Protocol 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

Compound: Paltusotine

Study Phase: 2

Sponsor Name: Crinetics Pharmaceuticals, Inc.

Legal Registered Address: 6055 Lusk Blvd
San Diego, CA 92121, USA

Regulatory Agency Identifier Number(s)

IND: 154584

EudraCT: 2022-000762-18

EU CT Number: 2024-511922-30-00

Version: 7.0

Protocol Date: 21 January 2025

DOCUMENT HISTORY/PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Original Protocol (Version 1.0)	20 August 2021
Protocol Amendment (Version 2.0)	24 September 2021
Protocol Amendment (Version 3.0)	16 December 2021
Protocol Amendment (Version 3.1)	29 January 2022
Protocol Amendment (Version 4.0)	05 April 2022
Protocol Amendment (Version 5.0)	21 March 2023
Protocol Amendment (Version 6.0)	20 November 2023
Protocol Amendment (Version 7.0)	21 January 2025

SPONSOR SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Crinetics Pharmaceuticals, Inc. (herein, Crinetics or Sponsor)

Responsible Medical Officer:

PPD
PPD Clinical Research

Sponsor's Medical Contact:

See last page for electronic signature manifestation

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PPD
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PPD Clinical Research
PPD

Date

Protocol Number: CRN00808-11

A Randomized, Parallel Group Study to Evaluate the Safety, Pharmacokinetics, and Dose Response of Paltusotine Treatment in Subjects with Carcinoid Syndrome

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I have read and I understand this protocol. I will conduct this protocol as outlined herein and will make all reasonable efforts to complete the study within the designated time.

I agree to conduct this trial in accordance with the Declaration of Helsinki, the International Council for Harmonization (ICH), Guideline for Good Clinical Practice (GCP), applicable local legislation including the EU Clinical Trials Regulation (CTR) (EU No 536/2014) and all applicable regulatory requirements.

I will provide copies of the protocol and access to all information furnished by Crinetics Pharmaceuticals, Inc. to study personnel under my supervision. I will discuss material with them to ensure that they are fully informed about the study.

I understand that the study may be terminated, or enrollment suspended at any time, by Crinetics Pharmaceuticals, Inc., with or without cause, or by me, if it becomes necessary to do so in the best interests of the study subjects.

Site name: _____

Site address: _____

Phone number: _____

Principal Investigator:

Name and title (printed): _____

Signature: _____

Date: _____

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CRN00808-11 SUMMARY OF CHANGES

Version 6.0 to Version 7.0

This Summary of Changes includes all changes made from Version 6.0 to Version 7.0

This amendment is to ensure the protocol is compliant with EU Clinical Trials Regulation (CTR) (EU No 536/2014) and includes adverse drug reaction (ADR) updates which align with the revised Paltusotine Investigator's Brochure.

Underlined text in the table denotes added text; strikethrough text denotes deleted text.

Section	Summary of Changes	Rationale
Throughout protocol	• Revised text for clarity as needed • Revised/updated order of headings, text and/or tables, version number, dates, and footnotes as needed • Revised abbreviations and definitions as needed	Minor corrections for clarity or consistency
Throughout protocol	• Updated Sandostatin and Somatuline references • Deleted text referring to "ongoing COVID 19 pandemic"	Minor updates to align with current version or current events
Responsible Medical Officer	PPD PPD Clinical Research	Updated study information
Sponsor's Authorized Officer	**Sponsor's ~~Authorized Officer~~Medical Contact:** PPD PPD PPD PPD Clinical Research PPD	Updated study information
Principal Investigator Signature Page	I agree to conduct this trial in accordance with the Declaration of Helsinki, the International Council for Harmonization (ICH), Guideline for Good Clinical Practice (GCP), applicable local legislation including the EU Clinical Trials Regulation (CTR) (EU No 536/2014) and all applicable regulatory requirements.	Updated to ensure compliance with EU CTR (EU No 536/2014).
Synopsis/Figure 1	~~For subjects completing the OLE Phase, EOS Visit will be at Week 62.~~	Updated to align with definition of EOS in Section 4.1.6
Synopsis/Screening	***Antidiarrheal ~~Agents~~ Agent Use During Screening (Concomitant Medications)*** Antidiarrheal agents, diphenoxylate and loperamide, are considered concomitant medications and may be used ~~during screening~~ as recommended by the Investigator.	Updated to comply with Clinical Trial Regulation (CTR) EU No 536/2014.
Synopsis/Screening	***Rescue Medication Use During Screening (Auxiliary Medicinal Product)*** Short-acting octreotide is considered a rescue medication (ie, auxiliary medicinal product) CCI CCI Investigators should CCI CCI CCI	Updated to comply with Clinical Trial Regulation (CTR) EU No 536/2014.

Section	Summary of Changes	Rationale
Synopsis/Randomized Treatment Phase	~~***Rescue Treatment of Breakthrough Carcinoid Syndrome Symptoms***~~ ***Antidiarrheal Agent Use During RTP*** ***Rescue Medication Use During RTP***	Updated to comply with Clinical Trial Regulation (CTR) EU No 536/2014.
2.2 Background	~~Paltusotine is also under development for the treatment of acromegaly, with two Phase 2 trials completed and two Phase 3 trials ongoing in 2021. In these Phase 2 studies, paltusotine appeared to be well tolerated. The most common reported adverse events (AEs) included headache, arthralgia, diarrhea, and abdominal pain. No subjects discontinued from the Phase 2 studies due to AEs~~Additionally, the clinical program includes two completed Phase 2 studies (CRN00808-02, CRN00808-03) and one Phase 2 open-label long-term extension study (CRN00808-05) that is still ongoing in participants with acromegaly. The RC Phase of two Phase 3 studies (CRN00808-08, CRN00808-09) in participants with acromegaly have been completed, in addition to an RTP of one Phase 2 study (CRN00808-11) in participants with carcinoid syndrome. The OLE phases of these studies are still ongoing. ~~Additional details on the background of Carcinoid syndrome, treatment options, and nonclinical and clinical data on paltusotine can be found in the current Investigator's Brochure (IB).~~ Paltusotine was generally well tolerated across all studies in the clinical program with no unexpected safety signals. The safety profile of paltusotine includes adverse drug reactions (ADRs) of gastrointestinal events (diarrhea, abdominal pain, nausea, and abdominal discomfort), sinus bradycardia, and cholelithiasis, consistent with other SRL treatments.	Updated to align with current Investigator's Brochure
2.2 Background	This study will be conducted in compliance with the protocol, the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and with applicable local legislation including the Clinical Trial Regulation (CTR) EU No 536/2014.	Updated to comply with Clinical Trial Regulation (CTR) EU No 536/2014.

Section	Summary of Changes	Rationale
2.3.1 Safety Risk Assessment Table/CRN00808-11 Study Intervention-Paltusotine	**Summary of Data/Rationale for Risk:** ~~Gastrointestinal (eg, diarrhea, abdominal discomfort). Additional reported AEs found in IB~~ Diarrhea, abdominal pain, nausea, abdominal discomfort, bradycardia (including sinus bradycardia and bradycardia), and cholelithiasis have been identified as ADRs associated with paltusotine. Rationale: these AEs ~~are~~were generally mild or moderate~~. There were no~~ and did not lead to discontinuations ~~due to AEs in completed Phase 2~~in previous studies. **Mitigation Strategy:** Clinical monitoring, symptomatic measures, study drug interruption~~ or discontinuation~~ if necessary. Regular safety surveillance, including laboratory testing, physical examinations, AE monitoring, ECG monitoring, gall bladder monitoring, and evaluations for ~~cardiovascular safety.~~protocol-specified study drug stopping rules ~~provided in protocol~~.	Updated to align with current Investigator's Brochure.
2.3.2 Benefit Assessment	~~Furthermore,~~At this ~~mechanism of action~~time, it is ~~expected to~~unknown whether paltusotine will provide control of neuroendocrine tumor growth~~ comparable to that seen with octreotide LAR or lanreotide~~. ~~The overall safety profile of paltusotine appears to be consistent with those reported for other SRLs and common AEs observed with paltusotine are likely related to this mechanism of action~~. ADRs of bradycardia, gastrointestinal events (diarrhea, abdominal pain, nausea, and abdominal discomfort), and cholelithiasis have been identified. These AEs are generally mild or moderate and can be managed through the appropriate risk mitigation measures (eg, clinical monitoring, safety surveillance).	Updated to align with current Investigator's Brochure.
4.1.1 Screening	Antidiarrheal agents, diphenoxylate and loperamide, are considered concomitant medications and may be used as recommended by the Investigator.	Updated to comply with Clinical Trial Regulation (CTR) EU No 536/2014.
4.1.1 Screening	Short-acting octreotide is considered a rescue medication (ie, auxiliary medicinal product) and can be used according to Table 4. Investigators should CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]	Updated to comply with Clinical Trial Regulation (CTR) EU No 536/2014.

Section	Summary of Changes	Rationale
4.1.2.1. Treatment of Breakthrough Carcinoid Syndrome Symptoms During Randomized Treatment Phase	**4.1.2.1. ~~Rescue~~ Treatment of Breakthrough Carcinoid Syndrome Symptoms During Randomized Treatment Phase** ~~Rescue therapy with SA Octreotide is at the discretion of the Investigator. Options for rescue therapy are described in this section.~~ Diphenoxylate or loperamide may be used as needed at the discretion of the Investigator for improved symptom control at any time during the study except when short-acting octreotide is being used for rescue therapy. Investigators should CCI [redacted] CCI [redacted] CCI [redacted]	Updated to comply with Clinical Trial Regulation (CTR) EU No 536/2014.
4.1.6 End of Study Definition	The EOS is defined as the date of the last visit of the last subject in the study.	Added to define of the end of the clinical trial, to ensure compliance with EU CTR (EU No 536/2014).
4.1.7. Patient Input into Study Design	**4.1.7 Patient Input into Study Design** Patient insight was collected over several meetings (June 2021- June 2022) through a formalized Patient Leadership Council made up of 12 individuals living with carcinoid syndrome associated with NETs. These patients had a range of experiences including treating physician, medical treatments, geographic location, and age of diagnosis. In these meetings, the following topics were discussed: clinical study protocols, rescue therapy, frequency of visits, daily diary execution, study recruitment tactics and participants' preferred method of learning about potential studies. Results of these discussions were shared with the internal paltusotine study team and incorporated into study design where possible.	Added description of patient input into study design to ensure compliance with EU CTR (EU No 536/2014).
4.4. Justification for Duration of Treatment	**4.4 Justification for Duration of Treatment** The study was designed with an 8-week RTP to allow sufficient time to demonstrate dose-responsiveness of 40 vs 80 mg paltusotine. In addition, a 102-week OLE was included in the study to assess long-term safety in adults with Carcinoid syndrome.	Added to comply with Clinical Trial Regulation (CTR) EU No 536/2014.
4.5. Treatment After End of Trial Participation	**4.5 Treatment After End of Trial Participation** After the end of the study, subjects may resume regionally licensed Carcinoid syndrome treatment as prescribed by their healthcare provider.	Added to describe the arrangements for treatment options for subjects after their participation in the clinical trial has ended, to ensure compliance with EU CTR (EU No 536/2014).

Section	Summary of Changes	Rationale
6.1 Study Intervention(s) Administered	Paltusotine is the Investigational Medicinal Product (IMP), diphenoxylate atropine and loperamide are concomitant medications, and short-acting octreotide is a rescue medication (ie, auxiliary medicinal protect [AuxMP]). Investigators should CCI [redacted] CCI [redacted] CCI [redacted]	Added to clarify that paltusotine is the IMP for this trial and that rescue treatments are treated as auxiliary medicinal products.
6.1 Study Intervention(s) Administered Table	Table updated to add details for diphenyloxylate and loperamide.	Added to clarify that diphenyloxylate and loperamide are considered concomitant medications in this study.
6.2 Preparation/ Handling/Storage/ Accountability	At the end of the study (ie, close-out visit) and following reconciliation and documentation by the site monitor, all study drugs and related materials will be either returned to the Sponsor or a designee or destroyed locally following the review and approval of the site's destruction procedures.	Added a description of the arrangements for tracing, storing, destroying and returning the IMP and unauthorized auxiliary medicinal product in accordance with Article 51.
6.7.3. Rescue Medications (Auxiliary Medicinal Products)	**6.7.3 Rescue Medications (Auxiliary Medicinal Products)** Short-acting octreotide is considered a rescue medication (ie, auxiliary medicinal product) CCI [redacted] CCI [redacted]	Added to comply with Clinical Trial Regulation (CTR) EU No 536/2014.
8.4.4 Regulatory Reporting Requirements for Serious Adverse Events	• The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to both expedited and periodic safety reporting to the regulatory authority, IRB/IEC, and Investigators. • Suspected unexpected serious adverse reactions (ie, unexpected SAEs considered drug-related as assessed by the Investigator/Sponsor/authorized person) will qualify for expedited reporting and cross reporting to the IRB/IEC, Competent Authorities, and participating Investigators by Crinetics Pharmaceuticals, Inc. In the EU, Crinetics Pharmaceuticals, Inc. will act in compliance with the CTR EU No 536/2014.	Added to clarify the process for reporting of suspected unexpected serious adverse reactions by the sponsor to the Eudravigilance database.

Section	Summary of Changes	Rationale
8.10 Collection and Storage of Biological Samples	**8.10 Collection and Storage of Biological Samples** The Sponsor will comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial subjects. The Sponsor will comply with national requirements including those set in the CTR (EU) No 536/2014, Article 7.1 (h). A description of the arrangements to comply with CTR (EU) No 536/2014, Article 7.1 (h) is provided in the form 'Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)' submitted as a Part 2 document of this trials CTIS submission.	To describe the arrangements to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial subjects.
10.1.4 Data Protection	~~Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.~~ ~~The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.~~ ~~The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.~~ This trial will be conducted in accordance with the CTR EU No 536/2014 and General Data Protection Regulation (EU) 2016/679 (GDPR) in addition to the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements. If a subject revokes authorization to collect or use personal health data, the Investigator retains the ability to use all information collected before the revocation of subject authorization. For subjects that have revoked authorization to collect or use personal health data, attempts should be made to obtain permission to collect at least vital status (ie, that the subject is alive) at the end of their scheduled study period. All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject data. Subjects' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal	To update the description of the arrangements to comply with the applicable rules on the protection of personal data, to ensure compliance with EU CTR (EU No 536/2014).

Section	Summary of Changes	Rationale
	data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law. To protect the rights and freedoms of subjects with regard to the processing of personal data, subjects will be assigned a single, subject-specific numerical code. Any subject records or data sets that are transferred to the Sponsor will contain the numerical code; subject names will not be transferred. All other identifiable data transferred to the Sponsor will be identified by this single, subject-specific code. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to their actual identity and medical record ID. In case of data transfer, the Sponsor will protect the confidentiality of subjects' personal data consistent with the clinical study agreement and applicable privacy laws. Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. The Sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of Sponsor information or systems.	
10.1.7 Data Quality Assurance	• The study will be conducted according to GCP (as outlined by ICH topic E6, step 5 guidelines) and in compliance with applicable local legislation including the EU CTR (EU No 536/2014). • The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the Clinical Study Protocol, SOP, GCP, and all applicable local regulatory requirements including the EU CTR (EU No 536/2014). • Study records and source documents must be preserved for at least ~~15~~25 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application in an ICH region or as per local requirements, whichever is the longer time period. • The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information. The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with Directive 95/46/EC: Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data and in a form satisfactory to the Sponsor.	Updated to comply with Clinical Trial Regulation (CTR) EU No 536/2014.

AuxMP=Auxiliary Medicinal Product, CTR=Clinical Trials Regulation, CFR=Code of Federal Regulations, EOS=End of Study, EU=European Union, GCP=Good Clinical Practice, IEC=Independent Ethics Committee, IMP=Investigational Medicinal Product, IRB=Institutional Review Board

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title

A Randomized, Parallel Group Study to Evaluate the Safety, Pharmacokinetics, and Dose Response of Paltusotine Treatment in Subjects with Carcinoid Syndrome.

Rationale

Carcinoid syndrome usually occurs in intestinal neuroendocrine tumors (NETs) with liver metastases, which makes surgical cure very difficult in most patients. Excess serotonin and other hormonally active substances (including histamine, tachykinins, kallikrein, and prostaglandins) produced by some NETs are responsible for the symptoms collectively referred to as Carcinoid syndrome (Vinik, 2018). These symptoms most commonly include cutaneous flushing (seen in 85%) and recurrent watery diarrhea and cramping (seen in 75%-85%). Carcinoid syndrome is confirmed biochemically with documentation of elevations of serum serotonin or the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA). While long-acting somatostatin receptor ligand (SRL) therapies are mainstay treatments for Carcinoid syndrome, relief of Carcinoid syndrome symptoms at labeled doses is inadequate for many patients. Long-acting SRL therapies have also demonstrated efficacy in prolonging progression free- survival in patients with nonfunctional, metastatic, well or moderately differentiated enteropancreatic NETs (Rinke, 2009; Caplin, 2014; Kunz, 2015; Chan and Kulke, 2016; Oronsky, 2017). Long-acting SRL therapies may be associated with significant dose-to-dose exposure variability related to injection techniques. For example, nurses at MD Anderson Cancer Center successfully delivered only 52% of 328 octreotide long-acting release (LAR) injections to the intramuscular space when evaluated by computed tomography (Boyd, 2013). Negative experiences with chronic injections of long-acting SRL therapies, particularly octreotide LAR, also have been identified in patients with Carcinoid syndrome, including injection site pain or soreness (Adams, 2019).

A daily oral treatment such as paltusotine may achieve higher drug concentrations in the liver, which is the most common source of the vasoactive mediators causing Carcinoid syndrome symptoms. Paltusotine, an orally administered nonpeptide somatostatin type 2 receptor (SST2) agonist, has the potential to improve treatment outcomes, achieving symptom control while eliminating painful injections.

The purpose of this study is to evaluate the safety, pharmacokinetic (PK), and dose response of paltusotine treatment in subjects with Carcinoid syndrome.

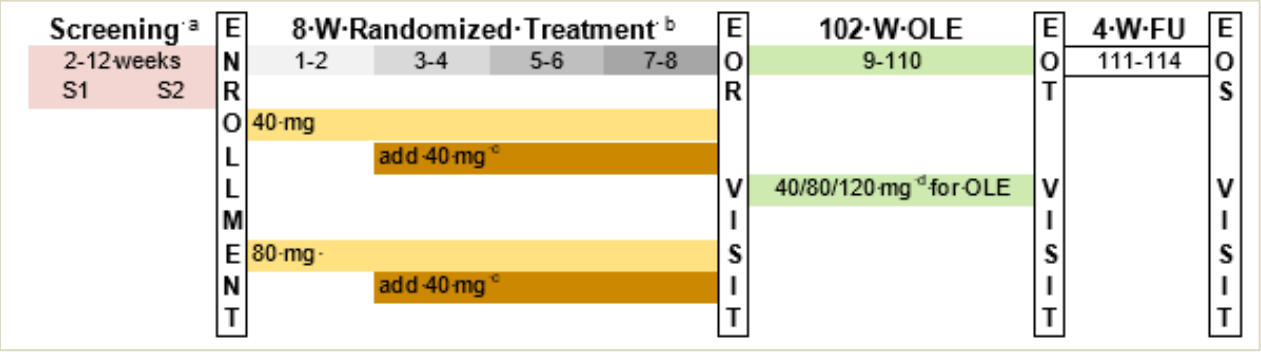
Overall Design

This is a Phase 2, randomized, open-label, parallel-group, multi-center study. The study includes a Screening Period of up to 12 weeks. After completion of Screening, subjects will be randomly assigned to 40 mg QD vs. 80 mg once daily (QD) open-label dose groups for 8 weeks, referred to as the Randomized Treatment Phase (RTP). A dose up-titration by 40 mg QD is an option based on symptomatology once during the first 4 weeks of the Randomized Treatment Phase.

Following the completion of the Randomized Treatment Phase, subjects may be eligible to enter the Open-Label Extension (OLE) Phase of the study in which they will receive paltusotine for 102 weeks. Subjects who complete the Randomized Treatment Phase, and for whom the

Investigator recommends continuation of treatment on paltusotine, may be eligible to participate in the OLE Phase. There will be a 4-week follow-up as depicted in Figure 1. The total duration of paltusotine treatment is up to 110 weeks or up to 28 months. This is summarized and presented in Figure 1.

Figure 1: Study Schema



EOR=End of Randomized Treatment Phase; EOS=End of Study; EOT=End of Treatment; W=week; FU=follow-up; LAR=long-acting release; OLE=Open-Label Extension
Note: The 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 LAR and the expected visit S2 is not longer than the usual interval between injections for the subject.
[b] It is anticipated that subjects will complete the 8 weeks of Randomized Treatment Phase. Subjects who complete the Randomized Treatment Phase, and for whom the Investigator recommends continuation of treatment on paltusotine, may be eligible to participate in the OLE Phase.
[c] If subjects have recurrent carcinoid symptoms that require short-acting octreotide, the dose will be up-titrated once by 40 mg QD at the Day 14 or Day 28 visit (Section 4.1).
[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).

Screening

The Screening Period will vary from 2 to 12 weeks, depending on when subjects meet the qualifying criteria for randomization as described below.

Subjects will be eligible for Screening if they are:

- Not currently treated with any SRL therapy for at least 12 weeks prior to Screening, and are actively symptomatic (average of ≥4 bowel movements (BM)/day or >2 flushing episodes per day in at least 2 days over a period of 2 weeks)

  OR

- Currently symptomatically controlled (average <4 bowel movements [BMs]/day and average ≤2 flushing episodes/day over a 2-week period) while treated with lanreotide, octreotide LAR, or short-acting octreotide (immediate release octreotide injection or oral octreotide) and who are willing to wash out of their medication

The completion of an electronic Symptom Diary will continue daily throughout Screening beginning within 1 day of S1, and through Week 12 of the study (through Randomized Treatment Phase and 4 weeks into OLE) and then at selected time periods in the OLE Phase (Section 8.2.1). During the Screening Period, data from the diary will be used to assess initial

screening symptom frequencies and, for those who wash out of lanreotide or octreotide, to assess post-washout symptom frequencies. Stool consistency according to the Bristol scale and abdominal pain according to a numeric rating scale (NRS) will also be recorded in the electronic Symptom Diary. In addition to determining eligibility for randomization, the Screening Period will be used to assess the understanding and compliance of the subject with the electronic Symptom Diary. Some endpoints use Baseline defined from the Screening Period which is defined as the last 7 days prior to start of randomized treatment. Otherwise, Baseline is defined as the last value prior to start of randomized treatment.

Subjects Not Currently Treated with Any SRL Therapy

For subjects not currently treated with any SRL therapy, 2 Screening visits (S1 and S2) will be scheduled in the Screening Period. After completing the initial eligibility assessment in S1, a 2-week assessment of untreated symptom frequencies (BMs and flushing episodes) will be initiated. At the S1 visit, plasma 5-HIAA levels will be assessed. If the plasma 5-HIAA result is ≥2× the upper limit of normal (ULN), and the 2-week assessment is complete, demonstrating the subject meets symptomatic qualifying criteria (average of ≥4 BM/day OR >2 flushing episodes per day in at least 2 days over the period of 2 weeks), the Day 1 randomization visit should be scheduled (Figure 2). Subjects not meeting these criteria will be considered screen failures.

Subjects Controlled Symptomatically Using Pretrial SRLs

Subjects Using Lanreotide or Octreotide LAR

For subjects using pretrial lanreotide or octreotide LAR, 2 Screening visits (S1 and S2) will be scheduled. Both S1 and S2 are determined based on the subject's injection schedule, which is ascertained prior to trial entry. Subjects will not continue their lanreotide or octreotide LAR after the informed consent is given at S1.

Screening Visit 1 (S1) should be scheduled after the subject's last dose of pretrial lanreotide or octreotide LAR. The second Screening Visit (S2) will occur approximately 2 weeks after S1 (Figure 3). The interval between S1 and S2 should not be longer than the usual interval between injections for the subject. The 2-week interval between S1 and S2 will be used for the assessment of the subject's baseline symptom control.

At the S2 Visit, the degree of symptom control resulting from pretrial lanreotide or octreotide LAR dosing will be assessed. For subjects who are controlled symptomatically using pretrial SRLs, adequate symptom control is defined as having an average of <4 BM/day and an average of ≤2 flushing episodes/day over a 2-week period. Only subjects with adequate symptom control over a 2-week period following S1 will continue into the Screening Period for up to 10 weeks after S2. During this time, the subject's diary will be closely monitored for changes in flushing and BMs.

Subjects may qualify for trial entry as the result of an increase in the occurrence of either BMs or of flushing. Eligible subjects will have an increase in symptoms during a 7-day period after S2, compared to the period between S1 and S2, of either:

- An average increase ≥1 BM/day over the average daily BM frequency observed in the period between S1 and S2 AND
- An absolute frequency of ≥3 daily BMs in at least 4 days within the 7-day period

OR

- An increase in daily average flushing episodes AND
- At least 3 flushing episodes on at least 1 day

If the subject does not qualify for the Day 1 randomization visit within 10 weeks of S2, the subject will be considered a screen failure (Figure 3).

Subjects Using Short-acting Octreotide

For subjects using regular doses of short-acting octreotide (immediate release octreotide injection or oral octreotide) for the prevention of Carcinoid syndrome symptoms pretrial, 2 Screening visits (S1 and S2) will be scheduled in the Screening Period. After S1, a 2-week assessment of treated symptom frequencies (BMs and flushing episodes) will be initiated. The subject should continue pretrial dosing of short-acting octreotide at the most recent pretrial dose and administration frequency during this period. Completion of the electronic Symptom Diary should begin within 1 day of S1. S2 will occur approximately 2 weeks after S1.

At the S2 Visit, symptom control from short-acting octreotide will be assessed. Subjects may qualify for trial entry as the result of an increase in the occurrence of either BMs or of flushing. Eligible subjects will have an increase in symptoms during a 7-day period after S2, compared to the period between S1 and S2, of either:

- An average increase ≥1 BM/day over the average daily BM frequency observed in the period between S1 and S2 AND
- An absolute frequency of ≥3 daily BMs, in at least 4 days of the 7-day period

OR

- An increase in daily average flushing episodes AND
- At least 3 flushing episodes on at least 1 day

If the subject does not qualify for the Day 1 randomization visit within 10 weeks of S2, the subject will be considered a screen failure Figure 3.

Antidiarrheal Agent Use During Screening (Concomitant Medications)

Antidiarrheal agents, diphenoxylate or loperamide, are considered concomitant medications and may be used during Screening as recommended by the Investigator. Investigator should refer to guidelines provided by the Sponsor for recommending antidiarrheal agents to the subjects (Table 3). Diphenoxylate or loperamide may be used as needed at the discretion of the Investigator for improved symptom control at any time during the study except when short-acting octreotide is being used for rescue therapy.

Rescue Medication Use During Screening (Auxiliary Medicinal Product)

Short-acting octreotide is considered a rescue medication (ie, auxiliary medicinal product) CCI [redacted] Investigators should CCI [redacted] All administrations of short-acting octreotide or antidiarrheal medications should be recorded in the electronic Symptom Diary.

Rescue therapy with SA octreotide is at the discretion of the Investigator. Options for therapy are described below.

If there is a delay in scheduling the Day 1 randomization visit for subjects in Screening who have met the symptomatic criteria qualifying them for randomization, subjects may begin short-acting octreotide. Subjects also will receive instructions on how to use short-acting octreotide 200 µg up to 3 times daily, at the discretion of the Investigator, when symptomatic criteria are met (Table 4). Short-acting octreotide must be stopped no later than 12 hours prior to the randomization visit.

Randomized Treatment Phase

Once all Screening assessments are complete and the subject's eligibility is verified by the Investigator and confirmed by the Medical Monitor via submission of the Medical Monitor Eligibility Verification Form, the subject will be randomized to 40 mg QD vs. 80 mg QD for the 8-week Randomized Treatment Phase. On Day 1 of the Randomized Treatment Phase, the Investigator will query the subject to identify the most troublesome target symptom as assessed by the subject (BM or flushing). The target symptom will be documented. Subjects will be provided on Day 1 with sufficient paltusotine 20 mg tablets for 40 mg QD or 80 mg QD for 14 days and will return to the site on Day 14. Scheduled study visits will occur on Days 28, 42, and 56. An evaluation on Day 56 (referred to as Week 8 in the SOAs) will be made for potential enrollment in the OLE Phase. Beginning at W2, visits may be performed at home at the discretion of the Investigator, with home health care support as needed.

Antidiarrheal Agent Use During RTP

Diphenoxylate or loperamide may be used as needed for improved symptom control at any time during the study except when short-acting octreotide is being used for rescue therapy. Possible treatment regimens for breakthrough symptoms of Carcinoid syndrome occurring during the study are delineated in Table 5.

Rescue Medication Use During RTP

On Day 1, all subjects who have not already received instructions on how to use short-acting octreotide 200 µg up to 3 times daily, at the direction of the Investigator, will receive instructions for rescue therapy when criteria are met (Table 6). Study staff should instruct subjects on the criteria for initiating and stopping short-acting octreotide as described in Table 6. Short-acting octreotide should not be given for at least 12 hours before biomarker sample collection.

All administrations of short-acting octreotide or antidiarrheal medications should be recorded in the study diary.

If the subject experiences Carcinoid syndrome symptoms that meet protocol criteria for short-acting octreotide rescue, another option to treat the symptoms is to increase the respective dose by 40 mg QD based on symptomatology to a maximum dose of 80 or 120 mg QD once during the first 28 days. No dose increases are allowed after Day 28 through the remaining 4 weeks of the Randomized Treatment Phase. Table 7 summarizes the dose adjustments during the Randomized Treatment Phase of the study.

Open-Label Extension Phase

Subjects completing the 8 weeks Randomized Treatment Phase may begin the OLE Phase of the study if, in the opinion of the Investigator, the subject may benefit from OLE Phase participation.

For those rolling over into the OLE, the initial OLE dose will be based on frequency of rescue treatments and study drug tolerability, as assessed by the Investigator (Table 8). The first dose of OLE will be administered at the clinical research site on Week 8 (Day 56) visit. If the subject experiences Carcinoid syndrome symptoms that meet protocol criteria for short-acting octreotide rescue during the OLE Phase, the dose may be increased by 40 mg QD to a maximum dose of 120 mg QD (ie, the maximum dose will be reached at 1 study visit for subjects starting at 80 mg and at 2 study visits for subjects starting at 40 mg; Table 8). In the event that the worsening of Carcinoid syndrome symptoms that meet protocol criteria for short-acting octreotide rescue (Section 4.1.3) occurs between the scheduled visits and the Investigator determines it is appropriate to increase the subject's dose before the next scheduled visit, an unscheduled visit can be added in order to increase the subject's dose. The site should perform a triplicate echocardiogram (ECG) at 1 to 3 hours postdose and 24-hour continuous cardiac (Holter) monitoring 5 to 7 days after the dose increase if the dose is increased to 120 mg. A paltusotine predose blood draw for PK, safety labs and postdose PK blood draw at 1 to 3 hours should also be done. Subjects not continuing in the OLE study will have their last Randomized Treatment Phase dose administered at the Week 8 visit.

The completion of an electronic Symptom Diary will continue daily throughout Screening beginning within 1 day of S1 and through Week 12 of the study (through Randomized Treatment Phase and 4 weeks into OLE) and then selected time periods in the OLE Phase (Section 8.2.1).

Subjects who have previously completed the OLE (when the OLE concluded at Week 58) may rejoin the OLE at the same dose they were previously on if they meet the following conditions: (1) the Investigator has determined that the subject's disease is stable, (2) safety assessments, including chemistry, hematology, urinalysis, and baseline electrocardiogram, show no significant changes compared to previous evaluations, and (3) approval from the Medical Monitor.

Once these three conditions are met, the subject may reenter the OLE after discontinuation of their current SSA therapy, with the timing at the discretion of the Investigator. The subject will reenter the OLE at the Week 58 timepoint and follow the Summary of Activities (SOA) as described in Table 2.

Study Completion and Early Termination

Study completion and early termination (ET) for subjects are each defined separately for the Randomized Treatment Phase and the OLE Phase. Completion of Randomized Treatment Phase and the OLE Phase of the study requires that subject complete the final visit within each phase (End of Study [EOS] Visit for Randomized Treatment Phase and the OLE Phase) (Table 5 and Table 6). Subjects discontinuing early from Randomized Treatment Phase or the OLE Phase of the study should be treated with standard treatment as recommended by the Investigator and will have an ET Visit.

End of Randomized Treatment Phase and End of Treatment

Completion of last scheduled dosing in Randomized Treatment Phase is defined as End of Randomized Treatment Phase (EOR) and completion of last scheduled dosing in OLE Phase is defined as End of Treatment (EOT).

End of Study

An EOS Visit will occur to collect the safety data and other assessments as detailed in the SOAs.

An EOS Visit will be 28 days after last dose of study drug and is required for subjects who completed the study or early terminated.

Objectives and Endpoints of the Study

Objectives	Endpoints[a]
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, 12-lead ECG, and 24-hour continuous cardiac monitoring (only for subjects 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 subjects 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 subjects who meet flushing entry criteria only:</u> • Have a >30% reduction compared with Baseline in the mean daily number of flushing episodes. <u>In subjects 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 subjects in the different dose arms	Proportion of target symptom responders by dose during the last week of the Randomized Treatment Phase: • Subjects 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 subject the most at Baseline.)

Objectives	Endpoints[a]
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
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 subject 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 subject 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

Objectives	Endpoints[a]
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
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 subject-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 subjects 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, 12-lead ECG, and ophthalmic assessments
Pharmacokinetics	
To assess the PK of 40, 80, and 120 mg paltusotine	Steady state trough levels at each dose at EOT

Objectives	Endpoints[a]
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: In subjects who meet diarrhea entry criteria only: • Have less than 4 mean bowel movements daily, and have a >20% reduction in the mean daily number of bowel movements compared with Baseline In subjects who meet flushing entry criteria only: • Have a >30% reduction compared with Baseline in the mean daily number of flushing episodes In subject who meet both diarrhea and flushing entry criteria: Have less than 4 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
	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 subject-reported carcinoid symptom severity and change	• PGI-S at EOT • PGI-C at EOT
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

Objectives	Endpoints[a]
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 subjects rush to the bathroom): • From the last week prior to Baseline to the last week prior to EOT

BM=bowel movement; ECG=electrocardiogram; EORTC QLQ-C30=EORTC Quality of Life questionnaire; EORTC QLQ-GI.NET21=EORTC Quality of Life questionnaire in GI NET; EOR=end of randomized Treatment Phase; EOS=End of Study; EOT=end of treatment; 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; OLE=Open-Label Extension; PGI-C=Patient Global Impression - Change; PGI-S=Patient Global Impression of Severity; PK=pharmacokinetic; QD=once a day; TEAE=treatment-emergent adverse events

[a] All endpoint assessments, except biochemical markers of Carcinoid syndrome and safety laboratories to be collected in daily electronic diary.

Number of Subjects

Approximately 30 subjects (15 subjects/arm) will be enrolled in the study. Subjects taking proton-pump inhibitors (PPIs) at Screening may contribute up to 6 subjects enrolled in the study. Subjects who screen fail may be reconsidered for enrollment after a new and successful Screening Period.

Duration and Intervention Groups

Total Duration of the Study

The study is comprised of a Screening Period up to 12 weeks and 2 treatment phases (Randomized Treatment Phase and OLE Phase) with a Safety Follow-up (EOS Visit) 4 weeks after the last dose. Subjects who are randomized to participate in the Randomized Treatment Phase and continue in the OLE Phase will complete the study in up to 110 weeks or 28 months.

The study will consist of:

- Screening Period: 2 to 12 weeks
- Randomized Treatment Phase: 8 weeks
  - Randomized 1:1 to 40 mg or 80 mg for up to 8 weeks
- OLE Phase: 102 weeks
- EOS Visit: 4 weeks post last dose of study drug

Study Drug

Paltusotine will be provided as 20 mg tablets, packaged in 36 count, high-density polyethylene bottles containing desiccant cannister. During the Randomized Treatment Phase, those assigned to 40 mg will take two 20 mg tablets daily and those assigned to 80 mg will take four 20 mg tablets daily. Those who require 120 mg will take six 20 mg tablets daily.

Scientific Rationale for Study Design

This study consists of a Randomized Treatment Phase followed by an OLE Phase. A randomized parallel-group design allows for a rigorous assessment of the safety and efficacy associated with each dose. These data will be useful for dose selection in the design of subsequent trials.

The OLE Phase will provide important long-term safety and efficacy information that will also inform later stage trial designs. Standardized dose titration criteria are provided in the protocol taking into account reasonable treatment goals and study drug toleration.

Subject safety will be ensured using protocol defined criteria for treatment discontinuation and rescue therapy with short-acting octreotide and antidiarrheal medication.

Statistical Methods

Formal sample size calculations were not performed. A total of 30 subjects with Carcinoid syndrome is considered suitable to assess the study objectives for PK in subjects with Carcinoid syndrome.

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.

1.2. Schedule of Activities

Table 1: Schedule of Activities - Randomized Treatment Phase

STUDY PROCEDURES	Screening Period		Randomized Treatment Phase					ET	Follow-up
Week (Day) **W=week; D=day**	**W -12[b] to D -1**		**W1 (D1)**	**W2 (D14)**	**W4 (D28)**	**W6 (D42)**	**W8 (D56)**	**-**	**28 days after last dose**
Visit Name	S1	S2	-	-	-	-	EOR	ET[c]	FU/EOS[d]
Window Period (Days)[a]	-	±3	-	±2	±2	±3	±3	-	±2
Onsite Visit	X	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Obtain informed consent	X[f]	-	-	-	-	-	-	-	-
Verify eligibility	X[g]	X	-	-	-	-	-	-	-
Eligibility checklist/ Randomization	-	-	X	-	-	-	-	-	-
Health history, demographics, Baseline characteristics	X[g]	-	-	-	-	-	-	-	-
Full physical including neurological exam, weight, height (height at Screening only)	X	-	X	-	-	-	X	X	-
Target symptom evaluation			X						
Dispense electronic Symptom Diary[h]	X[g]	-	-	-	-	-	-	-	-
Subject completes electronic Symptom Diary daily from S1 to EOR[i,]	X[g]	X	X	X	X	X	X	X	-
Investigator reviews electronic Symptom Diary	-	X	X	X	X	X	X	X	-
Symptom-directed and neurological physical exam	-	X	-	X	X	-	-	-	-
Vital signs	X	X	X	X	X	X	X	X	X
12-lead ECG[j]	X	-	X	X	X	X	X	X	-
Continuous cardiac (Holter) monitoring	-	X	-	X[k]	X[k]	-	X[k]	-	-
Ophthalmic Assessments [l]	X*	X*	X*	X*	X*	X*	X*	X*	
Biliary/gallbladder ultrasound	X[m]	-	-	-	-	-	-	-	-

STUDY PROCEDURES	**Screening Period**		**Randomized Treatment Phase**					**ET**	**Follow-up**
Week (Day) **W=week; D=day**	**W -12[b] to D -1**		**W1 (D1)**	**W2 (D14)**	**W4 (D28)**	**W6 (D42)**	**W8 (D56)**	**-**	**28 days after last dose**
Visit Name	S1	S2	-	-	-	-	EOR	ET[c]	FU/EOS[d]
Window Period (Days)[a]	-	±3	-	±2	±2	±3	±3	-	±2
Onsite Visit	X	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
AE monitoring	X[g]	X	X	X	X	X	X	X	X
Review of prior & concomitant therapies	X[g]	X	X	X	X	X	X	X	X
Pregnancy test[n]	X	-	X (predose)	X	X	X	X	X	X
Clinical laboratory tests (hematology, chemistry, urinalysis)	X[g]	-	X	-	X	X	X	X	X
Serology (HIV, Hepatitis B, and Hepatitis C)	X[g]	-	-	-	-	-	-	-	-
Thyroid hormones and HbA1c	X[g]	-	X	-	X	-	X	X	-
SARS-CoV-2 testing[o]	X[g]	-	X	-	-	-		-	-
Carcinoid syndrome biomarkers (plasma 5-HIAA and pancreastatin[p]; serum chromogranin A and serotonin)	X[g]	-	X	-	X	X	X	X	X
Genotype blood sample (optional)	-	-	X[q]	-	-	-	-	-	-
Paltusotine predose fasting PK	-	-	-	X	X	X	X	-	-
Paltusotine postdose PK[r]	-	-	X	X	X	X	X	-	-
Lanreotide or octreotide PK[s]	-	X	X	X	X	X	X	-	-
Study drug administered during visit	-	-	X	X[t]	X[t]	X	X	-	-
Dispense study drug	-	-	X	X	X	-	X[u]	-	-
Study drug accountability	-	-	-	X	X		X	X	-
EQ-5D-5L EORTC: QLQ-C30, QLQ-GI.NET21 and FACT-CSI	-	-	X	-	-	-	X	X	-
PGI-S	-	-	X	-	X	-	X	X	-
PGI-C	-	-	-	-	X	-	X	X	-

STUDY PROCEDURES	Screening Period		Randomized Treatment Phase					ET	Follow-up
Week (Day) **W=week; D=day**	**W -12[b] to D -1**		**W1 (D1)**	**W2 (D14)**	**W4 (D28)**	**W6 (D42)**	**W8 (D56)**	**-**	**28 days after last dose**
Visit Name	S1	S2	-	-	-	-	EOR	ET[c]	FU/EOS[d]
Window Period (Days)[a]	-	±3	-	±2	±2	±3	±3	-	±2
Onsite Visit	X	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Treatment Preference Question	-	-	-	-	-	-	X	X	-
Subject Interview	-	-	-	-	-	-	X[v]	X	-
Roll-over to OLE	-	-	-	-	-	-	X	-	-

5-HIAA=5-hydroxyindoleacetic acid, AE=adverse event, CS=Carcinoid syndrome, D=Day, ECG=electrocardiogram, 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, EOR=End of Randomized Treatment Phase, EOS=End of Study, ET=Early Termination, FACT-CSI=Functional Assessment of Cancer Therapy – Carcinoid Syndrome Symptom Index, FU=Follow-up, HbA1c=hemoglobin A1c, HIV=human immunodeficiency virus, NET=neuroendocrine tumor, OCT=optical coherence tomography, OLE=Open-Label Extension, PCR=polymerase chain reaction, PGI-C=Patient Global Impression of Change, PGI-S=Patient Global Impression of Severity, PK=pharmacokinetic, SARS-CoV-2=severe acute respiratory syndrome coronavirus 2, S1= Screening Visit 1, S2=Screening Visit 2, W=Week

a All visit dates are projected based on the number of days with Day 1 being the day of randomization which corresponds to Week 1 for the study. The subsequent visit weeks in the Schedule of Activities Table 1 (eg, Week 2/Day 14) signify the end of the week.
b For subjects using long-acting lanreotide or octreotide or short-acting octreotide, see washout instructions in Section 4.1.1.
c This visit is for subjects who discontinue early.
d Follow-up/EOS Visit will be 28 days after last dose for those who completed EOR and do not enter OLE Phase, or those who early terminated from the study.
e Beginning at W2, visits may be performed at home at the discretion of the Investigator with home health care support as needed.
f Informed consent can be obtained on a different day prior to any study procedures of S1 visit being performed in the event of scheduling issue with the subject and this interval should be no more than 2 weeks approximately.
g Procedure is required to be performed on the first day of S1.
h In rare cases when the electronic Symptom Diary cannot be used, exceptions may be allowed upon discussion with the Sponsor to complete the Symptom Diary on paper.
i The completion of an electronic Symptom Diary will continue throughout Screening beginning within 1 day of S1, Week 1 through Week 12 (throughout Randomized Treatment Phase), and selected time periods in the OLE Phase (Section 8.2.1).
j Triplicate ECG to be performed at Screening, 1-3 hours after supervised administration of first dose of study drug, and any subsequent visit where the dose is increased (to 80 or 120 mg) (Section 8.3.3).
k The 24-hour continuous cardiac (Holter) monitoring should be performed ~5 to 7 days after the first 120 mg dose. For W8, continuous cardiac (Holter) monitoring should be performed if the subject is rolling into the OLE and increasing the dose to 120 mg.
l Visual Acuity, Fundus Photography, OCT, Visual Fields. *Initial ophthalmic testing should be performed as soon as practical and then at approximately 6-month intervals, preferably associated with scheduled visits whenever possible, through study completion. If the most recent ophthalmic assessment is performed within 3 months of ET, there is no need to repeat at ET.
m In the event of a scheduling issue, biliary/gallbladder ultrasound can be performed at any time during the Screening Period prior to verification and confirmation of subject eligibility.

n Female subjects of childbearing potential must have a negative serum pregnancy test at Screening. All pregnancy tests at other visits will be urine pregnancy tests. If the result of a urine pregnancy test is positive, then the result will be confirmed with a serum pregnancy test.
o SARS-CoV-2 antigen test to be conducted according to local lab procedures, if required as per local regulations.
p Pancreastatin will not be collected and analyzed for subjects enrolled in EU countries.
q If not collected at W1 (D1) visit, may be collected at W2 (D14) visit.
r Postdose PK is taken between 1 and 3 h postdose which corresponds to the T_{max} of paltusotine.
s Octreotide and lanreotide PK sample is to be collected from previously treated subjects only for visit S2 and during Randomized Treatment Phase.
t Dose adjustment is allowed once at either Week 2 or Week 4. See Table 7.
u Only for subjects entering the OLE Phase.
v The Subject Interview will be available to subjects only in certain countries.

Table 2: Schedule of Activities - Open-Label Extension Phase

STUDY PROCEDURES	Open-Label Extension Phase[a]												
Week (Day) W=week; D=day	**W8 (D56)**	**W10 (D70)**	**W12 (D84)**	**W24 (D168)**	**W36 (D252)**	**W48 (D336)**	**W58[m] (D406)**	**W70 (D490)**	**W82 (D574)**	**W96 (D672)**	**W110 (D770)**	**-**	**4 Weeks after ET/ EOT**
Visit Name	-	-	-	-	-	-	-	-	-	-	**EOT**	**ET[b]**	**FU/ EOS[c]**
Window (Days)	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	-	±7
Onsite Visit	X[d]	X	X[d]	X[d]	X	X[d]	X	X	X[d]	X[d]	X	X	X
Full physical including neurological exam, weight	X	-	-	-	-	-	X	-	-	-	X	X	-
CT or MRI tumor imaging [e]	-	X	-	-	X	-	-	X	-	-	X	X	-
Symptom-directed and neurological physical exam	-	-	X	X	X	X	X	X	X	X	-	-	-
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject completes electronic Symptom Diary daily at specified periods [f]	X	X	X	X	X	X	X	X	X	X	X	X	-
12-lead ECG[g]	X	X	X	X	X	X	X	X	X	X	X	X	-
Continuous cardiac (Holter) monitoring	~5-7 days after the first 120 mg dose										-	-	-
Ophthalmic assessments [h]	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	-
Investigator reviews electronic Symptom Diary	X	X	X	X	X	X	X	X	X	X	X	X	-
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests (hematology, chemistry, urinalysis)	X	-	-	X	X	X	X	X	X	X	X	X	-

STUDY PROCEDURES	**Open-Label Extension Phase[a]**												
Week (Day) W=week; D=day	**W8 (D56)**	**W10 (D70)**	**W12 (D84)**	**W24 (D168)**	**W36 (D252)**	**W48 (D336)**	**W58[m] (D406)**	**W70 (D490)**	**W82 (D574)**	**W96 (D672)**	**W110 (D770)**	**-**	**4 Weeks after ET/ EOT**
Visit Name	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**EOT**	**ET[b]**	**FU/ EOS[c]**
Window (Days)	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	-	±7
Onsite Visit	X[d]	X	X[d]	X[d]	X	X[d]	X	X	X[d]	X[d]	X	X	X
Thyroid hormones and HbA1c	-	-	-	-	X	-	X	-	X	-	X	X	-
Carcinoid syndrome biomarkers:(plasma 5-HIAA and pancreastatin; serum chromogranin A and serotonin)	X	-	-	X	X	X	X	X	X	X	X	X	X
Paltusotine pre- and postdose PK[j]	X	-	-	X	-	-	X	X	-	-	X	-	-
Study drug administered during visit[k]	X	X	X	X	X	X	X	X	X	X	X	-	-
Lanreotide or octreotide PK[l]	-	-	X	X	-	-	-	-	-	-	-	-	-
Dispense study drug	X	X	X	X	X	X	X	X	X	X	-	-	-
Study drug accountability	X	X	X	X	X	X	X	X	X	X	X	X	-
EQ-5D-5L, EORTC QLQ-C30, QLQ-GI.NET21, and FACT-CSI	X	-	X	-	-	-	X	-	X	-	X	X	-
PGI-C	X		X	X	X	X	X		X		X	X	
PGI-S	X		X	X	X	X	X		X		X	X	

AE=adverse event, CT=computed tomography, D=Day, ECG=electrocardiogram, 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, EOS=End of Study, EOT=End of Treatment, ET=Early Termination, FACT-CSI=Functional Assessment of Cancer Therapy – Carcinoid syndrome Symptom Index, FU=Follow-up, HbA1c=hemoglobin A1c, MRI=magnetic resonance imaging, NET=neuroendocrine tumor, OLE=Open-Label Extension, PGI-C=Patient Global Impression of Change, PGI-S= Patient Global Impression of Severity, PK=pharmacokinetic, W=Week

a All visit dates are projected based on the number of days from D1 and the subsequent visit weeks in the Schedule of Activities Table 2 (eg, Week 10/Day 70) signify the end of the week. Data from the Week 8 Visit will be used as Baseline (D1) data in the OLE.

b This visit is for subjects who discontinue early.

c Follow-up/EOS Visit will be 28 days after last dose for subjects completing OLE Phase or terminating early. Subjects are to continue to self-administer study drug until the EOT (Week 110), except when subjects are dosed during a study visit, they will receive study intervention directly from the Investigator or designee, under medical supervision.

d Visits may be performed at home at the discretion of the Investigator with home health care support as needed.

e Refer to Imaging Section 8.8. While on study drug, CT or MRI scan should be obtained approximately 6 months after the subject's most recent pretrial scan. The choice of CT or MRI scan should be consistent with previous scans. If an assessment is performed within 3 months of ET, there is no need to repeat at ET.

f An electronic Symptom Diary completed daily will be completed from Week 8 through Week 12, and selected time periods in the OLE Phase (Section 8.2.1).

g Triplicate ECG should be performed 1 to 3 hours after supervised administration of study drug, where the dose is increased (to 80 or 120 mg) (Section 8.3.3).

h Visual Acuity, Fundus Photography, OCT, Visual Fields. *Initial ophthalmic testing should be performed as soon as practical and then at approximately 6-month intervals, preferably associated with scheduled visits whenever possible, through study completion. If the most recent ophthalmic assessment is performed within 3 months of ET, there is no need to repeat at ET.

i All pregnancy tests during this phase will be urine pregnancy tests. If the result of a urine pregnancy test is positive, then the result will be confirmed with a serum pregnancy test.

j Predose PK should be a fasting sample. Postdose PK is taken between 1 and 3 h postdose which corresponds to the T_{max} of paltusotine.

k In cases of poor tolerability, the Investigator may reduce dose based on his/her assessment.

l Octreotide and lanreotide PK samples are to be collected from previously treated subjects only.

m Subjects who previously completed the OLE (when the OLE was until Week 58) are eligible to reenter OLE. Week 58 visit will be used as the visit time point where the subjects reenter the study. The dose level will be at the dose they were at when they previously completed the OLE.

2. INTRODUCTION

2.1. Study Rationale

Carcinoid syndrome usually occurs in intestinal neuroendocrine tumors (NETs) with liver metastases, which makes surgical cure very difficult in most patients. While long-acting somatostatin receptor ligand (SRL) therapies are mainstay treatments for Carcinoid syndrome, relief of Carcinoid syndrome symptoms at labeled doses is inadequate for many patients. Long-acting SRL therapies have also demonstrated efficacy in prolonging progression-free survival in patients with nonfunctional, metastatic, well or moderately differentiated enteropancreatic NETs (Rinke, 2009; Caplin, 2014; Kunz, 2015; Chan and Kulke, 2016; Oronsky, 2017). Long-acting SRL therapies may be associated with significant dose-to-dose exposure variability related to injection techniques. For example, nurses at MD Anderson Cancer Center successfully delivered only 52% of 328 octreotide long-acting release (LAR) injections to the intramuscular space when evaluated by computed tomography (CT) (Boyd, 2013). Negative experiences with chronic injections of long-acting SRL therapies, particularly octreotide LAR, also have been identified in patients with Carcinoid syndrome, including injection site pain or soreness (Adams, 2019). A daily oral treatment such as paltusotine may achieve higher drug concentrations in the liver, which is the most common source of the vasoactive mediators causing Carcinoid syndrome symptoms. Paltusotine has the potential to improve treatment outcomes, achieving symptom control while eliminating painful injections.

The purpose of this study is to evaluate the safety, pharmacokinetic (PK), and dose response of paltusotine treatment in patients with Carcinoid syndrome.

2.2. Background

Neuroendocrine tumors (NETs) arise from cells of the enteroendocrine system in the gastrointestinal tract (approximately 70% of cases), the lung (approximately 25% of cases), and more rarely, the pancreas. The estimated 20-year limited duration prevalence of NETs in the United States as of 01 January 2014 was 171,321. Approximately 48% of these tumors are locally advanced or metastatic at the time of diagnosis (Dasari, 2017). Approximately 10 to 20% (Halperin, 2017) of these tumors may present with symptoms of chronic flushing and diarrhea, referred to as Carcinoid syndrome.

Excess serotonin and other hormonally active substances (including histamines, tachykinins, kallikreins, and prostaglandins) produced by some NETs are responsible for the symptoms collectively referred to as Carcinoid syndrome (Vinik, 2018). These symptoms most commonly include cutaneous flushing (seen in 85%) and recurrent watery diarrhea and cramping (seen in 75%-85%). Carcinoid syndrome is confirmed biochemically with documentation of elevations of serum serotonin or the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) in plasma or urine. Once biochemical confirmation of Carcinoid syndrome is established, imaging studies are conducted to stage the tumor. Multiphasic contrast enhanced CT scanning of the abdomen is often used to initiate localization and to assess for the presence of metastatic disease. Abdominal magnetic resonance imaging (MRI) is preferred by some because of increased sensitivity for the detection of metastatic disease in the liver. Whenever possible, tumor histology, including assessment of proliferative indices, is important for diagnostic, prognostic, and treatment planning purposes.

Carcinoid syndrome is usually caused by well-differentiated NETs, nearly 90% of which express somatostatin receptors (SSTRs) (Vinik, 2018) and 80% of patients with Carcinoid syndrome respond to octreotide (Kvols, 1986). The dominant target for octreotide is somatostatin type 2 receptor (SST2). Therefore, SSTR imaging can be useful for localizing NETs not visualized with CT or MRI, providing whole body images of tumor burden as well as documenting tumoral expression of SSTRs prior to treatment with SRLs. Currently, positron emission tomography (PET) tracers for SSTR imaging (eg, ^{68}Ga-Dotatate and ^{68}Ga-Dotatoc, and ^{64}Cu-Dotatate) in combination with CT are preferred relative to ^{111}In-pentetreotide imaging because of increased spatial resolution and sensitivity for detection of small tumors.

Paltusotine (formerly CRN00808) is an orally administered nonpeptide SST2 agonist currently under development by Crinetics Pharmaceuticals, Inc. for the treatment of Carcinoid syndrome. Additionally, the clinical program includes two completed Phase 2 studies (CRN00808-02, CRN00808-03) and one Phase 2 open-label long-term extension study (CRN00808-05) that is still ongoing in participants with acromegaly. The RC Phase of two Phase 3 studies (CRN00808-08, CRN00808-09) in participants with acromegaly have been completed, in addition to an RTP of one Phase 2 study (CRN00808-11) in participants with carcinoid syndrome. The OLE phases of these studies are still ongoing.

Paltusotine was generally well tolerated across all studies in the clinical program with no unexpected safety signals. The safety profile of paltusotine includes adverse drug reactions (ADRs) of gastrointestinal events (diarrhea, abdominal pain, nausea, and abdominal discomfort), sinus bradycardia, and cholelithiasis, consistent with other SRL treatments.

This study will be conducted in compliance with the protocol, the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and with applicable local legislation including the Clinical Trial Regulation (CTR) EU No 536/2014.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of paltusotine may be found in the IB.

2.3.1. Safety Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CRN00808-11 Study Intervention – Paltusotine		
Side effects	Diarrhea, abdominal pain, nausea, abdominal discomfort, bradycardia (including sinus bradycardia and bradycardia), and cholelithiasis have been identified as ADRs associated with paltusotine. Rationale: these AEs were generally mild or moderate and did not lead to discontinuations in previous studies.	Clinical monitoring, symptomatic measures, study drug interruption if necessary. Regular safety surveillance, including laboratory testing, physical examinations, AE monitoring, ECG monitoring, gall bladder monitoring, and evaluations for protocol-specified study drug stopping rules.
CRN00808-11 Study Intervention – Short-Acting Octreotide[a]		
Side effects	Gallbladder (eg, cholelithiasis, cholecystitis, cholangitis, pancreatitis) Cardiac function (eg, complete atrioventricular block, bradycardia, arrhythmia, conduction abnormalities, other electrocardiogram changes) Gastrointestinal (eg, pancreatitis, diarrhea, loose stools, nausea, and abdominal discomfort) Pregnancy (eg, risk of pregnancy with normalization of IGF-1 and growth hormone) Glucose metabolism (eg, hypoglycemia, hyperglycemia) Thyroid function (eg, hypothyroidism, goiter) Nutrition (eg, may alter absorption of dietary fats, decreased vitamin B12 levels, and abnormal Schilling's Tests)	Regular safety surveillance, including laboratory testing, physical examinations, AE monitoring, and evaluations for cardiovascular safety. Study drug stopping rules provided in protocol

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CRN00808-11 Study Procedures		
Blood draws	Pain, bleeding, or infection possible. Rationale: Needed for safety evaluation of study drug	Symptomatic measures
MRI or CT scans	Claustrophobia, dizziness, mild nausea, numbness, tingling, muscle twitches, tiny flashing lights in field of vision, or momentary imbalance after leaving the magnet. Possible use of intravenous contrast with associated risk of renal injury (in people with severe kidney disease) or hypersensitivity reaction Rationale: Monitoring NET tumor status	Standard of care symptomatic and preventative management measures
Ultrasound	Ultrasound waves may heat the tissues slightly and, in some cases, also can produce small pockets of gas in body fluids or tissues. Rationale: Needed for monitoring gallbladder and biliary ducts	Symptomatic measures
Scintigraphy / PET scan	Low dose radiation exposure from these scans. Uncommon side effects may include fever, flushing, headache, low blood pressure, joint pain, nausea, sweating and weakness	Symptomatic measures
Distance-corrected visual acuity testing Visual field testing	There are no known risks or complications associated with these tests.	None needed
Fundus photography OCT of the macula	Some subjects may experience some eye dryness or fatigue.	Symptomatic measures

AE(s)=adverse event(s); CT=computed tomography; IB=Investigator's Brochure; IGF-1=insulin-like growth factor 1; MRI=magnetic resonance imaging; NET=neuroendocrine tumor, OCT=optical coherence tomography.
[a.] Source: (Sandostatin LAR 2024)

2.3.2. Benefit Assessment

Based on nonclinical data, paltusotine is expected to have benefit in the treatment of Carcinoid syndrome (see current Investigator's Brochure).

Completed Phase 2 studies CRN00808-02 and CRN00808-03 showed evidence for insulin-like growth factor 1 (IGF-1) maintenance in acromegaly subjects previously treated with octreotide LAR or lanreotide monotherapy who were switched to paltusotine oral monotherapy for a period of 13 weeks. Overall, IGF-1 levels after the switch to paltusotine were similar to those at Baseline during treatment with octreotide LAR or lanreotide injections. Results from the ongoing OLE study CRN00808-05 support the long -term maintenance of effect and safety profile in subjects with acromegaly. Because octreotide LAR and lanreotide are approved first line treatments for both acromegaly and Carcinoid syndrome and because the pharmacologic effect of

paltusotine is similar to that of octreotide LAR and lanreotide, the evidence from clinical studies of paltusotine in acromegaly supports the hypothesis that it also will be effective in Carcinoid syndrome. At this time, it is unknown whether paltusotine will provide control of neuroendocrine tumor growth.

ADRs of bradycardia, gastrointestinal events (diarrhea, abdominal pain, nausea, and abdominal discomfort), and cholelithiasis have been identified. These AEs are generally mild or moderate and can be managed through the appropriate risk mitigation measures (eg, clinical monitoring, safety surveillance). In addition to protocol specified safety surveillance, Investigators in clinical trials for paltusotine are advised to monitor subjects based on the known side effect profile of SRLs, to monitor for neuroendocrine tumor growth, and manage as clinically appropriate.

This protocol (Section 10.1.8) has incorporated flexibility in the need for in-person visits at study sites while safeguarding the health and well-being of trial subjects and minimizing risk to trial and study data integrity.

2.3.3. Overall Benefit: Risk Conclusion

Based on the available information, the known and potential risks of treatment with paltusotine are considered acceptable in relation to the potential benefits of treatment in subjects with Carcinoid syndrome.

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives and Endpoints of the Study

Objectives	Endpoints[a]
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, 12-lead ECG, and 24-hour continuous cardiac monitoring (only for subjects 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: In subjects who meet diarrhea entry criteria only: • Have less than 4 mean bowel movements daily • Have a >20% reduction in the mean daily number of bowel movements compared with Baseline In subjects who meet flushing entry criteria only: • Have a >30% reduction compared with Baseline in the mean daily number of flushing episodes. In subject who meet both diarrhea and flushing entry criteria: • 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 subjects in the different dose arms	Proportion of target symptom responders by dose during the last week of the Randomized Treatment Phase: • Subjects 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 subject 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
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

Objectives	Endpoints[a]
To evaluate the effect of paltusotine treatment on the 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 subject 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 subject 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[a]
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 subject-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 subjects 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, 12-lead ECG, and ophthalmic assessments
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 subjects who meet diarrhea entry criteria only:</u> • Have less than 4 mean bowel movements daily, and have a >20% reduction in the mean daily number of bowel movements compared with Baseline <u>In subjects who meet flushing entry criteria only:</u> • Have a >30% reduction compared with Baseline in the mean daily number of flushing episodes <u>In subject who meet both diarrhea and flushing entry criteria:</u> Have less than 4 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

Objectives	Endpoints[a]
	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
	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 subject-perceived carcinoid symptom severity and change	• PGI-S at EOT • PGI-C at EOT
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 subjects rush to the bathroom): • From the last week prior to Baseline to the last week prior to EOT

BM=bowel movement; ECG=electrocardiogram; EORTC QLQ-C30=EORTC Quality of Life questionnaire; EORTC QLQ-GI.NET21=EORTC Quality of Life questionnaire in GI NET; EOR=end of randomized Treatment Phase; EOS=End of Study; EOT=end of treatment; 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; OLE=Open-Label Extension; PGI-C=Patient Global Impression - Change; PGI-S=Patient Global Impression of Severity; PK=pharmacokinetic; QD=once a day; TEAE=treatment-emergent adverse events

[a] All endpoint assessments, except biochemical markers of Carcinoid syndrome and safety laboratories to be collected in daily electronic diary.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, randomized, open-label, parallel-group, multi-center study. The study includes a Screening Period of up to 12 weeks. After completion of Screening, subjects will be randomly assigned to 40 mg QD vs. 80 mg QD open-label dose groups for 8 weeks, referred to as the Randomized Treatment Phase. A dose up-titration by 40 mg QD is an option based on symptomatology during the first 4 weeks of the Randomized Treatment Phase.

Following completion of the Randomized Treatment Phase, subjects may be eligible to enter the Open-Label Extension (OLE) Phase of the study in which they will receive paltusotine for 102 weeks. Subjects who complete the Randomized Treatment Phase, and for whom the Investigator recommends continuation of treatment on paltusotine, may be eligible to participate in the OLE Phase. There will be a 4-week follow-up as depicted in Figure 1. The total duration of paltusotine treatment is up to 110 weeks or up to 28 months. This is summarized and presented in Figure 1.

4.1.1. Screening

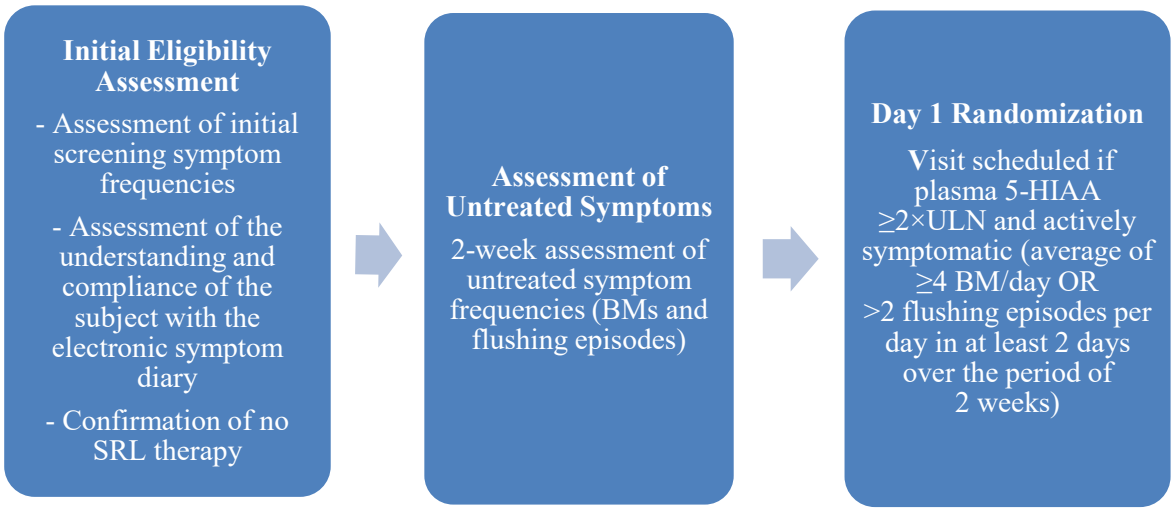
The Screening Period will vary from 2 to 12 weeks, depending on when subjects meet the qualifying criteria for randomization as described below.

Subjects will be eligible for Screening if they are:

- Not currently treated with any SRL therapy for at least 12 weeks prior to Screening and are actively symptomatic (average of ≥4 bowel movements (BM)/day or >2 flushing episodes per day in at least 2 days over a period of 2 weeks), OR
- Currently symptomatically controlled (average <4 bowel movements [BMs]/day and average ≤2 flushing episodes/day over a 2-week period) while treated with lanreotide, octreotide LAR, or short-acting octreotide (immediate release octreotide injection or oral octreotide) and who are willing to wash out of their medication.

The completion of an electronic Symptom Diary will continue daily throughout Screening beginning within 1 day of S1, and through Week 12 of the study (through Randomized Treatment Phase and 4 weeks into OLE) and then during selected time periods in the OLE Phase (Section 8.2.1). During the Screening Period, data from the diary will be used to assess initial screening symptom frequencies and, for those who wash out of lanreotide or octreotide, to assess post-washout symptom frequencies. Stool consistency according to the Bristol scale and abdominal pain according to a numeric rating scale (NRS) will also be recorded in the electronic Symptom Diary. In addition to determining eligibility for randomization, the Screening Period will be used to assess the understanding and compliance of the subject with the electronic Symptom Diary. Some endpoints use Baseline defined from the Screening Period which is defined as the last 7 days prior to start of randomized treatment. Otherwise, Baseline is defined as the last value prior to start of randomized treatment.

Figure 2: Screening Schematics for Subjects Not Currently Treated with Any SRL Therapy



BMs=bowel movements, 5-HIAA=5-Hydroxyindoleacetic acid, SRL=somatostatin receptor ligand, ULN=upper limit of normal

For subjects not currently treated with any SRL therapy, 2 Screening visits (S1 and S2) will be scheduled in the Screening Period. After completing the initial eligibility assessment in S1, a 2-week assessment of untreated symptom frequencies (BMs and flushing episodes) will be initiated. At the S1 visit, plasma 5-HIAA levels will be collected. If the plasma 5-HIAA result is ≥2× the upper limit of normal (ULN), and the 2-week assessment is complete, demonstrating the subject meets symptomatic qualifying criteria (average of ≥4 BM/day OR >2 flushing episodes per day in at least 2 days over the period of 2 weeks), the Day 1 randomization visit should be scheduled (Figure 2) after completing S2. Subjects not meeting these criteria will be considered screen failures.

For subjects using pretrial lanreotide or octreotide LAR, 2 Screening visits (S1 and S2) will be scheduled. Both S1 and S2 are determined based on the subject's injection schedule, which is ascertained prior to trial entry. Subjects will not continue their lanreotide or octreotide LAR after the informed consent is given at S1.

Screening Visit 1 (S1) should be scheduled after the subject's last dose of pretrial lanreotide or octreotide LAR. The second Screening Visit (S2) will occur approximately 2 weeks after S1 (Figure 3). The interval between S1 and S2 should not be longer than the usual interval between injections for the subject. Completion of the Symptom Diary should begin within 1 day of S1. The 2-week interval between S1 and S2 will be used for the assessment of the subject's baseline symptom control.

At the S2 Visit, the degree of symptom control resulting from pretrial lanreotide or octreotide LAR dosing will be assessed. For subjects who are controlled symptomatically using pretrial SRLs, adequate symptom control is defined as having an average of <4 BM/day and an average of ≤2 flushing episodes/day over a 2-week period. Only subjects with adequate symptom control over a 2-week period following S1 will continue into the Screening Period for up to 10 weeks after S2. During this time, the subject's diary will be closely monitored for changes in flushing and BMs.

Subjects may qualify for trial entry as the result of an increase in the occurrence of either BMs or of flushing. Eligible subjects will have an increase in symptoms during a 7-day period after S2, compared to the period between S1 and S2, of either:

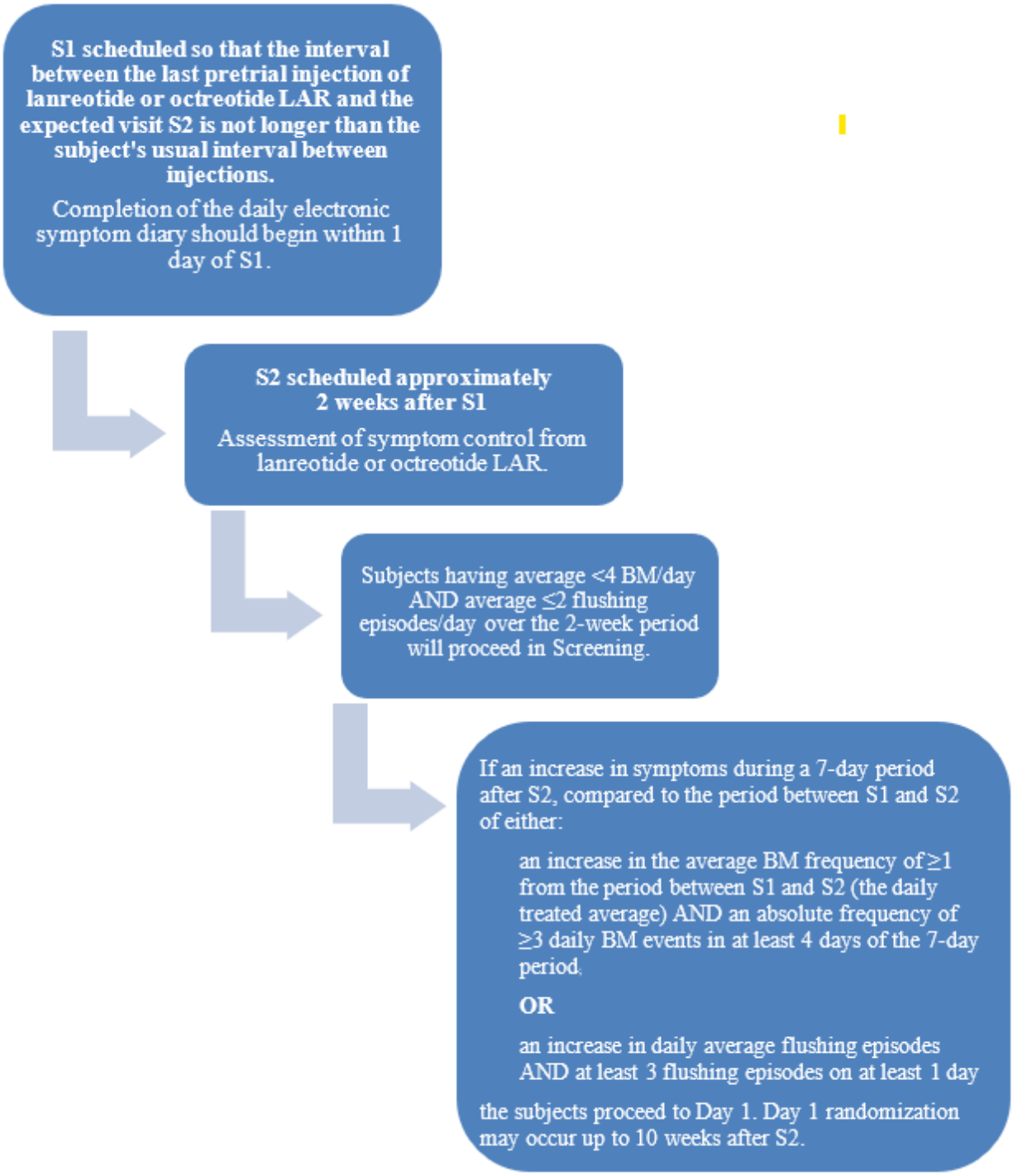
- An average increase of ≥1 BM/day over the after daily BM frequency observed in the period between S1 and S2 AND
- An absolute frequency of ≥3 daily BMs, in at least 4 days within the 7-day period

OR

- An increase in daily average flushing episodes AND
- At least 3 flushing episodes on at least 1 day

If the subject does not qualify for the Day 1 randomization visit within 10 weeks of S2, the subject will be considered a screen failure (Figure 3).

Figure 3: Screening Schematics for Subjects Using Pretrial Lanreotide or Octreotide LAR



Note: Subject is a screen failure if Day 1 cannot be scheduled within 10 weeks of S2.
BMs=bowel movements; LAR=long-acting release; S1=Screening Visit 1; S2=Screening Visit 2; ULN=upper limit of normal.

For subjects using regular doses of short-acting octreotide (immediate release octreotide injection or oral octreotide) with or without combined long-acting SRL therapy (lanreotide or octreotide LAR) for the prevention of Carcinoid syndrome symptoms pretrial, 2 Screening visits (S1 and S2) will be scheduled in the Screening Period. The interval between S1 and S2 should not be longer than the usual interval between injections of lanreotide or octreotide LAR for the subject. Completion of the Symptom Diary should begin within 1 day of S1. The 2-week interval between S1 and S2 will be used for the assessment of the subject's baseline symptom control.

After S1, a 2-week assessment of treated symptom frequencies (BMs and flushing episodes) will be initiated. The subject should continue pretrial dosing of short-acting octreotide at the most recent pretrial dose and administration frequency during this period. Completion of the electronic Symptom Diary should begin within 1 day of S1. S2 will occur approximately 2 weeks after S1 (Figure 4).

At the S2 Visit, symptom control from regular short-acting octreotide, with or without lanreotide or octreotide LAR, will be assessed. Subjects may qualify for trial entry as the result of an increase in the occurrence of either BMs or of flushing. Eligible subjects will have an increase in symptoms during a 7-day period after S2, compared to the period between S1 and S2, of either:

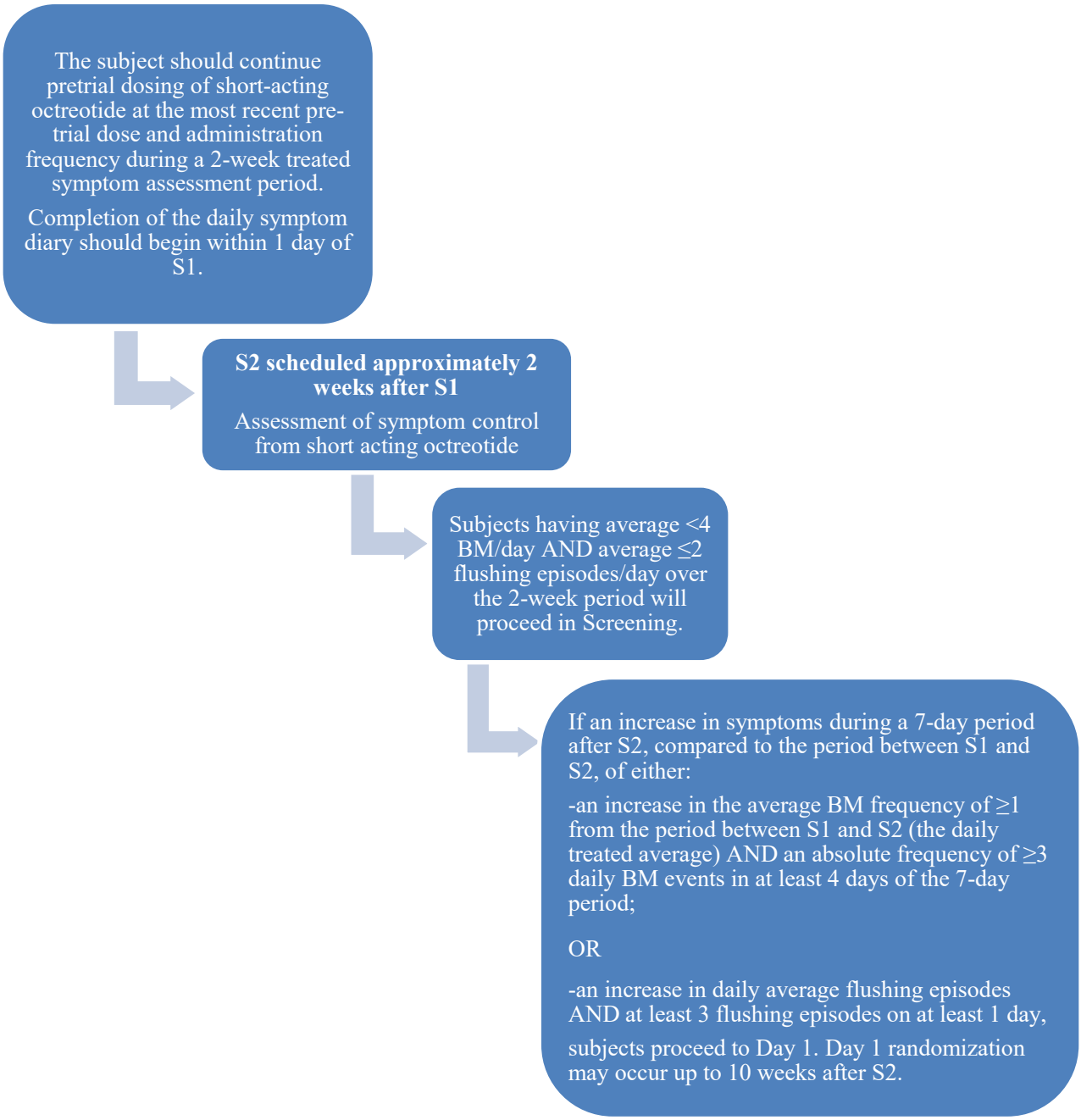
- An average increase ≥1 BM/day over the average daily BM frequency observed in the period between S1 and S2 AND
- An absolute frequency of ≥3 daily BMs in at least 4 days of the 7-day period

OR

- An increase in daily average flushing episodes AND
- At least 3 flushing episodes on at least 1 day

If the subject does not qualify for the Day 1 randomization visit within 10 weeks of S2, the subject will be considered a screen failure (Figure 3).

Figure 4: Screening Schematics for Subjects Using Regular Doses of Short-acting Octreotide



Note: Subject is a screen failure if Day 1 cannot be scheduled within 10 weeks of S2.
BMs=bowel movements; S1=Screening Visit 1; S2=Screening Visit 2.

Antidiarrheal agents, diphenoxylate and loperamide, are considered concomitant medications and may be used as recommended by the Investigator.

Investigator should refer to guidelines provided by the Sponsor for recommending antidiarrheal agents to the subjects during Screening (Table 3).

Table 3: Oral Antidiarrheal Agents During the Screening Period

Regimen	Criteria for Initiating	Dose and Frequency
Diphenoxylate	As needed for improved symptom control	5 mg ≤4×daily as needed
Loperamide	As needed for improved symptom control	4 mg initiation, 2 mg after each loose bowel movement as needed; total daily dose ≤16 mg

Short-acting octreotide is considered a rescue medication (ie, auxiliary medicinal product) and can be used according to Table 4. Investigators CCI [redacted] CCI [redacted] CCI [redacted]

If there is a delay in scheduling the Day 1 randomization visit for subjects in Screening who have met the symptomatic criteria qualifying them for randomization, subjects may begin short-acting octreotide. Subjects also will receive instructions on how to use short-acting octreotide 200 µg up to 3 times daily, at the direction of the Investigator, when symptomatic criteria are met (Table 4). Short-acting octreotide must be stopped no later than 12 hours prior to the randomization visit.

Table 4: Use of Short-acting Octreotide During the Screening Period

Pretrial Treatment Status	Required to Start Short-acting Octreotide*	Criteria for Stopping Short-acting Octreotide
Not currently treated with any SRL therapy	≥4 BM/day for 2 consecutive days or if flushing frequency is ≥3 flushing episodes/day for at least 1 day	Symptom relief for 24 hours after initiation of short-acting octreotide
SRL treated: Octreotide LAR Short-acting octreotide Lanreotide	Increased bowel movement frequency with ≥2 BM/day for 2 consecutive days above the Screening daily treated average measured between S1-S2 or ≥3 flushing episodes/day for at least 1 day	Symptom relief for 24 hours after initiation of short-acting octreotide

BM=bowel movement; LAR=long-acting release; S1=Screening Visit 1; S2=Screening Visit 2; SRL=somatostatin receptor ligand
*Symptoms requiring treatment are defined as diarrhea or flushing episodes of severe intensity, ie, symptoms which prevent normal everyday activities.

Diphenoxylate or loperamide may be used as needed for improved symptom control at any time during the study except when short-acting octreotide is being used for rescue therapy. All administrations of short-acting octreotide or antidiarrheal medications should be recorded in the study diary.

4.1.2. Randomized Treatment Phase

Once all Screening assessments are complete and the subject's eligibility is verified by the Investigator and confirmed by the Medical Monitor via submission of the Medical Monitor Eligibility Verification Form, the subject will be randomized to 40 mg QD vs. 80 mg QD for the 8-week Randomized Treatment Phase. On Day 1 of the Randomized Treatment Phase, the Investigator will query the subject to identify the most troublesome target symptom as assessed by the subject (BM or flushing). The target symptom will be documented. Subjects will be provided on Day 1 with sufficient paltusotine 20 mg tablets for 40 mg QD or 80 mg QD for 14 days and will return to the site on Day 14. Scheduled study visits will occur on Days 28, 42, and 56. A determination on Day 56 (referred to as Week 8 in the SOAs) will be made for potential enrollment in the OLE Phase. Beginning at W2, visits may be performed at home at the discretion of the Investigator, with home health care support as needed.

4.1.2.1. Treatment of Breakthrough Carcinoid Syndrome Symptoms During Randomized Treatment Phase

Diphenoxylate or loperamide may be used as needed at the discretion of the Investigator for improved symptom control at any time during the study except when short-acting octreotide is being used for rescue therapy. Investigators should CCI [redacted] CCI [redacted] CCI [redacted] Possible treatment regimens for breakthrough symptoms of Carcinoid syndrome occurring during the study are delineated in Table 5.

On Day 1, all subjects who have not already received instructions on how to use short-acting octreotide 200 µg up to 3 times daily, at the direction of the Investigator, will receive instructions for rescue therapy when criteria are met (Table 6). Study staff should instruct subjects on the criteria for initiating and stopping short-acting octreotide as described in Table 6. Short-acting octreotide should not be given for at least 12 hours before biomarker sample collection.

All administrations of short-acting octreotide or antidiarrheal medications should be recorded in the study diary.

Table 5: Possible Treatment Regimens for Breakthrough Symptoms

Regimen	Criteria for Initiating	Dose/Frequency
Diphenoxylate	As needed for improved symptom control	5 mg ≤4×daily as needed
Loperamide	As needed for improved symptom control	4 mg initiation, 2 mg after each loose BM as needed; total daily dose ≤16 mg
Short-acting octreotide	Table 6 rescue criteria	200 µg up to 3×daily until criteria for stopping (Table 6) are met

Table 6: Short-acting Octreotide Rescue Therapy

Pretrial Treatment Status	Criteria for Starting Short-acting Octreotide*	Criteria for Stopping Short-acting Octreotide*
Not currently treated with any SRL therapy	After 3 days of starting study drug or a new study drug dose, ≥4 BM/day for 2 consecutive days or if flushing frequency is ≥3 flushing episodes/day for at least 1 day	Symptom relief for 24 hours after initiation of short-acting octreotide
SRL treated: Octreotide LAR, Short-acting octreotide Lanreotide	After 3 days of starting study drug or a new study drug dose, increased bowel movement frequency with ≥2 BM/day for 2 consecutive days above the Screening daily treated average measured between S1-S2 or ≥3 flushing episodes/day for at least 1 day	Symptom relief for 24 hours after initiation of short-acting octreotide

Notes: If the criteria for rescue therapy are met on a second occasion between visits and the subject starts the second course of short-acting octreotide, the subject should stay on short-acting octreotide regularly until the next scheduled visit
BM = bowel movement; LAR = long-acting release; S1 = Screening Visit 1; S2 = Screening Visit 2; SRL=somatostatin receptor ligand
*Symptoms requiring treatment are defined as diarrhea or flushing episodes of severe intensity, ie, symptoms which prevent normal everyday activities.

If the subject experiences Carcinoid syndrome symptoms that meet protocol criteria for short-acting octreotide rescue, another option to treat the symptoms is to increase the respective dose by 40 mg QD based on symptomatology to a maximum dose of 80 or 120 mg QD once during the first 28 days (see Table 7). No dose increases are allowed after Day 28 through the remaining 4 weeks of the Randomized Treatment Phase of the study. Table 7 summarizes the dose adjustments during the randomized, parallel-group portion of the study.

Table 7: Dose Adjustments During Randomized Treatment Phase

Carcinoid Symptom Criteria	Tolerability Criteria	Dose Adjustment
On Day 14 or Day 28: no rescue treatment initiated or required during preceding 7 days	Acceptable tolerability of current dose	No dose change
On Day 14 or Day 28: ≥1 rescue treatment initiated or required during preceding 7 days	Acceptable tolerability of current dose	40 mg→80 mg or 80 mg→120 mg*
Any time during Randomized Treatment Phase	Unacceptable tolerability of 80 or 120 mg doses	80 mg→40 mg or 120 mg→80 mg

ECG = electrocardiogram
Note: Triplicate ECG should be performed at Screening, 1-3 hours after supervised administration of first dose of study drug, and any subsequent visit where the dose is increased (to 80 or 120 mg) (Section 8.3.3). Continuous cardiac (Holter) monitoring (24 hour) should be performed approximately 5-7 days after the first 120 mg dose.
*The first dose of paltusotine and the initial dose after the 40 mg increase to 80 mg or 80 mg increase to 120 mg should be administered at the clinical research site.

4.1.3. Open-Label Extension Phase

Subjects completing the 8 weeks Randomized Treatment Phase may begin the OLE Phase of the study if, in the opinion of the Investigator, the subject may benefit from OLE Phase participation.

For those rolling over into the OLE, the initial OLE dose will be based on the frequency of rescue treatments and study drug tolerability, as assessed by the Investigator. The first dose of OLE will be administered at the clinical research site on Week 8 (Day 56) visit. If the subject experiences Carcinoid syndrome symptoms that meet protocol criteria for short-acting octreotide rescue during the OLE Phase (Table 6 Section 4.1.2.1), the dose may be increased by 40 mg QD to a maximum dose of 120 mg QD (ie, the maximum dose will be reached at 1 study visit for subjects starting at 80 mg and at 2 study visits for subjects starting at 40 mg; Table 8). In the event that the worsening of Carcinoid syndrome symptoms that meet protocol criteria for short-acting octreotide rescue (Table 6 Section 4.1.2.1), occurs between the scheduled visits and the Investigator determines it is appropriate to increase the subject's dose before the next scheduled visit, an unscheduled visit can be added in order to increase the subject's dose. Subjects in the OLE Phase who are uptitrated to the 80 mg or 120 mg dose will need to swallow the first dose under the supervision in the research center. Triplicate ECGs will be performed 1 to 3 hours after supervised administration of study drug where the dose is increased (to 80 or 120 mg). 24-hour continuous cardiac (Holter) monitoring should be performed 5 to 7 days after the first 120 mg dose. For W8, continuous cardiac (Holter) monitoring should be performed if the subject is rolling into the OLE and increasing the dose to 120 mg. A paltusotine predose blood draw for PK, safety labs and postdose PK blood draw at 1 to 3 hours should also be done. If the subject is on 120 mg of paltusotine and meets rescue criteria, they should be discontinued from the study for lack of efficacy (Section 7.1).

Subjects not continuing in the OLE study will have their last Randomized Treatment Phase dose administered at the Week 8 visit.

Subjects who have previously completed the OLE (when the OLE concluded at Week 58) may rejoin the OLE at the same dose they were previously on if they meet the following conditions: (1) the Investigator has determined that the subject's disease is stable, (2) safety assessments, including chemistry, hematology, urinalysis, and baseline electrocardiogram, show no significant changes compared to previous evaluations, and (3) approval from the Medical Monitor.

Once these three conditions are met, the subject may reenter the OLE after discontinuation of their current SSA therapy, with the timing at the discretion of the Investigator. The subject will reenter the OLE at the Week 58 timepoint and follow the SOA as described in Table 2.

Table 8: Dose Adjustments during Open-Label Extension Phase

Carcinoid Symptom Criteria	Tolerability Criteria	Dose Adjustment
On Day 56: no rescue treatments initiated or required during preceding week After Day 56: <2 rescue treatments initiated or required during scheduled visit interval	Acceptable tolerability of current dose	No dose change
On Day 56: ≥1 rescue treatment initiated or required during preceding week After Day 56: ≥2 rescue treatments** initiated or required during scheduled visit interval	Acceptable tolerability of 40 mg Acceptable tolerability of 80 mg	40 mg→80 mg* 80 mg→120 mg*
At any time	Unacceptable tolerability of 80 or 120 mg doses	80 mg→40 mg or 120 mg→80 mg

Note: Triplicate ECG should be performed 1-3 hours after supervised administration of study drug where the dose is increased (to 80 or 120 mg) (Section 8.3.3). Continuous cardiac (Holter) monitoring (24 hour) should be performed 5-7 days after the first 120 mg dose.
*The initial dose after the 40 mg increase to 80 mg or 80 mg increase to 120 mg should be administered at the clinical research site. Subjects starting the Open-Label Extension Phase at 40 mg who increased to 80 mg may have an additional dose increase to 120 mg.
**Second rescue treatment occurs after having met stopping criteria for initial short-acting octreotide rescue (Table 6).

The completion of an electronic Symptom Diary will continue daily throughout Screening beginning within 1 day of S1, and through Week 12 of the study (through Randomized Treatment Phase and 4 weeks into OLE) and then selected time periods in the OLE Phase (Section 8.2.1).

4.1.4. Study Completion and Early Termination

Study completion and early termination (ET) for subjects are each defined separately for the Randomized Treatment Phase and the OLE Phase. Completion of Randomized Treatment Phase and the OLE Phase of the study requires that subject complete the final visit within each phase (End of Study [EOS] Visit for Randomized Treatment Phase and the OLE Phase) (Refer to Table 1 and Table 2). Subjects discontinuing early from Randomized Treatment Phase or the OLE Phase of the study should be treated with standard treatment as recommended by the Investigator and will have an ET Visit.

4.1.5. End of Randomized Treatment Phase and End of Treatment

End of Randomized Treatment Phase (EOR) is defined as completion of last scheduled dosing in Randomized Treatment Phase.

End of Treatment (EOT) is defined as completion of last scheduled dosing in OLE Phase.

4.1.6. End of Study

End of Study (EOS) is defined as the date of the last visit of the last subject in the study.

An EOS Visit will occur to collect the safety data and other assessments as detailed in the SOAs (Section 1.2).

An EOS Visit will be 28 days after last dose of study drug and is required for subjects who completed the study or early terminated.

4.1.7. Patient Input into Study Design

Patient insight was collected over several meetings (June 2021- June 2022) through a formalized Patient Leadership Council made up of 12 individuals living with carcinoid syndrome associated with NETs. These patients had a range of experiences including treating physician, medical treatments, geographic location, and age of diagnosis. In these meetings, the following topics were discussed: clinical study protocols, rescue therapy, frequency of visits, daily diary execution, study recruitment tactics and participants' preferred method of learning about potential studies. Results of these discussions were shared with the internal paltusotine study team and incorporated into study design where possible.

4.2. Scientific Rationale for Study Design

This study consists of a Randomized Treatment Phase followed by an OLE Phase. A randomized parallel-group design allows for a rigorous assessment of the safety and efficacy associated with each dose. These data will be useful for study design and dose selection in subsequent trials.

The OLE will provide important long-term safety and efficacy information that will also inform later stage trial designs. Standardized dose adjustment criteria are provided in the protocol taking into account reasonable treatment goals and study drug toleration.

Subject safety will be ensured using protocol defined criteria for study drug discontinuation and rescue therapy with short-acting octreotide subcutaneous injections and antidiarrheal medication.

4.3. Justification for Dose

The duration of treatment and dose range to be explored in CRN00808-11 is based on dose response and safety information from paltusotine healthy volunteer and acromegaly trials as well as clinical information pertaining to approved octreotide LAR and lanreotide for treatment of Carcinoid syndrome.

Dose and exposure-response analyses of completed Phase 2 acromegaly trial data with paltusotine have shown that the appropriate starting dose of paltusotine is 40 mg because it results in similar IGF-1 suppressive activity as long-acting SRL therapies; exposure-response modeling suggests this dose maintains trough effective concentration $(EC)_{80}$ in most subjects.

The starting dose of approved long-acting SRL therapies for Carcinoid syndrome is the same or higher as the starting dose for acromegaly (Sandostatin LAR 2024; Somatuline Depot 2024); therefore, the starting dose of paltusotine for this Phase 2 trial CRN00808-11 in Carcinoid syndrome will be 40 mg (same dose as for acromegaly subjects), with higher doses also being examined in this trial. The Sponsor expects 40 mg to be a well-tolerated starting dose for subjects who enroll CRN00808-11 as this dose has been well tolerated in studies in subjects with

acromegaly. Although subjects naïve to long-acting SRL therapies are also eligible, the Sponsor expects these to be a small proportion of subjects enrolled. Further, current clinical practice generally excludes initiation of treatment with short-acting octreotide before starting treatment with octreotide LAR (Strosberg, 2020), indicating that a "run-in" period with lower SRL doses is not necessary for subjects who are initiating treatment with SRL therapies.

As of 31 August 2021, doses up to 80 mg have been studied in healthy volunteers and up to 40 mg have been studied in subjects with acromegaly. The Sponsor proposes to explore paltusotine doses up to 120 mg for this exploratory trial in Carcinoid syndrome subjects. While this is higher than the 40 to 60 mg dose range expected to result in IGF-1 suppression in acromegaly subjects, Carcinoid syndrome subjects may require higher doses than acromegaly subjects due to malabsorption syndromes commonly associated with Carcinoid syndrome or its treatment (Naraev, 2019). In addition, the pharmacokinetics (clearance and volume of distribution) of paltusotine may be different in Carcinoid syndrome subjects compared to acromegalics because of differences in liver and body composition which effect metabolic activity.

Current clinical recommendations for treating Carcinoid syndrome symptoms include starting with long-acting SRL therapies at maximum approved doses detailed in the respective Prescribing Information (octreotide LAR 30 mg every 4 weeks and lanreotide 120 mg every 4 weeks) and escalation up to 2 times this for refractory patients (Strosberg, 2020). Given this current practice and that paltusotine 60 mg QD is anticipated to be the maximum dose for the treatment of acromegaly, this study will evaluate a maximum dose of 120 mg QD in Carcinoid syndrome subjects to ensure a clinically relevant dose range for this condition is evaluated.

4.4. Justification for Duration of Treatment

The study was designed with an 8-week RTP to allow sufficient time to demonstrate dose-responsiveness of 40 vs 80 mg paltusotine. In addition, a 102-week OLE was included in the study to assess long-term safety in adults with Carcinoid syndrome.

4.5. Treatment After End of Trial Participation

After the end of the study, subjects may resume regionally licensed Carcinoid syndrome treatment as prescribed by their healthcare provider.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted. Once all screening assessments are completed, the subject's eligibility is verified by the Investigator and confirmed by the Medical Monitor via submission of the Medical Monitor Eligibility Verification Form prior to performing any Day 1 study procedures. Up to 6 subjects taking proton-pump inhibitors (PPIs) at Screening may enroll in the study.

5.1. Inclusion Criteria

1. Willing and able to provide written informed consent prior to any study-related procedures.
2. Willing and able to comply with the study procedures as specified in the protocol, including at least 70% compliance with electronic Symptom Diary for the 2-week period prior to the S2 Visit and prior to the Day 1 visit.

Demographics and Medical History

3. Male or female subjects ≥18 years of age, at the time of Screening.
4. Documented Carcinoid syndrome requiring medical therapy. Eligible subjects fall into one of the following categories:
   - Not currently treated with SRL agonists for at least 12 weeks prior to Screening, and actively symptomatic (average of ≥4 BM/day or >2 flushing episodes per day in at least 2 days over a period of 2 weeks). This can include treatment-naïve subjects.
   - Subjects currently treated with lanreotide, octreotide LAR, or short-acting octreotide (subcutaneous or oral) who are currently symptomatically controlled (average <4 BM/day and average ≤2 flushing episodes/day over a 2-week period) and willing to wash out of their medication. The subject must demonstrate symptomatic worsening after washout. These subjects must have at least one historical instance of an elevated 5-HIAA or serotonin level.
5. Evaluable documentation of locally advanced or metastatic histopathologically confirmed well-differentiated NET. Tumors must be Grade 1 or Grade 2 (Ki-67 index ≤20%, or a mitotic count of ≤20 mitoses per 10 high-power fields, if the Ki-67 index is not available) per the World Health Organization neuroendocrine neoplasm classification (Rindi and Inzani, 2020). Grade 3 tumors are not eligible.

WHO 2017	Mitoses/10 HPF*	Ki-67 Index*
Well-differentiated NENs		
NET grade 1	< 2	< 3
NET grade 2	2–20	3–20
NET grade 3	> 20	> 20

HPF = high-power fields; NEN = neuroendocrine neoplasms; NET = neuroendocrine tumor

6. No significant disease progression* as assessed by the Investigator within the last 6 months before initiation of study drug dosing.

   **Pretrial imaging with MRI or CT, the most recent of which should be no more than approximately 3 months prior to Screening, should be available and compared to a previous imaging study to assess disease stability for established subjects on SRL maintenance therapy, while clinical symptoms and/or biomarker assessments should be used to assess disease stability for newly diagnosed subjects naïve to SRLs.*

7. Historical documentation of positive SSTR tumor status by PET or somatostatin receptor scintigraphy.*

   **If subject does not have historical documentation, this can be done during Screening.*

Screening and Testing Evaluations

8. Plasma 5-HIAA ≥2× ULN during Screening for subjects not currently treated with any SRL therapy who are not washing out of SRLs.

Lifestyle Restrictions

9. Females who engage in heterosexual intercourse must be of nonchildbearing potential, defined as either surgically sterile (ie, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), OR be postmenopausal with at least 1 year of amenorrhea, OR must agree to use a *highly effective* method of contraception from the beginning of Screening to the last study visit.

   - Acceptable highly effective methods of contraception include:
     - Combined estrogen-progestin oral hormonal contraception associated with consistent inhibition of ovulation
     - Desogestrel-based progestin-only contraception associated with consistent inhibition of ovulation; this includes oral, injectable, and implantable methods
     - Intravaginal and transdermal hormone delivery methods
     - Intrauterine device (with or without hormone elution)
     - Bilateral tubal occlusion or ligation (must be documented)
     - Vasectomized partner (must be documented) or
     - Sexual abstinence (only when it is the usual and preferred lifestyle of the subject)

   In addition to these methods of contraception, the male partner should use a condom from the beginning of Screening to the last study visit.

10. If the subject is male, the subject should agree to use a condom when sexually active with a female partner of childbearing potential from Screening until at least 30 days after the last dose of study drug or be surgically sterile [ie, vasectomy with documentation]; or remain abstinent [when this is in line with the preferred and usual lifestyle]. Male subjects should also agree to not donate sperm for the duration of the study and until at least 30 days after the last dose of study drug.

5.2. Exclusion Criteria

Medical History and Medications	
1.	Diarrhea attributed to any condition(s) other than Carcinoid syndrome (including but not limited to fat malabsorption, bile acid malabsorption, short bowel syndrome, pancreatic exocrine insufficiency, infections, VIPoma, Zollinger-Ellison syndrome). Exception to this are subjects with prior cholecystectomy or small bowel resections, provided diarrhea is controlled prior to washout or if not currently treated with any SRL therapy.
2.	Uncontrolled/severe diarrhea associated with significant volume contraction, dehydration, or hypotension.
3.	Requires second line treatments (eg, telotristat) for control of Carcinoid syndrome symptoms in the opinion of the Investigator
4.	Treatment with specific NET tumor therapy <4 weeks before Screening (such as everolimus or sunitinib) or hepatic embolization, radiotherapy, peptide receptor radionuclide therapy (PRRT), and/or tumor debulking <12 weeks before Screening.
5.	Karnofsky performance status <60%.
6.	Major surgery within 8 weeks before Screening.
7.	History of another primary malignancy <3years prior to the date of first dose of study treatment unless at least one of the following criteria are met: • Adequately treated basal or squamous cell carcinoma of the skin • Cancer of the breast or cervix in situ • Previously treated malignancy, if all treatment for that malignancy was completed at least 3 years prior to first dose of study treatment, and no current evidence of disease. • Concurrent malignancy determined to be clinically stable and not requiring treatment.
8.	Life expectancy <12 months from Screening.
9.	Diabetes mellitus treated with insulin for less than 6 weeks prior to the study entry.
10.	Poorly controlled diabetes mellitus defined as having a hemoglobin A1c (HbA1c) ≥8.5% (ie, ≥69.5 mmol/mol) or estimated HbA1c based on fructosamine if HbA1c is not evaluable (eg, due to hemoglobinopathy).
11.	History of unstable angina or acute myocardial infarction within the 12 weeks preceding the Screening Visit or other clinically significant cardiac disease (including clinically significant carcinoid heart disease) at the time of Screening as judged by the Investigator.
12.	Known history of, or current alcohol or drug abuse, within the last year.
13.	Concomitant mental condition rendering him/her unable to understand the nature, scope, and possible consequences of the study, and/or evidence of poor compliance with medical instructions.

14.	Current use of medications that are strong inducers of cytochrome P450 3A4 (CYP3A4) (including but not limited to carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort) within 2 weeks prior to Screening because they may reduce systemic exposure to paltusotine. Current use of medications that are sensitive substrates of CYP3A4 with a narrow therapeutic index (including but not limited to tolvaptan, lomitapide, pimozide, dronedarone, dasatinib, sirolimus) as paltusotine may increase exposure of these medications.
15.	Unable to administer short-acting octreotide (octreotide acetate injection), or prior nonresponse documented with somatostatin agonists.
16.	Known allergy or hypersensitivity to any of the test materials or related compounds.
Screening Tests and Evaluations	
17.	Active COVID-19 confirmed or suspected based on SARS-CoV-2 testing and clinical symptoms.
18.	QT interval corrected using Fridericia's formula (QTcF) >480 msec (or QTcF >500 msec in the presence of complete bundle branch block) or PR interval >240 msec during Screening based on a central reading of an average of 3 ECGs each separated in time by approximately 1 minute after the subject has rested quietly in the supine position for at least 10 minutes without significant stimulation (noise, television, etc.).
Other Criteria	
19.	Clinically significant concomitant disease that is not a result of primary disease under study, including but not limited to cardiovascular disease, estimated glomerular filtration rate <30 mL/min/1.73 m^2, cirrhosis, baseline AST and/or ALT >2× ULN, and/or total bilirubin >1.5× ULN. (Subjects with previously diagnosed Gilbert's syndrome not accompanied by other hepatobiliary disorders and associated with total bilirubin <3.5 mg/dL [<51.3 µmol/L] will be permitted.)

5.3. Screen Failures

Subjects who fail to meet the eligibility criteria at any point during the Screening Period are defined as screen failures. The reason for each screening failure will be recorded. Refer to Section 4.1.1.

Subjects who fail screening assessments based on findings the Investigator believes are temporary and not reflective of the usual state of the subject (eg, HbA1c of ≥8.5% [69.5 mmol/mol] when the subject is usually well below this value, or clinical symptoms) can be considered for retesting of assessments that are considered atypical for subject's usual status. These cases should be discussed with the Medical Monitor.

In the event of rescreening, it may be determined that certain laboratory assessments conducted during the initial Screening Phase may not need to be repeated for individual subjects. The decision will be made on a case-by-case basis in discussion with the Medical Monitor.

Subjects who are screen failures because they did not meet clinical and/or biomarker criteria as specified in Section 4.1.1 cannot be rescreened.

If there is <70% compliance with completion of the electronic Symptom Diary between S1 and S2, the subject is a screen failure; however, the subject can rescreen if other eligibility requirements are met; this is allowed (one more attempt only). Site staff should reeducate the subject on the compliance with completion of the electronic Symptom Diary and document the retraining in the source documents.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s) or marketed product(s) intended to be administered to a study subject according to the study protocol.

6.1. Study Intervention(s) Administered

Study drug will be swallowed, with at least 8 ounces (237 mL) of water, after fasting at least 6 hours. No food, drink (except for water), or other medications will be allowed for at least 1 hour after study drug administration, including at the time of study drug administration. The first dose of the OLE Phase will be administered during the Week 8 visit for those continuing into the OLE Phase.

Paltusotine is the Investigational Medicinal Product (IMP), diphenoxylate atropine and loperamide are concomitant medications, and short-acting octreotide is a rescue medication (ie, auxiliary medicinal protect [AuxMP]). Investigators should CCI [redacted]
CCI [redacted]
CCI [redacted]

Intervention Name	Paltusotine	Short-acting octreotide	Diphenoxylate atropine	Loperamide
Type	Experimental drug (IMP)	Rescue medication (AuxMP)	Concomitant medication	Concomitant medication
Dose Formulation	Tablet	Solution in vial or prefilled syringe	Tablet	Tablet
Unit Dose Strength	20 mg	Details provided in Pharmacy Manual	Details provided in Pharmacy Manual	Details provided in Pharmacy Manual
Dosage Levels	40 mg (two 20 mg tablets), 80 mg (four 20 mg tablets), or 120 mg (six 20 mg tablets) once daily. See Section 6.5.	200 µg, up to 3×daily at the direction of the Investigator	5 mg up to 4×daily as needed	4 mg initiation, 2 mg after each loose bowel movement as needed; total daily dose ≤16 mg
Controlled Room Temperature	15-25°C (59-77°F)	Details provided in Pharmacy Manual	Details provided in Pharmacy Manual	Details provided in Pharmacy Manual
Route of Administration	Oral	Subcutaneous Injection	Oral	Oral
Sourcing	Provided centrally by the Sponsor	Sourced by institution and reimbursed by Sponsor or sourced centrally and supplied by Sponsor	Sourced by institution and reimbursed by Sponsor	Sourced by institution and reimbursed by Sponsor
Packaging and Labeling	Paltusotine will be provided in bottles and labeled as required (Section 6.2).	Details provided in Pharmacy Manual	Details provided in Pharmacy Manual	Details provided in Pharmacy Manual

AuxMP=auxiliary medicinal product, IMP=investigational medicinal product

6.2. Preparation/Handling/Storage/Accountability

The appointed team members will be identified at each center whose role in the study will be handling of the study intervention (ie, they will be responsible for the receipt and accountability of the study intervention). Furthermore, other tasks can be delegated to them in a clear manner by the Investigator and that will be documented and completed in the Study Staff Signature and Delegation Log.

The Investigator must ensure the availability of proper storage conditions for the study intervention(s). Study staff at the study site will take all steps to maintain adequate records and will ensure that the study intervention is stored as specified on the medication labels, in a strictly controlled, secure area, at appropriate temperature and in accordance with the protocol and any applicable regulatory requirements. Direct-to-patient shipments of study drug will be allowed in exceptional cases (ie, where subjects would not be able to attend onsite visits and would risk continued access to study drug). Study intervention will be provided by the Sponsor and are to be dispensed only in accordance with the protocol. Study intervention must not be dispensed to any person not enrolled in the study.

Paltusotine will be packaged in 36-count, high-density polyethylene bottles containing desiccant cannister.

Accurate inventory and accountability records of the study intervention will be kept by the appointed team member. Study intervention accountability must be performed for all delivered dispensing unit number. Returned study intervention (partly used or unused including empty packaging material) must be stored separately from nonallocated study intervention. The storage temperature should be monitored by recording the actual, minimum, and maximum temperatures using a calibrated thermometer or thermocouple, or by continuous recording using a qualified temperature monitoring system. The temperature should be evaluated and documented at least on working days on a temperature log. This log must be included in the Investigator Site File upon study termination.

The appointed study staff must contact the site monitor in case of temperature deviations outside the acceptable range. If the Investigator, the site staff, or the site monitor suspect that the study intervention is defective or potentially defective, Crinetics Pharmaceuticals or designee should be contacted immediately. Full details concerning study intervention handling eg, allocation, accountability, tracking, and recording will be provided in the Pharmacy Manual.

At the end of the study (ie, close-out visit) and following reconciliation and documentation by the site monitor, all study drugs and related materials will be either returned to the Sponsor or a designee or destroyed locally following the review and approval of the site’s destruction procedures.

6.3. Measures to Minimize Bias: Blinding

Not applicable.

6.4. Study Intervention Compliance

When subjects are dosed during a study visit, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose

administered in the clinic will be recorded in the source documents. Subjects in the OLE Phase who are up-titrated to the 120 mg dose will need to swallow the first dose under the supervision in the research center.

When subjects self-administer study intervention at home, compliance will be assessed at each visit. Compliance will be assessed by either direct questioning and/or counting returned tablets/vials during the site visits and documented in the source documents and relevant forms. Deviations from the prescribed dosage regimen should be recorded.

A record of the quantity of study intervention dispensed to and administered by each subject must be maintained and reconciled with study intervention and compliance records. Study intervention start and stop dates, including dates for study drug delays, drug interruptions and/or dose reductions, will also be recorded.

Further details are provided in the Pharmacy Manual and relevant monitoring plan.

Subjects will be instructed to return all used and unused study interventions (including paltusotine tablets and short-acting octreotide) at each study visit during the Randomized Treatment Phase. All returned study interventions should be stored, inventoried, reconciled, and returned according to applicable local regulations and study procedures.

6.5. Study Intervention Dose Modification

See Section 6.5.1 and Section 6.5.2 for the dose titration/adjustment in this study.

6.5.1. Dose Adjustment During the Randomized Treatment Phase

In the Randomized Treatment Phase, the subject will be randomized to 40 mg QD vs. 80 mg QD for the 8 week parallel-group phase. It is anticipated that subjects will complete the 8 weeks parallel dose without changing the dose of paltusotine assigned at randomization. However, if the subject experiences Carcinoid syndrome symptoms that meet protocol criteria for short-acting octreotide rescue, the dose may be increased once to a maximum dose of 120 mg QD during the first 28 days as tolerated. No dose increases are allowed after Day 28 through the remaining 4 weeks of the parallel-group phase of the study. The details are outlined in Table 7.

6.5.2. During the Open-Label Extension Phase

Subjects completing the 8 weeks Randomized Treatment Phase may begin the OLE Phase of the study if, in the opinion of the Investigator, the subject may benefit from OLE Phase participation.

The initial OLE dose will be chosen by the Investigator based on criteria of carcinoid symptom control and of tolerability and will start on Day 56 (Table 8).

6.6. Treatment of Overdose

There are no clinical data available on effects associated with overdose of the study drug. No documented incidents of overdose have occurred with paltusotine to date. Preclinical animal studies indicate bradycardia or hypertension may result from overdose. Signs, symptoms, or the clinical sequelae of a suspected overdose of study drug should be reported as an AE/serious adverse event (SAE). Overdose in the absence of clinical sequelae will be reported as a protocol deviation unless it is an intentional overdose taken with possible suicidal/self-harming intent.

Such overdoses should be reported regardless of sequelae. The recommended treatment of overdose with paltusotine would include supportive and symptomatic measures employed in the management of overdose with a drug with potential cardiovascular events.

Octreotide acetate injection given in intravenous boluses of 1 mg (1,000 µg) to healthy volunteers did not result in serious ill effects, nor did doses of 30 mg (30,000 µg) given intravenously over 20 minutes and 120 mg (120,000 µg) given intravenously over 8 hours to research subjects (Sandostatin LAR 2024). If overdose occurs, the healthcare provider should be contacted for symptomatic management as indicated.

6.7. Concomitant Therapy

6.7.1. Permitted Medications

Concomitant medications allowed in this study are those permitted medications used during Screening to control existing medical conditions and/or those used during the study, if medically needed, including antidiarrheal medications (such as diphenoxylate, loperamide).

All concomitant medications will be recorded in the subject's electronic case report form (eCRF). If a new medication should become necessary for any reason during the course of the study, the subject is required to inform the Investigator immediately, who will record the drug, the dose, start and stop dates, indication, route, and frequency. The Investigator is responsible for ensuring the new medication is not prohibited by the protocol and to contact the Medical Monitor for any questions or discussions.

6.7.2. Prohibited Medications

Any questions regarding prohibited medications should be discussed with the Medical Monitor or appropriate designee. Prohibited medications will not be allowed from start of the Screening Period and for the study duration and includes:

- Strong inducers of the drug metabolizing enzyme CYP3A4, including but not limited to apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort (because these medicines may decrease the concentration of paltusotine in the systemic circulation).
- Current use of medications that are sensitive substrates of CYP3A4 with a narrow therapeutic index (including but not limited to tolvaptan, lomitapide, pimozide, dronedarone, dasatinib, sirolimus) as paltusotine may increase exposure of these medications.
- Any standard drug for treatment of Carcinoid syndrome that is not used as a rescue medication during the Randomized Treatment Phase and OLE Phase.
- Any other investigational drug, unless approved by the Medical Monitor (eg, COVID-19 therapies).
- Randomized subjects who are not on PPIs on Day 1 should not start taking PPIs during the Randomized Treatment Phase.
- Treatment with NET specific therapy (eg, everolimus, sunitinib, PRRT therapy, hepatic embolization)

The Medical Monitor will review the subjects' medications prior to randomization to assess for potential clinically relevant interactions with paltusotine and to confirm eligibility.

6.7.3. Rescue Medications (Auxiliary Medicinal Products)

Short-acting octreotide is considered a rescue medication (ie, auxiliary medicinal product) CCI
CCI

7. DISCONTINUATION OF STUDY DRUG AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment/Participation

If the subject is eligible and in the opinion of the Investigator there may be benefit, subjects completing the Randomized Treatment Phase may begin the OLE Phase of the study. If the subject withdraws consent or, in the opinion of the Investigator, should be permanently discontinued from the study during the Randomized Treatment Phase (and would therefore, not be eligible for enrollment in the OLE), an ET Visit should be completed as specified in the SOAs (Section 1.2 and Section 4.1.4) and the subject should return to standard Carcinoid syndrome treatment as prescribed by the Investigator. This visit should be documented as appropriate. The Investigator will record the reason for the study discontinuation and provide or arrange for appropriate follow-up. In addition, the Investigator will report the subject's withdrawal to the responsible Medical Monitor within 24 hours.

Subjects will be withdrawn from the OLE Phase of the study if NET progression according to local standards is evident on scheduled or unscheduled imaging studies.

Reasons for a subject to discontinue the study treatment and/or participation in this clinical study include, but are not limited to:

1. Withdrawal of informed consent by the subject;
2. Occurrence of AEs for which study treatment and/or study participation discontinuation is desired by the subject or considered necessary by the Investigator, in consultation with the Medical Monitor;
3. Unacceptable tolerability of the lowest study drug dose (40 mg per day) in the opinion of the Investigator;
4. Other clinically significant potentially drug-related abnormalities (eg, newly developed or worsening hyperglycemia, hypersensitivity, symptomatic cholelithiasis, or pancreatitis);
5. Investigator's decision (ie, if in the Investigator's opinion it is not in the best medical interest for the subject to continue participation in the study for reasons other than AEs);
6. Need for administration of a prohibited concomitant medication;
7. Any other protocol deviation that may result in a significant risk to the subject's safety or protocol deviations that will interfere with assessment of the efficacy endpoints of this study, including subject's noncompliance with the study procedures/study protocol;
8. Pregnancy;
9. Lost to follow-up (the subject stopped coming for visits, and study personnel are unable to contact the subject);
10. Inability to fulfil study requirements and procedures;
11. Death.

7.1.1. Amylase or Lipase Study Drug Stopping Criteria

The Medical Monitor should be contacted promptly if amylase or lipase levels increase from Baseline by more than 2-fold and exceed 3× ULN. Testing should be repeated within 1 week and if the amylase or lipase elevation persists, study drug should be held. The Medical Monitor and Investigator will determine together the appropriateness of continued study participation.

7.1.2. Cardiac Study Drug Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from Baseline in QTcF after enrollment), the Investigator or qualified designee will determine if the subject can continue in the study and if any change in subject management is needed. Any new clinically relevant finding should be reported as an AE.

Cardiology consultation should be obtained within 7 days for new clinically important symptoms or findings judged by the Investigator to be reasonably likely to be of cardiac origin, eg, evidence for new arrhythmia, significant chest discomfort/pain, presyncope or syncope.

Discontinuation of study drug is required when a subject meets 1 of the clinically significant cardiac symptoms or findings as outlined below:

- Ventricular tachycardia;
- Based on the average of triplicate ECGs, QTcF >500 msec (or QTcF >530 msec in subjects with a bundle branch block) repeated on a second set of electrocardiograms (ECGs) at least 2 hours apart and confirmed by a stat central ECG reading;
- Torsades de pointes;
- Cardiac arrest;
- Pause >5 seconds;
- Type 2 second-degree block or third-degree atrioventricular block;
- New occurrence of clinically significant, symptomatic bradycardia;
- Based on the average of triplicate ECGs, an increase in QTcF >60 msec with an absolute QTcF <500 msec repeated on a second set of ECGs at least 2 hours apart and confirmed by a stat central ECG reading;
- Any supraventricular tachyarrhythmia associated with symptoms of hemodynamic response.

The Medical Monitor and Investigator will determine the appropriateness of any further study drug dosing after stabilization of any of the above events.

7.1.3. Liver Chemistry Abnormality Monitoring and Study Drug Stopping Criteria

Closely monitoring for abnormalities of liver tests and discontinuation for evidence of liver injury will be performed according to the following process:

- Detection of Liver Test Abnormalities

  All subjects will have a serum chemistry panel as per the SOAs. Confirmation of detected liver test abnormalities is required for any subject with 1 or more of the following:

  - ALT or AST >3× ULN (for subjects with ALT and AST <ULN at Baseline);
  - ALT or AST >3× ULN and >2× Baseline (for subjects with ALT or AST >ULN at Baseline);
  - Total bilirubin (TB) >2× ULN (for subjects with TB <ULN at Baseline);
  - TB >2× ULN and >2× Baseline (for subjects with TB >ULN at Baseline);
  - Alkaline phosphatase (ALP) >3× ULN (for subjects with ALP <ULN at Baseline);
  - ALP >3× ULN and >2× Baseline (for subjects with ALP >ULN at Baseline).

- Confirmation of Detected Liver Test Abnormalities

  If any of the above-listed liver test abnormalities are detected, they should be followed by repeat testing within 48 to 72 hours (of ALT, AST, ALP, TB and INR) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms.

  If the above-listed liver test abnormalities (and/or related symptoms) persist or worsen, initiate close observation to determine whether the abnormalities are improving or worsening over time. (See Close Observation recommendations below.) If close monitoring is not possible, the drug should be discontinued.

- Close Observation of Any Subject with Detected Liver Test Abnormalities

  Close observation includes:

  - Repeating ALT, AST, ALP, and TB tests 2 to 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic;
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases;
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets;
  - Assessment for acute viral hepatitis (including types A, B, C, D, and E as appropriate); autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease;
  - Obtaining a history of exposure to environmental chemical agents;

- Obtaining additional tests to evaluate liver function, as appropriate (eg, international normalized ratio);
- Considering gastroenterology or hepatology consultations.

Discontinuation of study drug for abnormal liver tests is required when a subject (with ALT and AST <ULN at Baseline) meets 1 of the conditions outlined below:

- ALT or AST >8× ULN;
- ALT or AST >5× ULN for more than 2 weeks;
- ALT or AST >3× ULN and (TB >2× ULN or INR >1.5);
- ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

7.1.4. Neurological Adverse Events

If a subject develops severe neurologic treatment-related AEs (including but not limited to seizures, worsening of tremors, decreased activity [eg, lethargy]) the study drug should be discontinued, and neurology consultation obtained. The Medical Monitor and Investigator will determine the appropriateness of any further study drug dosing if clinically appropriate after stabilization of any of the above events.

7.2. Lost to Follow-up

If a subject fails to attend scheduled assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

For subjects who are lost to follow-up (ie, subjects whose status is unclear because they fail to appear for the study visits without stating an intention to withdraw), the Investigator should document in the source documents all steps taken to contact the subject (eg, dates of telephone calls, registered letters, etc).

7.3. Criteria for Study Termination

The Sponsor reserves the right to discontinue the study at any time for any reason. Such reasons may include, but not limited to, the following:

- Inefficacy of the study intervention;
- Results from ongoing safety monitoring;
- Other medical or ethical reasons.

Regulatory Authorities also have the right to terminate the study for any reason.

In the event the study is terminated, Investigators and the Institutional Review Boards (IRBs) or Independent Ethics Committee (IECs) will be notified as soon as possible.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Demographics and Baseline Characteristics

Demographics will include age, sex, ethnicity, and race. Baseline characteristics will include history of Carcinoid syndrome, medical history, and concomitant medications. Target symptom will be evaluated at Baseline on Day 1.

8.2. Subject-reported Assessments

Planned time points for all subject-reported assessments are provided in the SOAs. When these assessments are done at the same visit, the order will be as follows: (1) Electronic Symptom Diary, (2) Patient Global Impression of Severity (PGI-S), (3) Patient Global Impression of Change (PGI-C), (4) EuroQoL 5 Dimensions 5 Level (EQ-5D-5L), (5) EORTC QLQ-C30 Quality of Life Questionnaire, (6) EORTC QLQ-GI.NET21 Quality of Life Questionnaire, (7) Functional Assessment of Cancer Therapy – Carcinoid Syndrome Symptom Index (FACT-CSI) (Shaunfield, 2021), and (8) Treatment Preference Question. These assessments will be completed using an electronic device (either through an application on the subject's electronic device or by a device provided by the Sponsor). Exceptions may be allowed upon discussion with the Sponsor to complete the Symptom Diary on paper.

8.2.1. Electronic Symptom Diary

Subjects will be asked to complete the electronic Symptom Diary, a brief Symptom Diary, daily at home beginning after the initial Screening and continuing throughout Screening beginning within 1 day of S1, Week 1 through Week 12 (throughout Randomized Treatment Phase and beginning of the OLE Phase), then for the rest of the OLE Phase, it should be completed daily approximately 2 weeks before the Week 24, 36, 48, 58, 70, 82, 96, and 110 visits (or simply during Week 23-24, Week 35-36, Week 47-48, Week 57-58, Week 69-70, Week 81-82, Week 95-96, and Week 109-110).

This electronic Symptom Diary will be used to assess the understanding and compliance of the subject and to measure the Baseline symptom frequencies of BMs and flushing frequency and severity, episodes of fecal urgency and incontinence, abdominal pain severity, and stool consistency. The Baseline symptoms of stool consistency will be evaluated according to Bristol scale and abdominal pain according to an NRS. To determine subject eligibility, screening data will be reviewed prior to study drug dosing (Section 5.1).

Subjects will be instructed to complete the diary at about the same time, every evening during the periods specified above. Site staff will review subject compliance with self-reported electronic Symptom Diary completion as outlined in the Study Reference Guide.

At least 5 days of diary data per 7-day period are required for the qualifying assessments for eligibility to be made.

Subjects will be asked to record use of all breakthrough symptom treatments in the daily electronic Symptom Diary.

In rare cases when the electronic Symptom Diary cannot be used, a paper diary may be used upon consultation with the Sponsor.

8.2.2. Global Impressions of Change and Severity

The PGI-S assesses the subject's perception of overall disease severity using a 4-point verbal rating scale (no symptoms, mild symptoms, moderate symptoms, and severe symptoms).

The PGI-C assesses the subject's perception of change in disease severity using a 7-point verbal rating scale (much better, moderately better, a little better, no change, a little worse, moderately worse, and much worse).

8.2.3. EQ-5D-5L

The EQ-5D-5L (5 severity levels EQ-5D), developed by the European Quality of Life (EuroQoL), is a standardized instrument to be completed by the subject for use as a measure of health outcomes applicable to a wide range of health conditions. It comprises 5 dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. Based on qualitative and quantitative studies conducted by the EuroQoL Group, there are 5 options (levels) under each domain: 'no problems', 'slight problems', 'moderate problems', 'severe problems', and 'unable to/extreme problems'. The responses to all 5 dimensions can be converted to a single summary index, utility (range: 0 to 1), by using value sets. Higher index values represent better health states.

8.2.4. EORTC QLQ-C30 Quality of Life Questionnaire

EORTC QLQ-C30 quality of life questionnaire will be used to assess health-related quality of life in subjects with cancer. The questionnaire entails 28 questions to assess health-related quality of life, each question can be answered on a 1 to 4 scale. Lower scores indicate a better quality of life. There are 2 additional questions, 1 to rate subjects' 'overall health in the past week' and 1 to rate the subjects' 'overall quality of life in the past week'. Each of these 2 questions can be answered on a 1 to 7 scale. Higher scores indicate a better quality of life.

8.2.5. EORTC QLQ-GI.NET21 Quality of Life Questionnaire

EORTC QLQ-GI.NET21 quality of life questionnaire will be used to follow up with symptoms in subjects with neuroendocrine carcinoids. There will be around 21 questions divided into the category of 'during the past week' and 'during the past 4 weeks', which will be used to follow up with symptoms in subjects. Each of the questions can be answered on a 1 to 4 scale. Lower scores indicate a better quality of life.

8.2.6. FACT-CSI

The 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 symptoms, 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). Lower total score indicates a better quality of life (Shaunfield, 2021).

8.2.7. Treatment Preference Question

The Treatment Preference Question is a single question regarding the subject's preferred treatment form, ie, previously used injections, oral study drug, or no preference.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SOAs.

8.3.1. Physical Examinations

A complete physical examination includes assessment of head (external), eyes, ears, nose and throat, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, central nervous system (including but not limited to assessments of alertness and orientation with respect to person, place and time, and involuntary movements such as tremor) and, where appropriate, other body systems. Symptom-related physical examinations should also include neurologic assessments as above (with weight measurement as appropriate).

Physical examination including weight measurement will be done at specified time points in SOA. Height measurement will be done at Screening only. The study site must use calibrated equipment with subjects required to remove their shoes and heavy objects from their clothing prior to height and weight measurement, respectively.

Any confirmed clinically significant physical examination abnormalities occurring after the moment of signing informed consent form (ICF) are to be recorded as AEs.

8.3.2. Vital Signs

Vital signs (blood pressure at rest, pulse rate, respiratory rate, and oral [or equivalent] body temperature) will be assessed as per standard practice at all visits including home visits.

Blood pressure (resting) should be measured with calibrated digital equipment in the supine position after resting quietly for 5 minutes.

Vital sign measurements will be repeated if clinically indicated or machine/equipment errors occur. Blood pressure and pulse rate measurements will be repeated at the Investigator's discretion. Any confirmed clinically significant vital sign measurements occurring before signing the ICF are to be designated as medical history.

8.3.3. Electrocardiograms

A standard 12-lead ECG will be performed in triplicate (approximately 1 minute apart) after the subject has rested quietly in the supine position for at least 10 minutes without significant stimulation (noise, TV, etc). Triplicate ECG should be performed at Screening, 1 to 3 hours after supervised administration of the first dose of study drug, and any subsequent visit where the dose is increased to 80 or 120 mg. The ECG parameters that will be assessed include a summary of findings as well as measurement of the heart rate, QT, QTcF, and PR intervals, and QRS duration based on the ECG machine readings.

All ECG assessments will be initially assessed by the Investigator for any findings that require immediate medical attention and will also be read by an ECG central reader. The clinical significance of any ECG findings will be determined by the Investigator and can include use of the central reading results when provided. The Investigator's assessment will be recorded in the eCRF. Potentially significant outlier values should be confirmed after review by the central ECG reader. Any ECG measurement determined to be clinically significant (occurring after signing

the ICF) will be noted as an AE on the appropriate eCRF page(s). Such abnormalities will be monitored until the end of the study or until resolution if considered related to the study drug.

Refer to Section 7.1.2 for cardiac withdrawal criteria and any additional ECG readings that may be necessary.

8.3.4. Continuous Cardiac Monitoring

Outpatient 24-hour continuous cardiac (Holter) monitoring and recording will be conducted as specified in the SOAs (Section 1.2). An adequate continuous cardiac monitor recording should be confirmed by the central reader as soon as possible after completion, so that a repeat continuous cardiac monitor recording may be performed, if necessary.

8.3.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and the SOAs (Section 1.2) for the timing and frequency.

All analyses must be done with the minimally required blood amount and the number of needle insertions should be minimized during the blood collection.

After sampling, blood collection tubes will be labeled and handled per the local institutional procedures.

All results (except PK and genotyping) will be reported to the Investigator after completion of analyses.

All laboratory reports received must be reviewed, assessed for clinical significance, signed, and dated by the Investigator or delegated sub-Investigator. A legible copy of all reports must be filed in a subject medical record (source document) for that visit. Any laboratory test result (occurring after the moment of signing ICF) considered by the Investigator to be clinically significant will be recorded as an AE and will be managed as described in Section 8.4.

8.3.6. Biliary/Gallbladder Ultrasound

Biliary/gallbladder ultrasound will be performed for subjects who have not had a prior cholecystectomy, according to the study site procedures for the evaluation of presence or absence of lithiasis or sludge or other significant biliary abnormalities. The results will be recorded.

8.3.7. Ophthalmic Assessments

Ophthalmic assessments will be conducted on all subjects. Initial ophthalmic testing should be performed as soon as practical and then at 6-month intervals, preferably associated with scheduled visits whenever possible, through study completion. Participants in Screening at the time of amendment approval are to have initial ophthalmic testing prior to randomization and study drug dosing. Assessments will be performed at a local facility with appropriate testing equipment and qualified personnel. The following assessments will be conducted:

- Corrected distance visual acuity evaluation
- Threshold visual fields (central 24 degrees, for instance, a Humphrey 24-2 Sita Fast)

- Fundus photography of the macula (single photograph centered on macula in each eye) and
- Optical coherence tomography of the macula

Detailed specifications for acceptable instrumentation, data acquisition, data collection, and test results distribution processes will be provided to the investigative sites in separate ophthalmic assessment guidance documents.

Visual acuity and threshold visual field results and images for fundus photography of the macula and optical coherence tomography of the macula will be transferred from the local testing facility to the designated data processing portal accessible by the Ophthalmic Central Reader.

8.4. Adverse Events, Serious Treatment-emergent Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

All medical conditions present prior to the study entry will be documented. However, medical conditions occurring after the moment of signing the ICF or a worsening of a medical condition present prior to the study entry are to be recorded as AEs. All AEs occurring after the study drug administration has started will be considered as treatment-emergent adverse events (TEAEs).

The Investigator or qualified designee is obliged to interview a subject at every visit and clarify/discuss with him/her any abnormality that may indicate any potential AE/TEAE.

Subjects should be informed that they do not have to wait for scheduled visits to report AEs/TEAEs.

AEs related to the study drug that are ongoing at early termination and at the EOS Visit (Week 114) for subjects continuing in the OLE Phase and at the EOS Visit (28 days after the last dose) for subjects not continuing in the OLE Phase will be followed for outcome information until resolution or stabilization. Nonserious AEs will not be followed past database lock.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

AEs will be recorded from signing ICF up to 4 weeks after the last dose of the study drug.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of knowledge of the event, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on TEAEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

8.4.2. Method of Detecting Adverse Events

Care will be taken not to introduce bias when screening for AEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE or TEAE occurrences.

8.4.3. Follow-up of Adverse Events

After the initial AE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts.

Any AE that occurs in the course of a clinical study must be monitored and followed up until:

- it has resolved;
- laboratory abnormalities have returned to normal;

OR

- steady state of the symptoms has been achieved.

If none of the above-mentioned alternatives apply, then the subject must be asked about the evolution of the AE at the follow-up visit 4 weeks after the last dose of the study drug (equivalent to EOS) and the status must be reported in the eCRF and this will end the follow-up process of this AE.

It is the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to both expedited and periodic safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Any SAE occurring after the ICF has been signed and up until 4 weeks after the last dose of study drug must be reported to the designated pharmacovigilance group.

Any such SAE due to any cause, whether or not related to the study drug, must be reported on the SAE reporting form within 24 hours of occurrence or when the Investigator becomes aware of the event. A properly completed SAE reporting form should be sent via email.

PPD

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. Serious AE reports must be provided whether or not the Investigator considers the event to be related to the study drug.

Appropriate measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to

determine the etiology of the problem. The Investigator must report all available additional follow-up information to the pharmacovigilance Group within 24 hours. All SAEs will be followed until the Investigator and Sponsor agree the event is satisfactorily resolved.

Suspected unexpected serious adverse reactions (ie, unexpected SAEs considered drug-related as assessed by the Investigator/Sponsor/authorized person) will qualify for expedited reporting and cross reporting to the IRB/IEC, Competent Authorities, and participating Investigators by Crinetics Pharmaceuticals, Inc. In the EU, Crinetics Pharmaceuticals, Inc. will act in compliance with the CTR EU No 536/2014.

Serious AEs occurring after the study termination must be reported only if considered study drug-related per Investigator judgment.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed until its resolution or stabilization.

Detailed information is given in Appendix 3.

8.4.5. Pregnancy

Female subjects of childbearing potential must have a negative serum pregnancy test at Screening. All pregnancy tests at other visits as specified in the SOAs will be urine pregnancy tests. If the result of a urine pregnancy test is positive, then the result will be confirmed with a serum pregnancy test. Pregnancy tests may be obtained at any time during the study as an unscheduled test if clinically appropriate. Subjects must discontinue study drug immediately in the event of pregnancy in a female subject. Any pregnancy will be reported by emailing a completed Pregnancy Report to the Sponsor's pharmacovigilance Group within **24 hours** of knowledge of the pregnancy to PPD The pregnancy will not be processed as a SAE. However, the Investigator will follow-up with the subject or female partner of the male subject (after obtaining informed consent, as appropriate) until completion of the pregnancy and must determine the outcome of the pregnancy in the shortest possible time. The Investigator should notify the Sponsor's pharmacovigilance Group of the pregnancy outcome by submitting a follow-up Pregnancy Report. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (eg, spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by emailing a completed SAE form to the Sponsor's pharmacovigilance Group within **24 hours** of knowledge of the event to PPD

8.5. Pharmacokinetics

During the Randomized Treatment Phase, and OLE Phase of the study, plasma samples will be collected for measurement of plasma concentration of study drug as specified in the SOAs. Instructions for the collection and handling of biological samples will be provided by the Sponsor in the Laboratory Manual. The actual date and time (24-hour clock time) of collection of each sample will be recorded. The actual date and time of last dose of study drug prior to each sample collection will also be recorded.

Plasma samples for lanreotide and octreotide will be collected for previously treated subjects only as per the SOAs (Section 1.2).

8.6. Pharmacogenomics

On Day 1, optional blood will be drawn for genotyping for the determination of the CCI [redacted]

Instructions for the collection and handling of biological samples will be provided by the Sponsor in the Laboratory Manual.

8.7. Biomarkers

Blood will be drawn at the time points on the SOAs to measure plasma 5-HIAA and pancreastatin; and serum chromogranin A and serotonin. Pancreastatin will not be collected and analyzed for subjects enrolled in EU countries.

Note: Short-acting octreotide should not be used for at least 12 hours before biomarker sample collection.

Instructions for the collection and handling of biological samples will be provided by the Sponsor in the Laboratory Manual.

8.8. Imaging and Tumor Surveillance

Imaging for surveillance of tumor progression will be performed using the same modality as previously used in each subject (MRI or CT scan).

8.8.1. Surveillance of Tumor Growth

The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors recommends initiating radiographic surveillance at six-months intervals (Strosberg, 2017). Subjects should have pretrial imaging assessment available within 3 months of Screening. After enrollment in the study, subjects should have an appropriate tumor surveillance imaging assessment (CT or MRI based on that which was used pretrial). Imaging assessments at Week 10, Week 36, Week 70, Week 110, and ET are included in Table 2 but can be adjusted to conform to the six-month interval recommendation for radiographic surveillance, based on the timing of pretrial imaging assessment and Screening duration.

If the Investigator has any clinical suspicion of tumor progression at any time during the study, at a time a surveillance scan is not already scheduled, unscheduled imaging or other appropriate testing may be performed. Clinical evidence for tumor progression could include but are not limited to any of the following: new or worsening pain or discomfort, new physical examination findings such as new or enlarged palpable abdominal masses, hepatomegaly, or jaundice or new elevations in liver function tests, or any NET biomarker. The Investigator should obtain imaging or other assessments that are appropriate for the clinical finding.

8.9. Additional Assessments

8.9.1. Subject Interview

Subjects may have the opportunity to participate in a qualitative interview conducted at the end of their participation in the Randomized Treatment Phase. The interview will only be available to subjects in certain countries and those applicable countries have the option explicitly stated in the consent form to confirm their agreement to participate in the interview. The interview will collect information in the subject's words regarding their own perceptions of their experiences with Carcinoid syndrome both before and during the clinical trial. Specifically, interview subjects will be asked to describe their Carcinoid syndrome symptoms and impacts before the clinical trial and their expectations of treatment prior to entering the study. Subjects will then be asked to describe how, if at all, their Carcinoid syndrome symptoms and impacts changed during the clinical trial, and to describe the meaningfulness of any changes experienced. The subject interviews will be performed via telephone and will be audio recorded and transcribed.

8.9.2. Unscheduled Visit

In the event that the worsening of Carcinoid syndrome symptoms that meet protocol criteria for short-acting octreotide rescue (Section 4.1.3) occurs between the scheduled visits, and the Investigator determines it is appropriate to increase the subject's dose before the next scheduled visit, an unscheduled visit can be added in order to increase the subject's dose. The site should perform a triplicate ECG at 1 to 3 hours postdose and 24-hour continuous cardiac (Holter) monitoring 5 to 7 days after the dose increase if the dose is increased to 120 mg. A paltusotine predose blood draw for PK, safety labs and postdose PK blood draw at 1 to 3 hours should also be done.

8.10. Collection and Storage of Biological Samples

The Sponsor will comply with the applicable rules for the collection, storage, and future use of biological samples from clinical trial subjects. The Sponsor will comply with national requirements including those set in the CTR (EU) No 536/2014, Article 7.1 (h).

A description of the arrangements to comply with CTR (EU) No 536/2014, Article 7.1 (h) is provided in the form 'Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)' submitted as a Part 2 document of this trial's CTIS submission.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No formal hypothesis testing is planned for this study.

9.2. Sample Size Determination

Formal sample size calculations were not performed due to the exploratory nature of the study design. A total of 30 subjects with Carcinoid syndrome is considered adequate to assess the study objectives for PK in subjects with Carcinoid syndromes. Subjects taking PPIs at Screening may contribute up to 6 subjects enrolled in the study.

9.3. Analysis Sets

The following analysis sets will be evaluated and used for presentation and analysis of the data in this study:

Safety Set (SS):

The SS includes all treated subjects. This set will be used for all safety and exploratory efficacy analyses.

Pharmacokinetic Set (PKS):

The PKS includes all subjects who have received any amount of study drug and have evaluable PK data. This set will be used for the PK analyses.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock of Randomized Treatment Phase. It will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important safety, efficacy, and key exploratory endpoints.

There will be 2 database locks, one for the Randomized Treatment Phase and the other for the OLE Phase of the study.

9.4.1. General Considerations

For continuous variables, the number of subjects (N), mean, median, interquartile range, standard deviation, minimum and maximum values will be presented. For discrete variables, the N and percent will be presented. These summaries will be presented for all endpoints by visit and dose group. Change from Baseline and change from EOR to each subsequent visit will also be presented.

9.4.2. Efficacy Analyses

9.4.2.1. Analyses

Pharmacokinetic Analysis:

Summary of steady state trough levels at each dose will be presented showing the N, mean, median, interquartile range, geometric mean, standard deviation, minimum and maximum values at EOR. The 95% confidence interval (CI) will be presented for the mean and geometric mean. All steady state trough levels as well as other PK analyses will be performed on the PK set.

Exploratory Analyses:

CCI [redacted]

Randomized Treatment Phase Exploratory Endpoints are as follows:

- Proportion of clinical responders by dose during the last week of the Randomized Treatment Phase. Subjects with missing data at the EOR will be considered nonresponders.

  In subjects who meet diarrhea entry criteria only:

  – Have less than 4 mean bowel movements (BMs) daily

  – Have a >20% reduction in the mean daily number of BMs compared with Baseline

  In subjects who meet flushing entry criteria only:

  – Have a >30% reduction compared with Baseline in the mean daily number of flushing episodes.

  In subjects who meet both diarrhea and flushing entry criteria:

  – Have less than 4 mean BMs daily

  – Have a >20% reduction in the mean daily number of BMs compared with Baseline

  – Have any reduction from Baseline in the mean daily number of flushing episodes

- Proportion of target symptom responders by dose during the last week of the Randomized Treatment Phase:

  – Subjects who met the target symptom (BM or flushing) response criteria. Target symptom is the symptom [either BM or flushing] that troubled the subject the most at Baseline.

- Change in mean daily BMs from Baseline Period of Screening to last week of Randomized Treatment Phase. The change for missing data will be set to 0.
- Change in mean daily number of flushing episodes from Baseline Period of Screening to the last week of Randomized Treatment Phase. The change for missing data will be set to 0.
- Change in worst flushing in last 24 hours (using a 0 to 10 NRS). The change score will be set to 0 if missing:
  - 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
- Change in mean daily target symptom episodes from the Baseline Period of Screening to the last week of the Randomized Treatment Phase. The change for missing data will be set to 0.
- Change from Baseline to EOR in biomarkers:
  - Plasma 5-HIAA
  - Plasma pancreastatin
  - Serum chromogranin A
  - Serum serotonin

Missing values of biomarkers at the end of the EOR will be left missing.

- Change in the use of short-acting octreotide:
  - Change in proportion of days on short-acting octreotide in the Screening Period, after subject has met entry criteria, to the proportion of days on short-acting octreotide of the last week of Randomized Treatment Phase
  - Change in mean daily dose of short-acting octreotide in the Screening Period, after subject has met entry criteria, to the mean daily dose of short-acting octreotide during the last week of Randomized Treatment Phase
- Change in mean daily fecal incontinence episodes (defined as accidental passing of BMs including solid stools, liquid stools, or mucus) from Baseline Period of Screening to the last week of the Randomized Treatment Phase
- Change in worst abdominal pain in the last 24 hours (using a 0 to 10 NRS). The change score will be set to 0 if missing:
  - From the mean Baseline Period of Screening to the mean in the last week of 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

- Change in "worst" (highest) stool score in the last 24 hours (Bristol scale). The change score will set to 0 for missing values:
  - From the mean Baseline Period in Screening to the mean in the last week of the Randomized Treatment Phase
  - From the highest score during the Baseline Period in Screening to the highest score during the last week of the Randomized Treatment Phase
- Change in health-related quality of life from Baseline to EOR for:
  - EORTC QLQ-C30
  - EORTC QLQ-GI.NET21 scores
  - EOR in EQ-5D-5L
  - FACT-CSI
- Patient global impressions of symptom severity and change:
  - Change from Baseline to EOR in PGI-S
  - PGI-C at EOR
- Change in treatment preference from Baseline (pretrial treatment) to EOR
- Change in mean daily urgency episodes (defined as BMs that make subjects rush to the bathroom) from the Baseline Period of Screening to last week of Randomized Treatment Phase

Open-Label Extension Phase Exploratory Endpoints are as follows:

- Incidence of NET progressive disease at EOT using 6-month interval imaging assessment while on paltusotine
- Proportion of clinical responders during the last week of the OLE Phase by dose

  In subjects who meet diarrhea entry criteria only:
  - Have less than 4 mean BMs daily, and have a >20% reduction in the mean daily number of BMs compared with Baseline

  In subjects who meet flushing entry criteria only:
  - Have a >30% reduction compared with Baseline in the mean daily number of flushing episodes

  In subject who meet both diarrhea and flushing entry criteria:
  - Have less than 4 mean BMs daily, and have a >20% reduction in the mean daily number of BMs 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
  - Subjects who met the target symptom (diarrhea or flushing) response criteria

- Change 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
- 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 in health-related quality of life from Baseline to EOT for:
  - EORTC QLQ-C30
  - EORTC QLQ-GI.NET21 scores
  - EOR in EQ-5D-5L
  - FACT-CSI
  - PGI-S
- 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
- Change in mean daily fecal incontinence episodes (defined as accidental passing of BMs including solid stools, liquid stools, or mucus) from the last week prior to Baseline to last week prior to EOT
- 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 last week of OLE
  - From the highest score during the last week prior to Baseline to last week of OLE
- Change in mean daily urgency episodes (defined as BMs that make subjects rush to the bathroom) from the last week prior to Baseline to the last week prior to EOT

9.4.2.2. Multiplicity

There will be no adjustment for type 1 error, as all analyses are exploratory.

9.4.3. Safety Analyses

Analysis of safety endpoints in the Randomized Treatment Phase and OLE will be based on the Safety Set (SS). For all endpoints that are defined as a mean over a 7- day period, the endpoint will be missing if 3 or more of the 7 days have missing data.

The safety endpoints consist of the safety and tolerability of the 3 doses of paltusotine (40 mg, 80 mg, and 120 mg) based on the 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 ECG, 24-hour continuous cardiac (Holter) monitoring tracing analysis (only for subjects on 120 mg dose), and ophthalmic assessments.

Summaries will be presented by dose level and study phase (Randomized Treatment Phase, and OLE Phase) for the SS.

Vital signs, select clinical laboratory results (see Section 10.2 Appendix 2), and ECG data will be summarized descriptively by visit. Their change scores from Baseline will also be derived and summarized by visit.

9.4.4. Protocol Deviations

Protocol deviations are defined as any failure to comply with the study protocol as approved by the IRB/IEC, whether planned or unplanned.

Protocol deviations will be handled in accordance with the procedures established for the study.

9.5. Interim Analysis

No formal interim futility analysis is planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 54, 56, and 312 of Title 21 of the Code of Federal Regulation, in compliance with ICH Good Clinical Practice (GCP) guidelines, and per all applicable local regulatory guidelines.

Declaration of Helsinki and amendments can be accessed via the website of the World Medical Association at https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

Conduct of the study must be approved by an appropriately constituted IRB/IEC. Approval is required for the Clinical Study Protocol, IB, protocol amendments, ICFs, and subject information sheets.

Amendments to the Clinical Study Protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of subjects or the conduct of the study will be classified as administrative amendments and will be submitted to the IRB/IEC and Regulatory Authorities for information only. The Sponsor (or designee) will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IRB/IECs for approval.

Should protocol deviations that affect subject safety occur, the Sponsor must be informed as soon as possible. Important protocol deviations will be included in the clinical study report (CSR). Reporting of protocol deviations to IRB/IECs will be performed in accordance with applicable Regulatory Authority mandates and IRB/IEC policies.

All subjects must meet all eligibility criteria in order to participate in the study. Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If during the course of a subject's post enrollment participation in the trial it is discovered that the subject did not meet all eligibility criteria, the subject will be discontinued if there is a safety concern upon discussion with the Investigator and the physician.

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

For each study subject, written informed consent will be obtained prior to any protocol-related activities. An ICF must be signed and dated personally by the subject and by the Investigator and/or the study team member designated by the Investigator to conduct the informed consent procedure.

As part of this procedure, the Investigator or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the subject is aware of the potential risks, inconveniences, or adverse effects that may occur. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and International Council for Harmonization (ICH) guidelines. The Investigator will provide the Sponsor or its representative with a copy of the IRB/IEC approved ICF prior to the start of the study.

10.1.4. Data Protection

This trial will be conducted in accordance with the CTR EU No 536/2014 and General Data Protection Regulation (EU) 2016/679 (GDPR) in addition to the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements.

If a subject revokes authorization to collect or use personal health data, the Investigator retains the ability to use all information collected before the revocation of subject authorization. For subjects that have revoked authorization to collect or use personal health data, attempts should be made to obtain permission to collect at least vital status (ie, that the subject is alive) at the end of their scheduled study period.

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject data. Subjects' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law. To protect the rights and freedoms of subjects with regard to the processing of personal data, subjects will be assigned a single, subject-specific numerical code. Any subject records or data sets that are transferred to the Sponsor will contain the numerical code; subject names will not be transferred. All other identifiable data transferred to the Sponsor will be identified by this single, subject-specific code. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to their actual identity and medical record ID. In case of data transfer, the Sponsor will protect the confidentiality of subjects' personal data consistent with the clinical study agreement and applicable privacy laws. Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. The Sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of Sponsor information or systems.

10.1.5. Safety Monitoring Committee

An unblinded 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.

10.1.6. Dissemination of Clinical Study Data

Once the study is completed and the CSR written, appropriate information will be provided for the clincialtrials.gov or clinicaltrialsregister.eu websites as required. All IRB/IECs will receive appropriate documentation with study results.

10.1.7. Data Quality Assurance

The study will be conducted according to GCP (as outlined by ICH topic E6, step 5 guidelines) and in compliance with applicable local legislation including the EU CTR (EU No 536/2014). The contract research organization maintains a quality assurance system with written Standard Operating Procedures (SOPs) to ensure that clinical trials are conducted, and data are generated, documented, and reported in compliance with the Clinical Study Protocol, GCP, and applicable regulatory requirements.

The Sponsor or its designee will perform the quality assurance and quality control activities of this study. However, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the Clinical Study Protocol, SOP, GCP, and all applicable local regulatory requirements including the EU CTR (EU No 536/2014). Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at the study sites and during data management to assure that safety and efficacy data are adequate and well documented.

Study records and source documents must be preserved for at least 25 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application in an ICH region or as per local requirements, whichever is the longer time period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information. The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with Directive 95/46/EC: Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data and in a form satisfactory to the Sponsor.

- All subject data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Electronic CRF completion guidance will be provided to Investigators.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Quality tolerance limits (QTLs) will be predefined in the Study Management Plan to identify systematic issues that can impact subject safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for the specified period of time after study completion as applicable per local and national regulations or institutional policies retention period require. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8. COVID-19 Procedures

The following preventive and protective safety measures will follow local government guidance, and subjects, monitors, and research staff can safely complete study procedures according to the protocol:

- SARS-CoV-2 testing will be carried out at Screening and as mentioned in SOA (refer to Section 1.2).
- Site staff to inform study subjects of changes to the study conduct, prior to change implementation. Verbal consent approved for use and in such cases, the consent process and subject consent must be documented in the study records.
- In-clinic visits may be missed for COVID-19 related reasons at the discretion of the Investigator. Missed visits / procedures will be classified as protocol deviations due to COVID-19. Subjects will not be discontinued from the study due to missed visits or procedures as a result of COVID-19. In order to minimize missed visits, home health care nursing may be used.
- Site staff to contact each subject by phone at least once monthly, in place of projected in-clinic study visits, to assess their status, safety and compliance. These phone calls will be captured as Unscheduled Visits due to COVID-19.
- During the OLE Phase, subjects will be supplied with a 3-month supply of study drug to guarantee continuous treatment. If COVID-19 related inability to conduct visits at sites continues beyond 3 months, all subjects will be resupplied with an additional

supply of study drug, to allow continued treatment. If local regulations allow, study drug will be shipped directly to a subject's home. In such cases, subjects must first provide informed consent (verbal or written) to share their personal contact information (eg, name, address, and phone number) with the courier service. This consent will be documented as described above.

- Onsite Monitoring Visits by study monitors will be canceled until it is safe for monitors to return to the study site and resume their regular monitoring activities, including complete drug accountability. If necessary (eg, for SAEs), review of data will be performed remotely with consideration made to minimize site staff burden.

10.1.9. Source Documents

The study will be monitored to ensure that it is conducted and documented properly according to the Clinical Study Protocol, GCP, and all applicable regulatory requirements.

Before the study start at a site initiation visit or at an Investigator's meeting, a Sponsor representative will review the protocol and the eCRF with the Investigators and their staff.

During the study, onsite monitoring visits will be made at appropriate times. Site monitors will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRF, the adherence to the Clinical Study Protocol and to GCP, the progress of enrollment, the completeness of the IRB/IEC records and the Investigator Site File, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the site monitor during these visits.

The Investigator must give the site monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables will be checked. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.1.10. Publication Policy

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this Clinical Study Protocol, subject to the terms of any such agreement. To facilitate such ownership, Investigators will be required to assign all such inventions directly to the Sponsor as will be set forth in the clinical study agreement.

10.2. APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in below will be performed by the site local laboratory.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Hemoglobin	RBC Indices*: Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration	WBC count with differential: Neutrophils Lymphocytes Monocytes* Eosinophils* Basophils*	
	Hematocrit			
	RBC count			
	Platelet count			
Clinical Chemistry	Total protein	Sodium	Phosphate	Aspartate aminotransferase
	Blood urea nitrogen	Potassium	Magnesium	Alkaline phosphatase
	Creatinine	Chloride	Albumin	Amylase
	Uric acid	Calcium	Total, direct, and indirect* bilirubin	Lipase
	Alanine aminotransferase	Glucose		
Thyroid Hormones and HbA1c	Free T4, and TSH		HbA1c	
Pregnancy testing	Serum and urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential)			
Routine Urinalysis	Specific gravity and appearance* White blood cells, protein, bilirubin, nitrites, ketones, blood, and pH, by dipstick			
Serology	HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody			
SARS-CoV-2 testing	By nasopharyngeal or salivary sampling			

*These lab safety parameters are intended for site evaluation only and will not be transferred to the Sponsor.
HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; LDL = low density lipoprotein; OLE = open-label extension; RBC = red blood cell; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; T4 = thyroxine; TSH = thyroid stimulating hormone; WBC = white blood cell.
Notes: Investigators must document their review of each laboratory safety report.
Fasting blood samples (unless otherwise indicated) should be collected after fasting at least 6 hours. No fasting blood samples are required for S1 visit.

10.3. APPENDIX 3: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1. Definition of Adverse Event

AE Definition
• An AE is any untoward medical occurrence in a clinical study subject, temporally associated with study participation, whether or not considered related to the study intervention. • NOTE: A TEAE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated in either intensity or frequency) that is temporally associated with the use of study drug.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator. • New conditions initially detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction between a concomitant medication and study drug. • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose in the absence of clinical sequelae will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe or increased in frequency than expected for the subject's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of Serious Adverse Event

A SAE is defined as any serious event that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from Baseline is not considered an SAE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Significant medical event

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/ SAE information in the EDC and on appropriate forms for the reporting of SAEs.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the pharmacovigilance unit in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the pharmacovigilance unit. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Any SAE occurring after the ICF has been signed and until 4 weeks after the last dose must be reported on SAE reporting form (Section 10.3.4) within 24 hours of occurrence or when the Investigator becomes aware of the event whether or not related to the study drug.

Investigators are not obligated to actively seek information on TEAEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a SAE, NOT when it is rated as severe.

Breakthrough symptoms requiring treatment are defined as diarrhea or flushing episodes of severe intensity, ie, symptoms which prevent normal everyday activities.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship using the following descriptors: not related, unlikely related, possibly related, probably related, and definitely related.

NOT RELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).

UNLIKELY: This category applies to those AEs that are judged to be unrelated to the study drug, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to the IMP if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the IMP; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the IMP; or (4) it does not reappear or worsen when the IMP is re-administered.

POSSIBLY: This category applies to those AEs for which a connection with the IMP administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of IMP; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the IMP.

PROBABLY: This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the IMP. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the IMP; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the IMP, yet drug-relatedness clearly exists (eg, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the IMP.

DEFINITELY: This category applies to those AEs that the Investigator feels are incontrovertibly related to the IMP. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the IMP; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with reexposure to the IMP (if rechallenge occurs); and (4) it follows a known pattern of response to the IMP.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which a SAE has occurred, and the Investigator has minimal information to include in the initial report to the pharmacovigilance unit. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the pharmacovigilance unit.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements. Possibly, probably, or definitely related will be recorded as related for regulatory reporting purposes.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the pharmacovigilance unit to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- Adverse event outcomes will be recorded as 1 of the following: Recovered/Resolved, Recovering/Resolving, Not Recovered/Not Resolved/Ongoing, Recovered/Resolved with sequelae, Fatal, Unknown.

Recovered/Resolved - One of the possible results of an adverse event outcome that indicates that the event has improved or recuperated. The subject recovered from the AE. Record the AE stop date.
Recovering/Resolving - One of the possible results of an adverse event outcome that indicates that the event is improving. No AE stop date should be recorded.
Not recovered/Not resolved/Ongoing - One of the possible results of an adverse event outcome that indicates that the event has not improved or recuperated. No AE stop date should be recorded.
Recovered/Resolved with sequelae - One of the possible results of an adverse event outcome where the subject recuperated but retained pathological conditions resulting from the prior disease or injury. Record the AE stop date. The AE stop date will represent the date the AE stabilized with no change in event outcome anticipated.
Fatal - The AE directly caused death. Record the date of death as the AE stop date.

Unknown - There is an inability to access the subject or the subject's records to determine the outcome (ie, subject withdraws consent or is lost to follow-up). No AE stop date should be recorded.

- The Investigator will submit any updated SAE data to the pharmacovigilance unit within 24 hours of receipt of the information.

10.3.4. Reporting of Serious Adverse Events

SAE Reporting to pharmacovigilance unit

- The primary mechanism for reporting a SAE to the pharmacovigilance unit will be done using the SAE report form. Any such SAE due to any cause, whether or not related to the study drug, must be reported on the SAE reporting form immediately (and under no circumstances should this exceed 24 hours) of occurrence or when the Investigator becomes aware of the event.
- Completed SAE reporting forms should be sent via email to: mailto:PPD

10.4. APPENDIX 4: ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AcroQoL	Acromegaly Quality of Life Questionnaire
AE	Adverse event
BM	Bowel movement
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
CT	Computed tomography
CTR	Clinical Trials Regulation
CYP3A4	Cytochrome P450 3A4
EC	Effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
EOR	End of Randomized Treatment Phase
EORTC QLQ-C30	EORTC Quality of Life questionnaire
EORTC QLQ-GI.NET21	EORTC Quality of Life questionnaire in GI NET
EOS	End of study
EOT	End of treatment
EQ-5D-5L	EuroQoL 5 Dimensions 5 Level
ET	Early termination
EuroQoL	European Quality of Life
FACT-CSI	Functional Assessment of Cancer Therapy – Carcinoid Syndrome Symptom Index
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HbA1c	Hemoglobin A1c
HIV	Human immunodeficiency virus
5-HIAA	5-Hydroxyindolacetic acid
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IGF-1	Insulin-like growth factor 1
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
LAR	Long-acting release
MRI	Magnetic resonance imaging

Abbreviation	Definition
N	Number of subjects
NET	Neuroendocrine tumor
NRS	Numeric rating scale
OCT	optical coherence tomography
OLE	Open-label extension
PET	Positron emission tomography
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PPIs	Proton-pump inhibitors
QD	Once a day
QTcF	QT interval corrected using Fridericia's formula
QTL	Quality tolerance limit
RBC	Red blood cell
RTP	Randomized Treatment Phase
SA	Short-acting
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Subcutaneous
S1	Screening Visit 1
S2	Screening Visit 2
SSA	somatostatin analog
SMC	Safety Monitoring Committee
SOAs	Schedule of Activities
SOP	Standard Operating Procedure
SRL	Somatostatin receptor ligand
SS	Safety Set
SSTR	Somatostatin receptor
SST2	Somatostatin type 2 receptor
TEAE	Treatment-emergent adverse event
T_{max}	Time to achieve maximum plasma concentration
ULN	Upper limit of normal

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Signature Page for VV-CLIN-002318 v2.0
CRN00808-11 Protocol 21 Jan 2025 v7.0

Approval	PPD Clinical Research/Clinical Sciences 21-Jan-2025 18:16:07 GMT+0000