS) with a range from 0 to 10, with 0 as none and 10 as extreme.

10.8.3.3.1. Mean Worst Flushing Score

The mean daily worst flushing score for Baseline Period is defined as the sum of the non-missing worst flushing score recorded in the symptoms diary for each day of the Baseline Period divided by the corresponding number of days with non-missing results.

The mean daily worst flushing score for each scheduled visit is the sum of the non-missing worst flushing score for the 7 days prior to each scheduled visit divided by the corresponding number of days with non-missing results.

10.8.3.3.2. Highest of Worst Flushing Score

The HIGHEST of the Worst flushing score during Baseline Period is the maximum NRS across the week prior to first dose of paltusotine (Day 1).

The HIGHEST of the Worst score for a scheduled visit is the maximum NRS across 7 days prior to the scheduled visit.

[redacted]

10.8.3.3.3. Changes from Baseline Period on Worst Flushing Score

Change of worst flushing score from Baseline Period to each scheduled visit will be analyzed using Estimand 2 as described in Section 10.8.3.1.2 for

Mean daily worst flushing score

Highest of the worst flushing score

10.8.3.4. Change from Baseline Period in Worst Abdominal Pain

The WORST abdominal pain in the last 24 hours is evaluated using numeric rating scale (NRS) with a range from 0 to 10, with 0 as no pain at all and 10 as highest level of pain.

The analysis of change from Baseline will be performed as described in Section 10.8.3.3 for

Mean worst abdominal pain

Highest of the worst abdominal pain

10.8.3.5. Change from Baseline Period in Worst Stool Score

The stool score in the last 24 hours uses the Bristol scale scored as separate hard lumps like nuts (score = 1); sausage shaped but lumpy (score = 2); like a sausage but with cracks on surface (score = 3); like a sausage or snake, smooth and soft (score = 4); soft blobs with clear-cut edges (passes easily) (score = 5); fluffy pieces with ragged edges, a mushy stool (score = 6); watery, no solid pieces (entirely liquid) (score = 7).

The analysis of change from Baseline will be performed as described in Section 10.8.3.3 for

Mean worst stool score

Highest of the worst stool score

10.8.3.6. Change from Baseline Period in Mean Daily Incontinence Episodes

Incontinence episodes are defined as accidental passing of bowel movements including solid stools, liquid stools, or mucus.

Change in mean daily number of incontinence episodes will be summarized as described above in Section 10.8.3.2.1, except that the subgroup analysis by baseline target symptom group will not be performed.

10.8.3.7. Change from Baseline Period in Mean Daily Urgency Episodes

Urgency episodes are defined as bowel movements that make participants rush to the bathroom.

Change in mean daily number of urgency episodes will be summarized as described above in Section 10.8.3.2.1, except that the subgroup analysis by baseline target symptom group will not be performed.

10.8.3.8. Change in the Use of Short-Acting Octreotide

Short-acting octreotide rescue can be used during the study if the participant experiences carcinoid syndrome symptoms that meet protocol criteria for use. The daily use of short-acting octreotide use is recorded in symptom diary.

10.8.3.8.1. Change in Proportion of Days on Short-acting Octreotide

Proportion of days on short-acting octreotide in the Baseline Period (after participant has met symptom entry criteria) is calculated as the number of days on short-acting octreotide during Baseline Period divides by the number of days with non-missing octreotide usage information in Baseline Period.

Proportion of days on short-acting octreotide at each scheduled visit is defined as the number of days on octreotide during last 7 days prior to scheduled visit divided by the number of days with non-missing octreotide usage information.

Change in the proportion of days on short-acting octreotide from the Baseline Period to each scheduled visit (7 days prior to the date of scheduled visit) will be summarized using Estimand 2 (Section 10.8.3.1.2).

10.8.3.8.2. Change in Proportion of Days on Short-acting Octreotide over RTP Period

The use of short-acting Octreotide will also be evaluated for the entire RTP phase.

The change in proportion of days on short-acting octreotide over RTP will be summarized using descriptive statistics appropriate for continuous variables using Estimand 2 as described in Section 10.8.3.1.2.

The proportion of days on octreotide over RTP phase is defined as total number of days on octreotide during the RTP phase divided by total number of days with non-missing octreotide usage information.

10.8.3.9. Target Symptom Responder

Target symptom is the symptom (either bowel movement or flushing) that troubled the participant the most at Baseline. *Target symptom responders at Week 8 and at Week 110* are defined as participants with at least 20% decline in the number of target symptom compared to baseline.

The mean daily BMs and mean daily flushing episodes are defined in Sections 10.8.3.2.1. The analysis of target symptom responder will be analyzed based on Estimand 1 as described in Section 10.8.3.1.1.

Non-response is defined as failing to meet the 20% reduction criteria due to any reason.

[redacted]

The target symptom responder analysis will be performed separately for participant with bowel movement and flushing episodes as baseline target symptom for RTP phase and OLE phase.

[redacted]

10.8.4. [redacted]

10.8.4.1. [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

10.8.4.2. [redacted]

[redacted]

10.8.4.3. [redacted]

[redacted]

[redacted]

10.8.4.4. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.8.4.5. [redacted]

[redacted]

[redacted]

[redacted]

10.8.4.6. [redacted]

[redacted]

10.8.5. Biomarkers Related to Carcinoid Syndrome Symptoms

Biomarkers for Carcinoid Syndrome will be summarized by the dose taken before the samples are taken and visit according to the schedule of assessments using descriptive statistics for continuous variables. At all post-baseline visits, change from baseline will also be summarized using Estimand 2 (Section 10.8.3.1.2, [redacted]) for the following biomarkers:

- Plasma 5-HIAA
- Plasma pancreastatin (non-EU sites only)
- Serum chromogranin A
- Serum serotonin

Biomarker results reported as less than the limit of quantitation (LLOQ) will be presented as "BLQ" in the listings and will be set as 0.5*LLOQ for summaries of concentrations.

The data may be graphicly presented by dose taken before the samples taken and scheduled visit for each biomarker listed.

10.8.6. Health-related Quality of Life (QoL)

The health-related quality of life measures will be summarized by visit according to the schedule of assessments and change from baseline for each post-baseline visits will be summarized as continuous variables using descriptive statistics, by randomized dose group and in overall.

10.8.6.1. EORTC QLQ-C30

The EORTC QLQ-C30 questionnaire is used to assess quality of life in participants with cancer. Each question can be answered on a 1 to 4 scale. It includes 5 functional scales (physical, emotional, social, role, cognitive), eight symptom scales/items (fatigue, pain, nausea/vomiting, constipation, diarrhea, insomnia, dyspnea, appetite loss, and financial difficulties). There are two additional questions for overall health and quality of life, each with 1 to 7 scale. The EORTC QLQ-C30 scales along with the item number, item range, and maximum number of missing values allowed within each scale are shown in Table 2 below.

Table 2: EORTC QLQ-C30 Scales (Version 3.0)

Scale/Domain	Item Range*	Item Numbers in Questionnaire	Max No. of Missing Items
Global health status/Quality of Life			
Global health status/Quality of Life	6	29, 30	1
Functional scales			
Physical function	3	1 – 5	2
Role functioning	3	6, 7	1
Emotional functioning	3	21 – 24	2
Cognitive functioning	3	20, 25	1
Social functioning	3	26, 27	1
Symptom scales/items			
Fatigue	3	10, 12, 18	1
Nausea and vomiting	3	14, 15	1
Pain	3	9, 19	1
Dyspnoea	3	8	0
Insomnia	3	11	0
Appetite loss	3	13	0
Constipation	3	16	0
Diarrhoea	3	17	0
Financial difficulties	3	28	0

* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3. The exceptions are the items contributing to global health status/quality of life, which are 7-point questions with range = 6.

The scoring of the EORTC QLQ-C30 is defined in the EORTC QLQ-C30 Scoring Manual[4]. The raw score for each domain is defined as the mean of the item scores within each domain. If more than 50% of the questions within each domain are missing, then the raw score for that domain is missing and no standardized score will be calculated. A standardized score for each domain, is derived as follows:

Functional scales: Standardized score = {1 - [(raw score – 1)/range]} x 100

Symptom scales /items: Standardized score = [(raw score – 1)/range] x 100

Global health status / QoL: Standardized score = [(raw score – 1)/range] x 100

All standardized scores range from 0 to 100. A high scale score represents a higher response level. Thus, a high 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 standardized scores for each scale and the change from baseline will be summarized by visit according to the schedule of assessments and presented by randomized dose and overall.

10.8.6.2. ORTC QoL - Gastrointestinal Neuroendocrine Carcinoid Module

The EORTC QLQ-GI.NET21 will be used to follow up symptoms from participants with neuroendocrine carcinoids. The questionnaire contains a total of 21 items: 4 single-item assessments relating to muscle and/or bone pain, body image, information, and sexual functioning, together with 17 items organized into 5 scales: endocrine symptoms, gastrointestinal symptoms, treatment-related symptoms, social functioning, and disease-related worries. The questions are divided into the category of 'during the past week' and 'during the past 4 weeks. Each of the questions can be answered on a 1 to 4 scale. Lower scores indicate a better quality of life.

The EORTC QLQ-GI.NET21 scales along with their item numbers, item range, and maximum number of missing values allowed within each scale are shown in Table 3.

Table 3: EORTC QLQ-GI.NET21 Scales (V3 English)

Scale	Item Range*	Item Number in Questionnaire	Man No. of Missing Items
Endocrine Symptoms	3	31 – 33	1
Gastrointestinal Symptoms	3	34 – 38	2
Treatment-Related Symptoms[a]	3	39, 40	1
Disease-Related Worries[a]	3	41, 43, 47	1
Social Functioning	3	42, 44, 49	1
Weight Loss	3	45	0
Weight Gain	3	46	0
Muscle and/or Bone Pain	3	48	0
Information	3	50	0
Sexual Functioning[a]	3	51	0

* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.
[a] Items 39, 40, 47, and 51 have the option "Not Applicable" (N/A) and scores should be calculated as for missing data.

The scoring of the EORTC QLQ-GI.NET21 is defined in the EORTC QLQ-GI.NET21 Scoring Manual[5]. The raw score is defined as the mean of the item scores within each domain. If more than 50% of the items within each domain are missing, then the raw score for that domain is missing. The maximum number of missing questions per domain is defined in the above Table 3.

A standardized score for each domain is derived as follows, where the range is defined as the difference between the maximum and minimum possible values of the raw score as shown in Table 3 above:

Standardized score = [(raw score – 1)/range] x 100

All Standardized scores range from 0 to 100, with a high score representing a high level of symptomatology or problems. The standardized scores for each scale and the change from baseline will be summarized by visit according to the schedule of assessments and presented by randomized dose group and in overall.

Graphic presentation by randomized dose and visit will be generated for the 5 sub scales.

10.8.6.3. EQ-5-Dimension 5-Level Questionnaire

The EQ-5D-5L[6] instrument includes a descriptive system questionnaire and the EQ Visual Analogue scale (EQ VAS).

The descriptive system comprises five dimensions that describe the participant's health state which include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five response levels that are scored 1 to 5 corresponding to no problems, slight problems, moderate problems, severe problems, and extreme problems. A profile value will then be derived per participant by combining the responses from the five questions into one 5-digit response and then be compared to a table of crosswalk values from the Crosswalk (EuroQol[6]) value set and assigned an index value based on the UK value set. Higher scores for each domain indicate higher levels of disability and will correspond with lower index value. No index value will be assigned for questionnaires that contain at least one missing domain response and the index value will be considered as missing.

The following table provides an example of how the health index value is assigned using the Crosswalk UK value set.

Mobility	Self Care	Usual Activity	Pain/ Discomfort	Anxiety/ Depression	Profile Value	Index
2	2	4	1	5	22415	0.216

The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' (Score = 100) and 'the worst health you can imagine' (Score = 0). Higher scores on the EQ-VAS indicate higher levels of overall health.

Descriptive statistics will be used to summarize the EQ-5D-5L index score, each of the five-dimension scores, and the VAS by visit according to the schedule of assessments. The change from baseline will also be summarized for all scheduled post-baseline scheduled visits by randomized dose group and overall.

10.8.6.4. FACT-CSI

The Functional Assessment of Cancer Therapy - Carcinoid Syndrome Symptom Index (FACT-CSI) is a 24-item instrument that can be scored as a single, multidimensional symptom index, consisting of the following domains: disease-related physical symptoms, disease-related emotional concerns, treatment side effects, and functional well-being. Subjects select a response to each statement on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). A lower total score indicates a better quality of life.

Table 4: FACT-CSI Domains

Domain	Items in Questionnaire	Max Number of Missing Items
Symptoms	GP1, HI7, C2, C5, ACT11, ITF1, C1, GAL4, ES1, CS1, CS2, M9	6
Emotional Concerns	BRM9, GE1, GE6,	1
Treatment Side Effects	GP5	0
Functional Well-being	D4, ITU2, AA8, CS3, An7, GF3, GF7, Lau5	4

The scoring of the FACT-CSI is defined in the FACT-CS Symptom Index Guidelines[7].

For items 1 – 21, item score = 4 - item response collected

For items 22 – 24, item score = item response collected

Domain Score = [(sum of item scores) x 24]/number of items answered within domain

CSI Score = [(sum of item scores) x 24]/number of items answered

The individual domain scores and CSI score will be summarized by visit and presented by randomized dose and overall. The individual domain score will be missing if more than half of the items within each domain have missing values. The CSI score is then calculated as the sum of each domain scores. An CSI score is considered to be an acceptable indicator of patient quality of life as long as overall item response rate is greater than 80% (e.g., at least 20 of 24 FACT items completed). In addition, the CSI score should only be calculated if all of the individual domain have valid scores.

10.8.7. Patient Global Impressions

The PGI-S is a series of single questions regarding symptom status of diarrhea, abdominal pain, flushing, and CS over the past two weeks scored ranging from 0 to 3 corresponding normal (no symptom), mild, moderate, and severe. The PGI-C is a series of questions regarding change in disease severity using a 7-point verbal rating scale scored from -3 to 3 which correspond to much better, moderately better, a little better, no difference, a little worse, moderately worse, and much worse compared to the start of the study.

PGI-S, change from baseline in PGI-S, and PGI-C will be summarized by visit and randomized dose groups as continuous variables.

10.8.8. Treatment Preference

The Treatment Preference Questionnaire is a single question regarding the participant's preferred treatment form, ie, previously used injections or oral study drug (or no preference) at Week 8 (EOR) visit. The categorical responses will be presented using counts and percentages. These results will be presented by randomized dose group and overall.

10.8.9. Incidence of NET Progression

Participants are required to have pretrial imaging assessment available within 3 months of Screening. After enrollment in the study, participants should have an appropriate tumor surveillance imaging assessment (CT or MRI based on that which was used pretrial). Imaging

assessments at Week 10 and Week 36 but can be adjusted to conform to the six-month interval recommendation for radiographic surveillance. The investigator will evaluate whether the participants had the tumor progression (Yes/No) based on the image.

[redacted]

10.9. Safety Analysis

The safety analysis will be performed separately for RTP phase and for OLE period. Safety endpoints include the following:

- Incidence of TEAEs, including serious TEAEs and TEAEs leading to discontinuation
- Change in safety parameters:
  - Clinical laboratory tests
  - Physical exam findings
  - Vital signs
  - 12-lead electrocardiogram (ECG)
  - 24-hour cardiac monitoring for participants who up-titrate to 120 mg

[redacted]

For safety endpoints, all analyses will be based on the observed data (ie, with no imputation of missing data), unless otherwise stated.

10.9.1. Extent of Exposure

The extent of exposure will be summarized for RTP phase and OLE phase separately.

The duration of study exposure (in days) and duration of final dose will be summarized by randomized dose groups and in overall. Duration of study drug exposure will be calculated as date of last dose – date of first dose + 1. Treatment compliance will be calculated based on expected and actual number of days participants received treatment from the EDC study drug dosing and will be presented in overall and separately for each dose group.

10.9.2. Adverse Events

Adverse events will be coded by system organ class (SOC) and/or preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 (or higher). AEs will be summarized for RTP phase and OLE phase separately.

Pretreatment AEs are those AEs with a start date prior to the first administration of study drug. All AE summaries will be restricted to treatment emergent adverse event (TEAEs), which are

defined as any AE that emerges during study treatment, having been absent pretreatment, or worsens in severity post treatment relative to the pretreatment state. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as such. Partial dates used in calculation are handled per Section 9.1.1.

An overall summary table of TEAEs including the number and percent of participants with at least one of the following and the number of TEAEs for each of the following will be presented by randomized dose group and overall:

- Any TEAE
- Any TEAE Related to Symptom of Carcinoid Syndrome
- TEAE Severity (mild, moderate, severe)
- Serious TEAE
- Treatment-related TEAE
- Treatment-related Serious TEAE
- TEAE leading to study discontinuation

A summary of TEAEs will be displayed by SOC and PT and presented in descending order of total incidence of SOC and PT within each SOC. This summary will be presented by randomized dose group and overall.

Separate tables will be generated for each of the following. Summaries will include the number and percentage of participants with events and be presented by randomized dose group and overall:

- TEAEs by PT (in descending order by total)
- Treatment-related TEAEs by PT (in descending order by total). Related is defined as relationship to paltusotine of "Possibly Related," "Probably Related," or "Definitely Related." At each level of participant summarization, a participant is classified according to the closest relationship to study drug if the participant reported one or more events. AEs with a missing relationship will be considered related for this summary.
- TEAEs by severity and PT. A participant is classified according to the highest severity if the participant reported one or more events within each PT. AEs with missing severity will be considered severe for this summary.
- Serious TEAEs by PT.
- Serious treatment-related TEAEs by PT.
- TEAEs leading to death by PT.
- TEAEs leading to treatment discontinuations by PT
- TEAEs leading to study discontinuations by PT
- A listing of deaths, SAEs or other significant TEAEs (defined as TEAEs leading to study treatment discontinuation, or withdrawal from study).

Detailed listings for all AEs, serious TEAEs, treatment-related TEAEs, AEs leading to the discontinuation of study, AEs leading to the discontinuation of treatment, and death will also be generated.

No statistical inference between treatments will be performed on AEs.

10.9.3. Clinical Laboratory Parameters

Descriptive statistics for continuous variables of clinical laboratory values and changes (from the baseline for RTP phase and from EOR for OLE phase, respectively) at each scheduled visit will be presented by randomized dose groups and overall for the following laboratory parameters:

Hematology: Erythrocytes; hematocrit; hemoglobin; leukocytes; lymphocytes; lymphocytes/total cells; neutrophils; neutrophils/total cells; platelets.

Chemistry: Alanine aminotransferase; albumin; alkaline phosphatase; amylase; aspartate aminotransferase; bilirubin (total and direct); calcium; chloride; creatinine; glucose; lipase; magnesium; phosphate; Potassium; protein (listed as total protein in CRF); sodium; urate (listed as uric acid in CRF); urea nitrogen (listed as blood urea nitrogen in CRF); albumin adjusted calcium;

Coagulation: Prothrombin international normalized ratio (INR)

Hemoglobin A1c

Thyroid Hormones: Thyrotropin (listed as thyroid stimulating hormone in CRF); free thyroxine (listed as Free T4 in CRF)

Quantitative urinalysis: pH;

Note: Albumin adjusted calcium (mmol/L) will be calculated as

Serum calcium (mmol/L) + 0.02 [normal albumin – participant's serum albumin (g/L)]

where normal albumin = 40 g/L .

Individual laboratory test results will be presented in a by-participant listing.

For laboratory data, if the raw data is reported as "<xx," then the imputed value will be 0.9* xx. If the raw data is reported as ">xx," then the imputed value will be 1.1*xx. The imputed values will be used for the summary stated above.

Liver test abnormalities will be presented in a by-participant listing. If a participant meets any of the following liver test abnormality criteria, present the baseline result, the first occurrence of the post baseline abnormality, and all subsequent results for that parameter.

- Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) <ULN at Baseline and >3×ULN post treatment
- ALT or AST >ULN at Baseline and >3×ULN post treatment and 2x the Baseline (OLE Baseline for the OLE phase) result
- Bilirubin (TB) <ULN at Baseline and >2×ULN post treatment
- TB >ULN at Baseline and >2×ULN post treatment and 2x the Baseline (OLE Baseline for the OLE phase) result

- Alkaline Phosphatase (ALP) <ULN at Baseline and > 3×ULN post treatment
- ALP >ULN at Baseline (OLE Baseline for the OLE phase) and >3×ULN post treatment and 2x the Baseline (OLE Baseline for the OLE phase) result

Note: For RTP phase, Baseline is the study baseline. Week 8 result is considered as OLE Baseline for OLE period.

Liver test abnormalities leading to treatment discontinuation will be presented in a by participant listing. If a participant meets any of the following liver test abnormality criteria, present the first occurrence and all subsequent results for that parameter.

- ALT or AST > 8×ULN at any visit
- ALT or AST >5×ULN for more than 2 weeks (there should be at least two values)
- ALT or AST >3×ULN and TB >2×ULN or international normalized ratio > 1.5 for more than 2 weeks. A participant is required to meet all these criteria at least twice.
- ALT or AST >3×ULN and AE = fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (eosinophils/leukocytes > 5%). The AE start date should occur ± 7 days from the date of this lab result.

10.9.4. Vital Signs

For RTP phase, descriptive statistics for vital signs for each visit and changes from baseline for each post baseline visit will be presented by randomized dose group and overall using Safety Set. The following vital signs measures will be summarized: systolic/diastolic blood pressure (mmHg); pulse rate (beats/min); and respiratory rate (breaths/min).

Similar summary will be provided for OLE phase using OLE Set. [redacted]

10.9.5. Electrocardiogram

ECG is required for all participants at Screening (baseline) and Week 1 visit (Day 1 visit, 1-3 hours after supervised administration of first dose of study drug). Starting from Week 2 visit, ECG is only required for participants who had a dose increase.

ECG measurements will be made in triplicate and assessed by a central reader. For summary purposes the average of the triple measurements will be used. If any of the three measurements are not available or more than three measurements are available, all available measurements will be used in the average.

Electrocardiogram measurement will be summarized for Baseline and Week 1 visit. Descriptive statistics for ECG parameters (the heart rate, QT, QTcF, and PR intervals, and QRS duration) for each scheduled visit and changes from baseline will be presented by randomized dose group using Safety Set.

A categorical summary of the following abnormal QTcF values will be presented: >450 msec, >480 msec, >500 msec, and >530 msec. Change from Baseline summaries will also be presented for measurements that represent a change of >30 msec and >60 msec at Week 1.

A listing of ECG results will be presented and participants with any QTcF >450 msec or a QTcF change from Baseline >30 msec, based on the average of the triplicates, will be flagged.

The investigator interpretation results are collected as normal, abnormal not clinically significant, abnormal clinically significant, and not evaluable. These will be summarized by randomized dose and visit. [redacted] For these summaries, the worst interpretation among the triplet results will be used.

10.9.6. Other Safety Parameters

10.9.6.1. 24-Hour Continuous Cardiac (Holter) Monitoring

Holter monitoring is performed for each randomized participant at Screening Visit 2 and is only scheduled to be performed for participants who are taking 120mg dose approximately 5 to 7 days after the first 120 mg dose. For participants who take 120mg, change from baseline will be summarized for the following parameters as maximum heart rate (beats/min), mean heart rate (beats/min), minimum heart rate (beats/min), and atrioventricular conduction with PR interval.

10.9.6.2. Weight and Body Mass Index

Weight (kg) and BMI (kg/m^2) will be summarized at baseline and each post-baseline visit by randomized dose group and overall. Change from baseline for RTP phase [redacted] will be presented [redacted].

Height, weight, and BMI will be presented in a by-participant listing.

10.9.6.3. Physical Examination

Physical examination data will be presented in a by-participant listing.

10.9.6.4. Gall Bladder Ultrasound

All gall bladder ultrasound data will be presented in a by-participant listing.

10.9.6.5. Ophthalmic Assessments

Ophthalmic assessment data will be summarized and presented in a by-participant listing.

10.9.7. Pharmacokinetic Analysis

10.9.7.1. Plasma Paltusotine Concentration

The listing of plasma paltusotine concentrations will be provided and may include the date/time of collection, the last dose date/time, elapsed time (in hours), dose level at time of sample collection, trough flag ("Y" if result is a trough, "N" otherwise), and dose-normalized value of concentration. PK concentrations will be reported to the same significant figures (ie, 3 significant figures for most cases).

Plasma paltusotine concentrations will be summarized by paltusotine dose level (ie, the participant's dose level at the time of sample collection) and pre-dose (trough) vs post-dose for each timepoint. The summary will be presented to 3 significant figures for evaluable participants

in the PK Population. Summary statistics will include mean, SD, %CV, median, min, max, nonzero n for geometric mean, geometric mean, geometric %CV, geometric SD, and 95% CI for the geometric mean, except N and nonzero n for geomean (no decimal)

Dose-normalized plasma paltusotine concentrations may be summarized by pre-dose (trough) vs post-dose for each timepoint. The dose-normalization algorithm is defined as: plasma concentration divided by the participant's dose level of paltusotine at the time the concentration sample was collected. Resulting unit is ng/mL/mg.

Plasma concentrations reported as less than the limit of quantitation (LLOQ) [redacted] will be presented as "BLQ" in the listings and will be set to zero (0) for summaries of concentrations.

10.9.7.2. Plasma Lanreotide and Octreotide Concentrations

The listing of plasma lanreotide and octreotide concentrations will be provided. PK concentrations will be reported to the same significant figures (ie, 3 significant figures for most cases).

Plasma concentrations reported as less than the limit of quantitation (LLOQ) [redacted] will be presented as "BLQ" in the listings and will be set to zero (0) for summaries of concentrations.

Dose-normalized plasma lanreotide and octreotide concentrations may be summarized for each timepoint (ie, by visit).

The dose-normalization algorithm is defined as: plasma concentration divided by the participant's dose level of lanreotide or octreotide at the time the concentration sample was collected. Resulting unit is pg/mL/mg.

11. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

- To be consistent with Crinetics Biometrics standards, the outputs for continuous variables will be presented as the number of participants (N), mean, standard error (SE), standard deviation (SD), median, minimum, and maximum. This is different from protocol specified outputs with N, mean, median, interquartile range, SD, minimum and maximum.
- Per protocol, change from baseline should be set as 0 if the post-baseline measurement of CS related symptoms is missing based on electronic symptom diary. Per this SAP, the missing data should not be imputed and will keep as missing for the analysis purpose.
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- 90% CI is proposed due to exploratory nature of the study instead of 95% as specified in protocol.
- [redacted].

12. REFERENCES

1. International Council on Harmonisation (ICH) E9 guideline entitled, “Guidance for Industry: E9 Statistical Principles for Clinical Trials”
2. International Council on Harmonisation ICH E9 (R1) guidelines entitled, “E9 (R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials”
3. ICH E3 guideline entitled, “Guidance for Industry: Structure and Content of Clinical Study Reports”
4. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.
5. Yadegarfar G, Friend L, Jones L, Plum LM, Ardill J, Taal B, Larsson G, Jeziorski K, Kwekkeboom D, Ramage JK and on behalf of the EORTC Quality of Life Group. Validation of the EORTC QLQ-GINET21 questionnaire for assessing quality of life of patients with gastrointestinal neuroendocrine tumours. British Journal of Cancer. 2013 Feb 5;108(2):301-10.
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8. Summary Review Center for Drug Evaluation and Research; Application number 208794 (Telotristat). July 29, 2015.