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Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome

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**A Phase 3, Randomized, Placebo-controlled, Parallel-group,
Multicenter, Double-blind Study to Evaluate the Efficacy and
Safety of Telotristat Etiprate (LX1606) in Patients with
Carcinoid Syndrome Not Adequately Controlled by
Somatostatin Analog (SSA) Therapy**

EudraCT Number: 2012-003460-47

<https://www.clinicaltrialsregister.eu/ctr-search/search?query=2012-003460-47>

Other Study ID Numbers: LX1606.1-301-CS

1. Study Objectives

1.1. Efficacy Objectives

1.1.1. Primary Objective

Primary objective of the study is to confirm that at least 1 or more dose groups of telotristat etiprate compared to placebo is effective in reducing the number of daily BMs from baseline averaged over the 12-week double-blind portion of the trial (Treatment Period) in patients not adequately controlled by current SSA therapy.

1.1.2. Secondary Objective(s)

The secondary objectives of this study are to assess the effects of telotristat etiprate versus placebo over the 12-week double-blind portion of the study in patients who are not adequately controlled by current SSA therapy as determined by:

- Change from baseline in urinary 5-HIAA levels at Week 12
- Change from baseline in the number of daily cutaneous flushing episodes averaged across all time points
- Change from baseline in abdominal pain averaged across all time points

1.1.3. Other Efficacy Objectives

To assess the effects of telotristat etiprate versus placebo over the 12-week double-blind portion of the study in patients not adequately controlled by current SSA therapy as determined by:

- Proportion of patients with durable response, defined as the proportion of responders with $\geq 30\%$ reduction in daily number of BMs for $\geq 50\%$ of time over the double-blind portion of the study
- Change from baseline in overall and domain scores of the EORTC QLQ-C30 & GI.NET21 averaged across all time points and at each study visit were collected

- Change from baseline in the daily number of cutaneous flushing episodes at each study week
- Change from baseline in abdominal pain averaged at each study week
- Change from baseline in BM frequency averaged at each study week
- Change from baseline in stool consistency averaged across all time points and averaged at each study week
- Proportion of weeks in which patients report adequate relief of CS symptoms associated with GI symptoms
- Proportion of patients that report adequate relief of CS symptoms associated with GI symptoms at each study week
- Change from baseline in subjective global assessment of CS symptoms on an 11-point Numeric Rating Scale (NRS) averaged across all time points and at each study week
- Proportion of days where urgency/immediate need to defecate is reported
- Proportion of days with reports of nausea
- Change from baseline in the sensation/severity of nausea averaged across all time points and at each study week
- Number of days with $\geq 30\%$ reduction in number of BMs from individual baseline mean
- Number of days with ≥ 1.5 reduction in number of BMs from individual baseline mean
- Time to first $\geq 30\%$ worsening in BM frequency, defined as time to the first day of a 2 consecutive weeks with a weekly mean BM frequency at least 30% above the individual baseline mean
- Time to first sustained $\geq 30\%$ improvement from baseline in BM frequency defined as time to the first day of a 2 consecutive weeks with a weekly mean BM frequency at least 30% below the individual baseline mean

- Time to a 3-point reduction in the weekly global assessment of severity of CS symptoms sustained for at least 50% of the subsequent weeks (evaluated in patients with at least 4 weeks of data from the week where they responded)
- Change from baseline in urinary levels of 5-HIAA averaged across all time points and at Week 6
- Change from baseline in plasma levels of 5-HIAA averaged across all time points and at each study week
- Relationship of change in BMs to change in stool consistency, adequate relief, nausea, urgency and abdominal pain
- Relationship of baseline and change from baseline in plasma and urinary 5-HIAA levels to change in number of BMs, proportional change in number of BMs, change in subjective global assessment, time to first improvement in BM frequency, time to first worsening in BM frequency, and change in symptoms (abdominal pain, stool consistency, urgency to defecate, and reports of nausea) over the treatment period
- Correlation between 5-HIAA levels in urine and plasma over time
- Change in the frequency of rescue short-acting SSA used to treat bowel-related CS symptoms

1.2. Safety Objectives

Evaluation of overall safety will be assessed as:

- Incidence of treatment-emergent adverse events (TEAEs)
- Changes from baseline in clinical laboratory results; vital signs results; and ECG findings

1.3. Pharmacokinetic (PK) Objective

The PK objective is to identify intrinsic and extrinsic factors contributing to variability in telotristat etiprate and LP-778902 exposure, but not limited to, age, sex, race, body mass index (BMI), renal impairment, hepatic impairment.

- Details of population PK analysis plan will be prepared in a separate document.

2. Investigational Plan

2.1. Overall Study Design

The study will be conducted as a Phase 3, randomized, placebo-controlled, parallel-group, multicenter, double-blind study in patients with CS not adequately controlled by SSA therapy to evaluate 2 oral dose levels of telotristat etiprate, 250 or 500 mg tid versus placebo.

Patients will enter into a Screening/Run-in Period of at least 3 to 4 weeks (depending of dosing frequency of SSA therapy) to establish baseline symptoms. Start of Screening and timing of first dose of study drug is designed to coincide with patients' regular SSA injection. Patients on infusion pump should have at least 3 weeks of Run-in data. During the Run-in Period, patients will continue to receive stable-dose SSA therapy in order to establish baseline characteristics and symptomatology. For the purposes of this study, stable-dose SSA therapy is defined as LAR or Depot SSA therapy or a continuous subcutaneous infusion via a pump at the same dose level and frequency for at least 3 months prior to the Run-in Period.

The SSA must be approved for use in CS in the patient's country of residence or prescriber's country of practice. In addition, therapy with rescue, short-acting SSA will be permitted. Only patients who complete the Screening/Run-in Period and who are 75% compliant with diary entries will be considered eligible for further participation in the study.

Following the Screening/Run-in Period, patients will be randomly assigned (1:1:1) on Day 1 to receive 1 of 2 oral dose levels of telotristat etiprate (250 or 500 mg) or placebo tid for 12 consecutive weeks (Treatment Period). A blinded titration period will occur during the first 7 days for patients assigned to 500 mg tid. During the titration period, all

patients will take 2 tablets tid (1 x 250 mg and 1 placebo or 2 placebo). After 7 days, patients will receive their assigned treatment and dose levels for the remaining 11 weeks of the Treatment Period. All patients must remain on their baseline dose of SSA therapy for the duration of the Treatment Period.

Upon completion of the Treatment Period, patients will continue in an Extension Period in which all patients will receive active study drug at the 500 mg tid dose level. To accomplish this dosing objective and maintain the integrity of the study blind for the first 12 weeks of the trial, a blinded transition period will occur during the first 7 days of the Extension Period (Week 13). During the transition period, all patients will undergo a 1-week blinded titration based upon their initial randomization. Patients initially randomized to placebo will take 2 tablets tid; given as telotristat etiprate 1 x 250 mg and 1 placebo tablet. Patients initially randomized to 250 or 500 mg tid will take 2 tablets tid; given as 2 x 250 mg tablets. After 7 days, all patients will receive open-label telotristat etiprate 500 mg tid for the duration of the Extension Period. The Table 2.1–1 depicts the flow through the transition.

Table 2.1–1 Transition Schema

Assigned Dose Regimen	Initial 12-week treatment (Treatment Period)	Week 13 titration period	Weeks 14 + (Extension Period)
Placebo	Placebo	250 mg tid*	500 mg tid*
250 mg tid*	250 mg tid*	500 mg tid*	500 mg tid*
500 mg tid*	500 mg tid*	500 mg tid*	500 mg tid*

* Telotristat etiprate

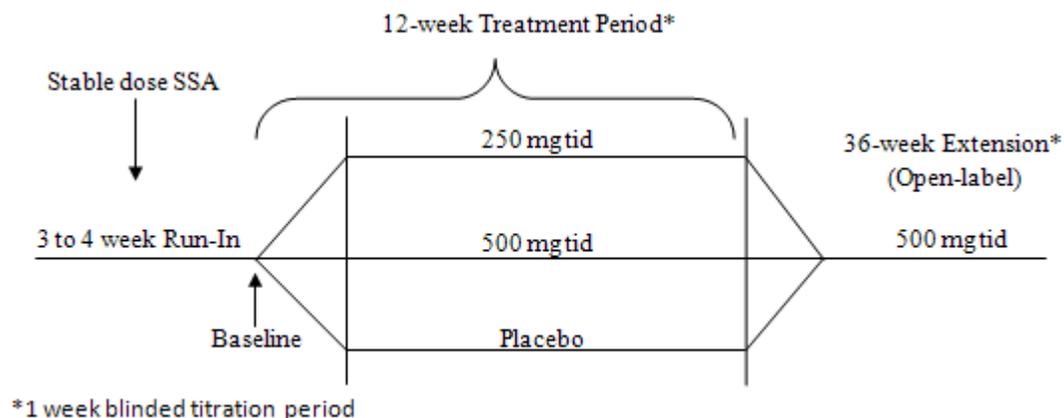
Downward dose adjustment of telotristat etiprate from 500 to 250 mg tid will be permitted during the Extension Period if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level may be discontinued from the study. After a period at the 250 mg dose level, patients may return to 500 mg tid dosing

at the discretion of the Investigator and in consultation with the Sponsor's medical monitor.

Upon withdrawal, all patients will be required to complete a 14-day Follow-up Period, during which time no study drug will be administered.

A Data Safety Monitoring Board (DSMB) will review safety data at specified time points throughout the study. The treatment schema is summarized in Figure 2.1–1.

Figure 2.1–1 Treatment Schema



3. Study Population

Patients with histopathologically-confirmed, well-differentiated, metastatic, neuroendocrine tumor (NET) and with a documented history of CS, who are currently experiencing ≥ 4 BMs per day and who are on at least a minimum stable-dose of SSA therapy, will be screened for this study. A minimum of 105 patients not adequately controlled by a stable-dose of FDA approved SSA therapy indicated for the treatment of CS are expected to participate in this study. Additional patients on SSA therapies approved in other participating countries will also be enrolled. Approximately 100 sites worldwide will participate in the study. The recruitment period is approximately 18 months from first patient enrolled. Patients may continue allowed medications as background therapy provided they remain on stable-doses throughout the Treatment Period.

3.1. Inclusion Criteria

Patients must meet all of the following criteria to be considered eligible to participate in the study:

1. Patients ≥ 18 years of age at the time of the Screening visit
2. Histopathologically-confirmed, well-differentiated metastatic NET with extent documented by computed tomography (CT), magnetic resonance imaging (MRI), or radionuclide imaging
3. A documented history of CS, and currently experiencing an average of ≥ 4 BMs per day during the Run-in Period. Confirmation of eligibility will be determined by measuring the mean number of BMs
4. Currently receiving a stable-dose SSA therapy. For the purposes of this study, stable-dose SSA therapy is defined as LAR or Depot SSA therapy or a continuous subcutaneous infusion via a pump. Patients must have been receiving the same dose level and frequency for at least 3 months prior to entering the Run-in Period.
5. Minimum dose of LAR or Depot SSA therapy (higher dose or more frequent intervals will exceed minimum dose). SSA therapy must be approved for use in CS in country of residence or prescribers' country of practice.
 - a. Octreotide LAR at 30 mg every 4 weeks
 - b. Lanreotide Depot at 120 mg every 4 weeks
 - c. Patients who cannot tolerate SSA therapy at a level indicated above will be allowed to enter at their highest tolerated dose
6. Patients of childbearing potential must agree to use an adequate method of contraception (defined as having a failure rate of $< 1\%$ per year) during the study and for 12 weeks after the Follow-up visit. Adequate methods of contraception for patients or partner include condoms with spermicide gel, diaphragm with spermicide gel, coil (intrauterine device), surgical sterilization, vasectomy, oral contraceptive pill, depot progesterone injections, progesterone implant, and abstinence during the study and for 12 weeks after the Follow-up Visit.
 - a. Childbearing potential is defined as those who have not undergone surgical sterilization, or those who are not considered postmenopausal. Postmenopause is defined as absence of menstruation for at least 2

years. If necessary, follicle-stimulating hormone (FSH) results >50 IU/L at Screening are confirmatory in the absence of a clear postmenopausal history.

7. Ability and willingness to provide written informed consent prior to participation in any study-related procedure.

3.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participating in the study:

1. Presence of diarrhea attributed to any condition(s) other than CS (including, but not limited to fat malabsorption or bile acid malabsorption)
2. Presence of more than 12 watery BMs per day associated with volume contraction, dehydration, or hypotension compatible with a “pancreatic cholera”-type clinical syndrome, as judged by the Investigator
3. Positive stool examination for enteric pathogens, pathogenic ova or parasites, or *Clostridium difficile* at Screening
4. Karnofsky Performance Status $\leq 60\%$
5. Clinical laboratory values for hematology (at Screening):
 - a. Absolute neutrophil count (ANC) ≤ 1500 cells/mm³; or
 - b. Platelets $\leq 75,000$ cells/mm³; or
 - c. Hemoglobin (Hgb) ≤ 9 g/dL for males and ≤ 8 g/dL for females
6. Hepatic laboratory values (at Screening) such that:
 - a. AST or ALT:
 - i. $5.5 \times$ ULN if patient has documented history of hepatic metastases; or
 - ii. $\geq 2.5 \times$ ULN if patient does not have documented history of hepatic metastases
 - b. Total bilirubin $>1.5 \times$ ULN (unless patient has a documented history of Gilbert’s Syndrome); or
 - c. ALP $\geq 5 \times$ ULN, if total bilirubin is $>$ ULN
 - i. No upper limit on the ALP value if the total bilirubin is \leq ULN

7. Serum creatinine $\geq 1.5 \times$ ULN
8. Treatment with any tumor directed therapy including, but not limited to: interferon, chemotherapy, mTOR inhibitors ≤ 4 weeks prior to Screening; or hepatic embolization, radiotherapy, radiolabelled SSA, and/or tumor debulking ≤ 12 weeks prior to Run-in
9. Major surgery defined as procedures requiring general anesthesia or major regional anesthesia within 8 weeks prior to Screening
10. A history of short bowel syndrome (SBS)
11. Pregnant or nursing (lactating) women
12. Positive pregnancy test
13. Life expectancy < 12 months from the Screening visit
14. Presence of any clinically significant findings at Screening medical history, or physical examination (relative to patient population) that, in the Investigator's or Medical Monitor's opinion, would compromise patient safety or the outcome of the study
15. Any other clinically significant laboratory abnormality at Screening that would compromise patient safety or the outcome of the study
16. Clinically significant cardiac arrhythmia, bradycardia, tachycardia that would compromise patient safety or the outcome of the study, or QTcF > 450 ms
17. A history of substance or alcohol abuse within 2 years prior to Screening
18. Administration of any investigational agent within 30 days of Screening or investigational therapeutic protein or antibody within 90 days prior to Screening
19. Previous exposure to telotristat etiprate
20. Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities

4. Criteria for Stopping Treatment/Study Withdrawal

4.1. Stopping Criteria

Individual patients may be discontinued from the study by the Investigator or the Sponsor at any time if either determines that it is not in the best interest of the patient to

continue (eg, continuation in the study represents a serious medical risk to the patient). This may include, but is not limited to, the presence of serious, life-threatening adverse events or adverse events that are unacceptable in nature, severity, or frequency as assessed by the Investigator.

Patients must be discontinued if they become pregnant (Section 7.3) or withdraw consent. Patients may be discontinued due to noncompliance with the protocol. While patients will be encouraged to complete the study, they may voluntarily withdraw at any time.

4.2. Procedures for Withdrawal

If a patient voluntarily withdraws or is discontinued from the study before completing the specified duration of treatment, they should be encouraged to continue clinic visits according to the study schedule.

Patients who discontinue study treatment, and who are not willing to continue clinic visits (eg, withdrawal of consent) should be encouraged to complete End-of-Study (EOS) assessments as identified in Tables 6.1-1 and 6.1-2 – Study Assessments and to agree to report any SAEs (Section 7.2) that occur within 30 days following the last dose of study treatment.

When patients withdraw consent from study participation, it must be recorded on the CRF whether the withdrawal of consent applies to specific aspects of the study such as discontinuation of study treatment, participation in study visits, contact by study personnel, or access to information about potential SAEs. If specific consent has not been withdrawn, study personnel should contact the patient (or a previously approved designee such as a caregiver, partner, or family member) at the scheduled Follow-up visit to inquire about health status.

The date the patient discontinues study treatment, the primary reason for study treatment discontinuation, study termination, and/or termination of participation (eg, withdrawal of consent), will be captured within the CRF.

4.3. Criteria for Termination of the Study

Sponsor, Investigator, study monitor, DSMB, or regulatory officials discover conditions arising during the study that indicate that the patient safety and/or scientific value of the study and/or quality of the study drugs have been compromised, the study should be halted or the study center's participation should be terminated. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study;
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product for any reason;
- Failure of the Investigator to enroll patients into the study at an acceptable rate;
- Failure of the Investigator to comply with pertinent governing body regulations;
- Submission of knowingly false information from the research facility to the Sponsor, study monitor, medical officer, or regulatory official;
- Insufficient adherence to protocol requirements
- Study termination and follow-up would be performed in compliance with applicable governing body regulations.

4.4. Clinical Stopping Rules

Criteria for individual patient withdrawal or study termination are summarized in Sections 4.1 and 4.3, respectively.

4.5. Method of Assigning Patients to Treatment

A randomization schedule will be generated by the contract research organization (CRO) performing data management for the study. This schedule will be prepared prior to the start of the Treatment Period. A hard-copy of the randomization schedule will be maintained in a restricted file cabinet and stored at the CRO performing data management for this study. The CRO will follow their established standard operating procedures (SOPs) regarding generation, security, and distribution of the randomization schedule.

Randomization will be centralized. Patients will receive their allocated treatment of telotristat etiprate or placebo according to a SAS-generated randomization schedule. Patients will be enrolled in consecutive order at each trial site and assigned a patient number in their order of inclusion in the study. Once it has been determined that a patient meets all eligibility criteria, the patient will be assigned a kit number from the randomization schedule via Interactive Web Response System (IWRS) and will receive their allocated study treatment.

The randomization will be stratified by baseline urinary 5-HIAA levels. This variable will be categorized as values of \leq ULN, $>$ ULN, and unknown (missing or uninterpretable). Randomly permuted blocks of a fixed size will be generated within each of the 3 stratum of urinary 5-HIAA to assure balance in patient assignments among the treatment groups.

4.6. Blinding and Unblinding of Study Medication

The study blind is to be maintained until all patients have completed the Treatment Period and until after the database has been locked. The study site receives documentation of patient study ID and treatment allocation through the IVRS/IWRS. The randomization code will not be available, with the exception of unblinding procedures listed below, to the CRO study team, study center personnel, Sponsor monitors, Sponsor project statisticians, or any other personnel employed or affiliated with the Sponsor, as well as Investigators and patients until after the database has been locked.

The IVRS/IWRS provides for unblinding procedures, if needed. During the study, the blind is to be broken if the safety of the patient is at risk and the treatment plan is dependent on the study treatment received. Unless the patient is at immediate risk, the Investigator must make diligent attempts to contact the Sponsor prior to unblinding the study treatment administered to a patient. Any request from the Investigator about the treatment administered to study patients for any other purpose must be discussed with the Sponsor. If the unblinding occurs without the knowledge of the Sponsor, the Investigator must notify the Sponsor as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

Unblinding may be performed for regulatory reporting purposes of adverse events; the unblinded information will be kept within the unblinded team responsible for expedited reporting of SAEs.

The blinding of the study will be broken by the CRO upon completion of the Treatment Period and after the database has been locked.

4.7. Replacement of Patients

The sample size requirement will be satisfied when 105 patients treated with stable-dose FDA approved SSA for CS have been randomly assigned to study treatment. Assignment to study treatment will stop once this requirement is met, however, there may be a slight overrun of patients given the specifics of the randomization process. Patients who do not complete the study will not be replaced.

4.8. Rescreening of Patients

Patients who are excluded during the screening period may be allowed to rescreen at the discretion of the medical monitor.

If the exclusion is due to out-of-range (OOR) laboratory values, patients approved for rescreening may have OOR tests repeated 1 time during the screening period.

Exclusionary tests may be redrawn 1 week after exclusionary results are received. A confirmatory result will exclude the patient from further participation.

5. Treatment

5.1. Prior and Concomitant Medications

5.1.1. Prior Medications

All medications and other treatments taken by patients within 30 days prior to the Run-in period will be recorded on the CRF.

5.1.2. Concomitant Medications

All concomitant medications taken by patients during the study will be recorded on the CRF. Treatment with prescription or over-the-counter antidiarrheal therapy, bile acid

sequestrants, or pancreatic enzyme is not prohibited. However, the use of these concomitant therapies should be associated with a documented history of disease (eg, fat malabsorption, bile acid malabsorption, or steatorrhea). The use of all concomitant medication should remain stable during the Run-in Period and the Treatment Period. An addition or change in dose or dose regimen of concomitant medication during this period is discouraged unless the patient is placed at undue safety risk.

Should the need arise to modify/adjust a patient's SSA therapy during the Treatment Period (with the exception of rescue short acting octreotide); the Medical Monitor should be contacted. The Investigator and Medical Monitor will make a determination if such a change would impact the safety of the patient and the integrity of the study. The Medical Monitor will determine if the patient can continue in the study.

5.1.3. Prohibited Medications or Concomitant Therapy

Treatment with any tumor directed therapy (including, but not limited to: hepatic embolization, interferon, chemotherapy, radiotherapy, radiolabelled SSA, or tumor debulking) during the Treatment Period is not permitted and may result in discontinuation of the patient. Cases will be reviewed on an individual basis for final disposition.

5.1.4. Administration of Study Medication

All patients will be instructed to take the study medication with food. "With food" means taking telotristat etiprate or matching placebo tablets within 15 minutes before or within 1 hour after a meal or snack. Patients will be instructed to take study drug 3 times daily during waking hours, with doses spaced approximately 6 hours apart.

Patients will be randomly assigned (1:1:1) on Day 1 to receive telotristat etiprate 250 or 500 mg tid or placebo tid. A blinded titration period will occur during the first 7 days for patients randomized to 500 mg tid. During the titration period, all patients will be administered 2 tablets; given as 1 telotristat etiprate 250 mg tablet plus 1 placebo tablet or 2 placebo tablets. After 7 days, patients will receive their assigned dose levels for 11 weeks.

Upon completion of the Treatment Period, patients will enter the Extension Period during which all patients will receive telotristat etiprate 500 mg tid after a blinded 1 week titration.

Patients who received the 500 mg tid dose level of telotristat etiprate during the Treatment Period will continue at the same dose level for the duration of the Extension Period. Patients that received 250 mg telotristat etiprate or placebo during the Treatment Period will titrate to a dose of 500 mg tid in a blinded fashion. A blinded transition period will occur during the first 7 days for all patients. During the transition period, all patients will be administered 2 tablets; given as 1 x 250 mg and 1 placebo or 2 x 250 mg. After 7 days, patients will receive open-label telotristat etiprate 500 mg tid for the duration of the study.

Downward dose adjustment of telotristat etiprate from 500 to 250 mg tid will be permitted during the Extension Period if evidence of intolerability emerges. Patients may resume 500 mg tid dosing at the discretion of the Investigator and in consultation with the medical monitor. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study.

Study medication and instructions will be dispensed to patients at each visit as described in the schedule of study procedures (Table 6.1-1 and 6.1-2).

5.1.5. Dose Adjustment

Dose adjustments, outside of the blinded titration period, of the study drug are not permitted during the Treatment Period. If safety concerns suggest that the current dose level could pose a risk to the patient, the Investigator should consult the medical monitor to determine an appropriate action regarding dosing and participation in the study.

Downward dose adjustment of telotristat etiprate, from 500 to 250 mg tid, will be permitted during the open-label Extension Period if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. After a period at the 250 mg dose level, patients may resume 500 mg tid dosing at the discretion of the Investigator after consultation with the medical monitor. Interruptions or delays in dosing throughout the entire study (Treatment and Extension

Periods) may be permitted after consultation with the medical monitor; at which time the patient will be reassessed for study continuation, dose reduction, or discontinuation.

6. Study Procedures

A schedule of study assessments is provided in Tables 6.1-1 and 6.1-2.

Select study visits may be performed outside of the investigative site (eg, in home visit) by a mobile research service at the discretion of the Investigator and Sponsor. Visits eligible for this service are identified in the schedule of study assessments in Tables 6.1-1 and 6.1-2.

Table 6.1-1 4 week SSA Administration

Procedure	Screening/Run-In (Up to -28 days)	Double-blind Period					Extension Period							Follow-up ⁵
		Day 1 ³	Week 2 ¹⁰	Week 6	Week 8 ¹⁰	Week 12	Week 14 ¹⁰	Week 18 ¹⁰	Week 20 ¹⁰	Week 24	Week 32 ¹⁰	Week 40 ¹⁰	Week 48/ EOS	Week 50 ^{5,10}
Tolerance (days)	± 7	NA	± 2	± 2	± 2	± 2	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 5
Inclusion/Exclusion criteria	X	X												
Medical history/Demographics	X	X												
Physical examination	X ⁷	X ⁸	X ⁴	X ⁴	X ⁴	X ^{4,8}	X ⁴	X ⁴	X ⁴	X ^{4,8}	X ⁴	X ⁴	X ⁸	X ²
Urine pregnancy test ¹		X												X
Serum pregnancy test ¹	X					X							X	
Hematology, Blood chemistry	X ¹⁴	X	X	X	X	X	X	X	X	X	X	X	X	X ²
Stool Sample	X ¹²													
Urinalysis	X	X				X							X	X ²
Chromogranin A		X				X				X			X	
Vital signs	X	X ¹³	X	X ¹³	X	X ¹³	X	X	X	X	X	X	X	X
ECG	X	X				X							X	X ²
Karnofsky Performance Scale	X													
Pharmacogenomic sample		X												
Daily diary:	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Number of bowel movements	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Stool form/consistency	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Urgency to defecate	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Sensation/severity of nausea	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Abdominal pain/discomfort	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Number of cutaneous flushing episodes	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Use of short-acting SSA therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Subjective global assessment of symptoms (NRS)		X	X	X	X	X	X	X	X	X	X	X	X	X
Subjective global assessment of adequate relief (weekly)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EORTC QLQC30 & GI.NET21		X		X		X				X			X	
Exit Interview Sub-Study						X								
Sleep and Depression Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X
LX1606 and LP-778902 plasma concentration and population PK (X ⁹)		X ⁹		X		X ⁹		X		X ⁹	X		X ⁹	
Plasma 5-HIAA		X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour urinary 5-HIAA, creatinine	X ⁶			X		X		X		X			X	X
Dispensation of LX1606		X	X ¹¹	X	X ¹¹	X	X ¹¹	X ¹¹	X ¹¹	X	X ¹¹	X ¹¹		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X

¹Females of child-bearing potential only. ²To be performed only if evaluation at Week 48/End of Study is abnormal. ³Assessments should be performed pre-dose. ⁴Brief physical examination only (symptom-oriented)
⁵Visit to be performed for subjects who withdraw early and will not return for a 2 week follow-up visit; In all other cases the EOS visit should be performed followed by the follow-up visit 2 weeks postdose. ⁶Urine collection containers to be dispensed at Screening Visit; 24-hour urine collection to be completed at least 2 weeks prior to Day 1. ⁷Height. ⁸Weight. ⁹Population PK sampling refer to Appendix B for additional details.
¹⁰Visits eligible to be conducted by mobile research service (MRS) at the discretion of the Investigator, MRS visits must be setup in advance, confirmed, and drug dispensation adjusted accordingly. ¹¹If visit is conducted by MRS service drug dispensation will not occur. Study drug dispensation will only occur during visits to Investigator study site. ¹²Negative result must be confirmed prior to randomization. ¹³A total of 3 BP measurements will be collected five minutes apart. ¹⁴Including PT and INR

Table 6.1-2 3 week SSA Administration

Procedure	Screening/Run-In (Up to -21 days)	Double-blind Period					Extension Period								Follow-up ⁵
		Day 1 ³	Week 3 ¹⁰	Week 6	Week 9 ¹⁰	Week 12	Week 15 ¹⁰	Week 18 ¹⁰	Week 21 ¹⁰	Week 24	Week 30 ¹⁰	Week 36 ¹⁰	Week 42 ¹⁰	Week 48/ EOS	Week 50 ^{5,10}
Tolerance (days)	± 7	NA	± 2	± 2	± 2	± 2	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 5
Inclusion/Exclusion criteria	X	X													
Medical history/Demographics	X	X													
Physical examination	X ⁷	X ⁸	X ⁴	X ⁴	X ⁴	X ^{4,8}	X ⁴	X ⁴	X ⁴	X ^{4,8}	X ⁴	X ⁴	X ⁴	X ⁸	X ²
Urine pregnancy test ¹		X													X
Serum pregnancy test ¹	X					X								X	
Hematology, Blood chemistry	X ¹⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X ²
Urinalysis	X	X				X								X	X ²
Stool Sample	X ¹²														
Chromogranin A		X				X				X				X	
Vital signs	X	X ¹³	X	X ¹³	X	X ¹³	X	X	X	X	X	X	X	X	X
ECG	X	X				X								X	X ²
Karnofsky Performance Scale	X														
Pharmacogenomic sample		X													
Daily diary:	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Number of bowel movements	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Stool form/consistency	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Urgency to defecate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Sensation/severity of nausea	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Abdominal pain/discomfort	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Number of cutaneous flushing episodes	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Use of short-acting SSA therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
· Subjective global assessment of symptoms (NRS)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subjective global assessment of adequate relief (weekly)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EORTC QLQC30 & GLNET21		X		X		X			X					X	
Exit Interview Sub-Study						X									
Sleep and Depression Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X
LX1606 and LP-778902 plasma concentration and population PK (X ⁹)		X ⁹		X		X ⁹		X		X ⁹		X		X ⁹	
Plasma 5-HIAA		X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour urinary 5-HIAA, creatinine		X ⁶		X		X		X		X				X	X
Dispensation of LX1606		X	X ¹¹	X	X ¹¹	X	X ¹¹	X ¹¹	X ¹¹	X	X ¹¹	X ¹¹	X ¹¹		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X

¹Females of child-bearing potential only. ²To be performed only if evaluation at Week 48/End of Study is abnormal. ³Assessments should be performed pre-dose. ⁴Brief physical examination only (symptom-oriented) ⁵Visit to be performed for subjects who withdraw early and will not return for a 2 week follow-up visit; In all other cases the EOS visit should be performed followed by the follow-up visit 2 weeks postdose. ⁶Urine collection containers to be dispensed at Screening Visit; 24-hour urine collection to be completed at least 2 weeks prior to Day 1. ⁷Height. ⁸Weight. ⁹Population PK sampling refer to Appendix B for additional details. ¹⁰Visits eligible to be conducted by mobile research service (MRS) at the discretion of the Investigator. MRS visits must be setup in advance, confirmed, and drug dispensation adjusted accordingly. ¹¹If visit is conducted by MRS drug dispensation will not occur. Study drug dispensation will only occur during visits to Investigator study site. ¹²Negative result must be confirmed prior to randomization. ¹³A total of 3 BP measurements will be collected five minutes apart. ¹⁴Including PT and INR

Restrictions during Study

Patients should be advised to avoid grapefruit juice for 2-3 hours prior to and following dosing while participating in the study.

Change in LAR or Depot SSA dose or dose regimen will not be permitted during the Treatment Period; short-acting octreotide rescue therapy is allowed.

6.1. Description of Study Assessments

6.1.1. Efficacy Assessments

Efficacy assessments include the following patient reported measures: number of daily BMs, EORTC QLQ-C30 & GI.NET21, subjective global assessment of symptoms associated with CS, need for rescue short-acting SSA therapy to treat bowel-related symptoms associated with CS, number of cutaneous flushing episodes, stool consistency, urgency to defecate, sensation/severity of nausea, and abdominal pain/discomfort.

Daily and weekly diaries completed by patients will be used to collect all efficacy assessments as outlined in Tables 6.1-1 and 6.1-2.

A description of the efficacy assessments is provided below.

6.1.1.1. Number of Daily Bowel Movements

Patients will record the number of daily BMs in the daily diary.

6.1.1.2. Subjective Global Assessment

A subjective global assessment of symptoms associated with CS will be evaluated using 2 methods in the diary.

Patients will first be asked to respond to the following question: "In the past 7 days, have you had adequate relief of your carcinoid syndrome bowel complaints such as diarrhea, urgent need to have a bowel movement, abdominal pain, or discomfort?"

Then patients will be asked the following question to assess global symptoms associated with CS on an 11-point scale: "Rate the severity of your overall carcinoid symptoms over the past 7 days on a scale from 0-10, where 0=no symptoms and 10 = worst symptoms ever experienced."

6.1.1.3. Use of Rescue Short-Acting Somatostatin Analogs

Patients will record the frequency and dose of subcutaneous injections of rescue, short-acting octreotide, if taken, in the daily diary.

6.1.1.4. Number of Cutaneous Flushing Episodes

Patients will record the number of daily cutaneous flushing episodes experienced in the daily diary.

6.1.1.5. EORTC QLQ-C30 & GI.NET21

Patients will complete the questionnaire during each visit as indicated in Tables 6.1-1 and 6.1-2.

6.1.1.6. Stool Consistency

In the daily diary, patients will provide a description of the average stool consistency for BMs based upon the Bristol Stool Scale.

6.1.1.7. Sensation of Urgency to Defecate

To assess sensation of urgency to defecate on a daily basis, patients will record in the daily diary a response to the following question: "Have you felt or experienced a sense of urgency or immediate need to pass stool today?"

6.1.1.8. Assessment of Sensation/Severity of Nausea

To assess sensation/severity of nausea on a daily basis, patients will records their response using a 4-point scale: 0=none, 1=mild, 2=moderate, 3=severe.

6.1.1.9. Assessment of Abdominal Pain

Patients will record in the daily diary the level of any abdominal pain they feel on a daily basis using an 11-point NRS. "Rate your worst abdominal (belly or tummy) pain in the past 24 hours, with "0" being "no pain" and "10" being "worst pain ever experienced"."

6.1.1.10. Exit Interview

A telephone interview will be conducted on a subset of patients upon completion or withdrawal from the placebo-controlled, double-blind treatment period.

The purpose of the exit interview will be to gain insight and understanding of patients' experiences with symptoms of CS and to assess relevance and clinical meaningfulness of symptom improvements (eg, reduction in BM frequency).

6.1.2. Clinical Laboratory Assessment

Clinical laboratory assessments will consist of hematology (complete blood count [CBC] with differential and platelet counts), blood chemistry (complete metabolic panel, liver function tests, and clotting profile [(PT, INR) at screening visit only]), and urinalysis. A stool sample

will be collected during the Screening Period for the purposes of exclusion of enteric pathogens, pathogenic ova or parasites, or Clostridium difficile. All laboratory tests will be performed by a central laboratory, with the exception of the urine pregnancy test, which will be performed by the study site with the provided laboratory kit.

The incidence of clinically significant laboratory values, as well as clinically significant shifts in laboratory values, should be reported as an AE in the patient's CRF (see also Section 7.1 for reporting of AEs related to laboratory abnormalities). The Investigator will assess any clinically significant values relevant to the patient population to determine if termination of the study drug is required.

6.1.2.1. Monitoring Hepatic Function

Patients with clinically significant abnormalities in liver function tests should be excluded from participating. However, the patient's clinical situation as a whole should be taken into account when evaluating hepatic transaminase elevations, which may represent a consequence of the underlying disease and/or therapeutic interventions. Patients with abnormalities in liver function test results as defined below should be further assessed by the Investigator and may have additional tests performed by the central laboratory as clinically indicated. The following describes the Sponsor's recommended approach to evaluating these events. This approach is not meant to replace the Investigator's clinical judgment.

These guidelines apply to the following events:

- 1) A new confirmed result (after Day 1 dosing) of ALT or AST $>3x$ ULN (in patients previously within normal range)

OR

- 2) A confirmed increase in transaminases above the patient's previous baseline to a degree that is significant in the clinical judgment of the investigator and ALT or AST $>3x$ ULN (in patients with previous abnormal liver-test results)

OR

- 3) Any occurrence of an elevation of ALT or AST $> 3x$ ULN and total bilirubin $>2x$ ULN (in any patient)

For any such event, the Investigator should discuss the follow-up approach with the Sponsor's Medical Monitor.

The Sponsor's recommended approach is as follows:

1. Schedule the patient for a follow-up visit within 3 days following the receipt of laboratory results to assess the patient and conduct further evaluation, to include the following:
 - a. Obtain repeat testing of ALT, AST, total bilirubin, and ALP through the central laboratory.
 - b. Reassess the patient through patient interview and physical examination to uncover new or emerging risk factors of liver injury including an increased use of alcohol, gallbladder disease, hemochromatosis, fatty liver, use of hepatotoxic concomitant medications (including acetaminophen), occupational exposures, liver metastases, and other causes for potential clues as to the underlying etiology of the event.
 - c. Continue to monitor the patient's transaminases and total bilirubin regularly until the liver tests return to baseline levels.

Additional recommendations include:

- Consider referral to a hepatologist or gastroenterologist
- Consider reimaging (eg, ultrasound, CT, or MRI) the liver and biliary tract
- Consider additional laboratory testing as clinically indicated. Laboratory assays available to the Investigator for further workup are described in the laboratory manual

Upon completion of hepatic assessment, the Investigator should review results with the Medical Monitor and assess study participation.

6.1.3. Pharmacodynamic Assessments

6.1.3.1. Plasma 5-HIAA

Fasting (≥ 6 hours) blood samples for measurement of 5-HIAA in plasma will be collected and analyzed by a specialty laboratory. All sample processing information will be supplied by the laboratory in a separate document/study manual. Efforts should be made to schedule these visits in the morning, with instructions to the patient to arrive in a fasted state and not dose prior to the blood draw.

6.1.3.2. Urinary 5-HIAA/Creatinine Clearance

24-hour urine samples will be collected and analyzed for 5-HIAA concentrations (as per Tables 6.1-1 and 6.1-2); the volume of urine collected over the 24-hour period will also be

recorded. 5-HIAA concentration will be determined at a central bioanalytical laboratory, and all sample collection and processing information will be supplied by the laboratory in a separate document/study manual.

Creatinine clearance will also be determined in order to verify that the volume of urine collected was sufficient to determine 5-HIAA concentrations.

6.1.3.3. Pharmacokinetic Assessments

Blood samples for the purposes of determining trough levels of telotristat etiprate (LX1606 - prodrug) and LP-778902 (active moiety) concentrations in plasma will be collected as indicated in Tables 6.1-1 and 6.1-2. Efforts should be made to schedule these visits in the morning, with instructions to the patient to arrive in a fasted state and not dose prior to the blood draw.

Additional samples will be collected from a subset of patients over a 6 hour timeframe as indicated in Table 6.2.3.3-1 for the purposes of a population PK analysis.

Detailed procedures for the drawing, preparation, storage, and shipping of samples will be provided in a separate laboratory manual.

Table 6.2.3.3-1: Schedule of Intensive PK Assessments

Schedule of Intensive PK Assessments								
Study day time (from 08:00 to 14:00)								
	Predose	Morning Dose¹	1 hr	2 hr	3 hr	4 hr	6 hr	Mid-Day Dose
Population PK Assessments	X		X ³	X ³		X ³	X ³	
Time of Day (Example)	Predose²	08:00	09:00	10:00	11:00	12:00	14:00	14:01

¹ With food

² Fasted

³ Samples should be collected within 5 minutes of scheduled collection time

6.1.3.4. Pharmacogenomic Sampling

A blood sample will be obtained on Day 1 from all patients qualifying for the treatment portion of the protocol and who have signed a consent form allowing collection of a blood sample for genetic testing. The blood sample obtained may be used for genetic profiling relevant to serotonin metabolism, GI motility, or other phenotypes or disorders relevant to CS.

6.1.3.5. Safety Assessments

In addition to the clinical laboratory assessments described in Section 6.2.2, monitoring of AEs is also considered a safety assessment and is described in detail in Section 7. Clinically significant changes compared with baseline findings for these variables may be reported as AEs on the CRF. Clinically significant changes compared with baseline values, which are determined to be adverse events, should be followed until the event has resolved, the condition has stabilized, etiology of the event is determined to be not related to study drug, or the patient is lost to follow-up.

6.1.3.6. Vital Sign Measurements

Measurement of vital signs will include assessment of blood pressure, respiratory rate, pulse rate, and oral temperature. Vital sign measurements should not be conducted within the 30 minutes immediately following any phlebotomy.

Efforts should be made to standardize blood pressure collection across all patients and visits. Patients should be seated for at least 5 minutes prior to collection. For multiple collections, as outlined in Tables 6.1-1 and 6.1-2, 3 measurements will be taken over a 15 minute period (5 minutes between each reading) while seated. All measurements will be collected using dedicated equipment, supplied by the Sponsor, assessed on the same arm, and by the same technician where possible.

Additional measurements may be obtained if clinically indicated. Vital sign measurements will be measured as indicated in Tables 6.1-1 and 6.1-2.

6.1.3.7. Physical Examinations

Complete physical examinations will be performed as outlined in Tables 6.1-1 and 6.1-2. Complete physical examinations will include a minimum of a review of the patient's general appearance, head, eyes, ears, nose, and throat (HEENT), neck, heart, lungs, abdomen, back and extremities, skin, and general neurological system.

Symptom-oriented physical examinations will be performed at all other time points and as clinically indicated.

In addition, height and weight will be captured at various time points as indicated in Tables 6.1-1 and 6.1-2. Efforts should be made to standardize height and weight collection across all patients and visits. Patients should be instructed to remove shoes and heavy clothing (eg, heavy coats, jackets) prior to measurement. For weight collection, an effort should be made to use the same scale throughout the study where possible. In instances where multiple scales may be used, efforts should be made to reset the scale to zero prior to collection of weight measurement.

6.1.3.8. Electrocardiograms

Electrocardiograms (12-lead ECGs) will be performed as specified in Tables 6.1-1 and 6.1-2.

6.1.3.9. Adverse Events of Special Interest

Monitoring of these events will be the responsibility of the DSMB. The process of data collection and assessment of the events will be detailed in a separate DSMB charter. Additional information will be collected if episodes of any of the following AEs of special interest occur.

6.1.3.10. Central Nervous System Events

Central nervous system events of special interest may include any clinically significant changes in mood, physical affect, or exacerbation of pre-existing CNS conditions (eg, depression, migraine headaches).

6.1.3.10.1. Depression Detection

Patients will be evaluated beginning at Day 1 (baseline) and at each subsequent visit for indications of depression. During each visit the patient will first be asked to respond to the question “During the past month, have you often been bothered by feeling down, depressed, or hopeless?” Followed by “During the past month, have you often been bothered by little interest or pleasure in doing things?” A positive response prior to Day 1 dosing will be captured on the medical history CRF page. Positive responses following the first dose will be captured as an AE and will be followed as an AE of special interest.

6.2. Other Assessments

6.2.1. Chromogranin A (CgA)

Blood samples for measurement of chromogranin A (CgA) levels will be collected as indicated in Tables 6.1-1 and 6.1-2.

6.2.2. Disease Progression

Data will also be collected on measures of disease progression as performed as standard of care (including, but not limited to: interpretation of clinical scans, Investigator assessment of disease status) while the patient is enrolled in the study.

6.2.3. Quality of Sleep Assessment

Quality of sleep will also be evaluated beginning Day 1 (baseline) and at each subsequent visit thereafter. Patients will be asked to respond to the following question “Since your last visit, how many times a night (on average) do you wake up due to your CS symptoms?” based on the following scale 0, 1, 2, 3, 4, >4.

6.3. Appropriateness of Assessments

The assessments used in this study conform to the usual clinical and laboratory assessments of patients with CS participating in clinical trials and are typical of a Phase 3 study.

6.3.1. Blood Collection

An attempt should be made to collect all samples as per the schedule outlined in Tables 6.1-1 and 6.1-2. Any portion of samples remaining after the required tests for this protocol have been completed will be destroyed.

7. Safety Reporting

Medical queries should be addressed to the medical monitor responsible for the region.

Sites in North America:

Michael Hamilton, MD
Senior Medical Director Oncology
INC Research
3201 Beechleaf Ct, Suite 600
Raleigh, NC 27604-1547
Phone: 240-421-1717
michael.hamilton@incresearch.com

Sites outside North America:

Rob J.W. Berg, MD, PhD
Medical Director Oncology
INC Research
De Cuserstraat 89
1081 CN Amsterdam
The Netherlands
Phone: +31 (0)203018528
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rob.berg@incresearch.com
Luis Mendoza, MD, PhD
Medical Monitor
INC Research, LLC
Zeleny pruh 1560/99
Praha 4
Prague, 14002
Czech Republic
Phone: +420 241 040 979
Fax: +420 241 040 978

Afterhours emergency medical coverage is available to site personnel should the regional medical monitor and regional backup medical monitor be unavailable.

Sites in North America dial 1-877-462-0134

Sites outside North America dial the country prefix number plus 1-877-462-0134. Prefix numbers are determined by accessing the AT&T Direct on-line link http://www.usa.att.com/traveler/access_numbers/country/index.jsp these calls are not toll-free.

7.1. Adverse Events

It is the responsibility of the Investigator to document all AEs that occur during the study. An AE includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs or symptoms occurring in any phase of the clinical study whether or not associated with the study medication and whether or not considered related to the study medication. This definition includes an exacerbation of pre-existing medical conditions or events, historical condition not present

prior to study treatment, which reappear following study treatment, intercurrent illnesses, hypersensitivity reactions, drug interaction, or the significant worsening of the disease under investigation that is not recorded elsewhere in the CRF. Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Any laboratory abnormality fulfilling the criteria for a SAE (Section 7.2) should be reported as such, in addition to being recorded as an AE. Any treatment-emergent abnormal laboratory result which is clinically significant, ie, meeting 1 or more of the following conditions, should be recorded as a single diagnosis AE:

- Is considered to be an SAE,
- Results in discontinuation from study treatment, or
- Results in a requirement for a change in concomitant therapy (ie, addition of concomitant therapy)

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is determined.

TEAEs are defined as any AEs reported after the first dose of randomized treatment on Day 1. Adverse events reported after consent of a patient, but before administration of study medication, will be reported in the Medical History.

AEs should not be solicited with leading questions that suggest specific signs or symptoms. Rather, AEs should be solicited by asking the patient a non-leading question such as: "Do you feel different in any way since receiving the dose or since the last assessment?"

The Investigator will evaluate all AEs with regard to the maximum intensity and relationship to study drug, as follows:

- Maximum intensity

Maximum intensity should be assigned using 1 of the following 3 severity grades:

- Mild: aware of event but easily tolerated
- Moderate: discomfort, enough to cause interference with usual activity
- Severe: incapacitating: patient unable to work or perform usual activities

Relationship to study drug

Not related:

- Does not follow a reasonable temporal sequence from administration of the drug
- Could be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment.

Possibly related:

- That follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), or
- For which the possibility of the study drug being the causative factor (eg, existence of similar reports attributed to the suspected drug and its analogues; reactions attributable to the pharmacological effect) could not be excluded, although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable.

Probably related:

- That follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), and
- For which the possibility of factors other than the drug, such as underlying disease, complications, concomitant drugs, or concurrent treatment, could not be excluded as the cause.

Definitely related:

- Follows a clear temporal sequence from administration of the study drug.
- Could not be possibly explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- Disappears or decreases on cessation or reduction in dose of the study drug.
- Reappears or worsens when the study drug is re-administered.
- Follows a response pattern known to be associated with administration of the study drug.

The degree of certainty with which an AE is attributed to treatment with study medication (or alternative causes, eg, natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of known pharmacology of the study medication and/or reaction of similar nature being previously observed with the study medication or the class of study medication.

All AEs should be followed for at least 30 days following the last dose of study drug or until the event has resolved, the condition has stabilized, or the patient is lost to follow-up. For each patient for whom an AE was reported that did not resolve before the end of the reporting period, follow-up information on the subsequent course of events must be submitted to the Sponsor. This requirement indicates that follow-up may be required for some AEs after the patient has completed his/her participation in the study

7.2. Serious Adverse Events

AN SAE is defined as any event that results in any of the following outcomes:

1. Death
2. Life-threatening situation, defined as one in which a patient is at immediate risk, in the Investigator's opinion, of death from the reaction as it occurs. This does not include an event that might have caused death if it had occurred in a more severe form;
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
4. Inpatient hospitalization or prolonging of an inpatient hospitalization;
5. Congenital anomaly/birth defect in the offspring of a patient who received study medication;
6. Medical or surgical intervention that is necessary to prevent 1 of the outcomes listed in this definition

Any SAE must be reported by telephone or facsimile within 24 hours of discovery of the event. Investigators should not wait to receive additional information to fully document the event before notifying the Sponsor of an SAE at:

Sites in North America must report to:

Safety Data Facsimile: 001 (832) 442-5917

Safety Hotline: 001 (877) 372-3597

Email address (in case of fax failure): drugsafetyfax@lexpharma.com

Sites outside North America must report to the country specific toll-free fax numbers identified below:

Australia: 1-800-256952

Belgium: 0800-773-82

Brazil: 0800-8914783

France: 0800-914459

Germany: 0800-181-9632

Italy: 800-872-912

Israel: 1-809-494158

Netherlands: 0800-023-2381

Spain: 900-809736

Sweden: 020-790-059

United Kingdom: 0-800-520-0928

Email Address (in case of fax failure): INCDrugsafety@INCRResearch.com

The telephone report should be followed by full written summary detailing relevant aspects of the SAE in question using the provided SAE report form. Where applicable, information from relevant hospital case records and autopsy reports should be obtained. The SAE should also be recorded on the AE page of the patient's CRF.

An SAE that occurs after completion of the study but, in the opinion of the Investigator, is related to the study medication, should be reported as described for an SAE. If an AE does not meet the regulatory definition of "serious" but is considered by the Investigator to be related to the study medication and of such clinical concern as to influence the overall assessment of safety, it must be reported as defined for an SAE.

All patients (including discontinued patients) with a SAE must be followed until the event resolves or reaches a new baseline, but for a minimum of 30 days after the last dose of study drug.

7.3. Suspected Unexpected Serious Adverse Reactions (SUSARs)

The FDA and/or other applicable Regulatory Authorities and all participating Investigators will be notified by a written Investigational New Drug Application (IND) safety report and/or other applicable regulatory report (eg, SUSAR) of any suspected adverse reaction that is both serious and unexpected, no later than 15 calendar days from the "date learned" of the event. In addition, all applicable regulatory bodies will be notified within 7 calendar days of any unexpected fatal or life-threatening suspected adverse reaction.

An adverse reaction is defined as any untoward and unintended response to an investigational medicinal product (IMP) related to any dose administered. This definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The definition also implies a reasonable possibility of a causal relationship between the event and the IMP.

An unexpected adverse reaction is any adverse drug event, which is not listed in the current Investigator's Brochure or is not listed at the specificity or severity that has been observed. For example, (A) a single occurrence of an event that is uncommon and known to be

strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome); (B) 1 or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture); (C) an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

An untoward and unintended response to a non-IMP is by definition not a SUSAR.

7.4. Precautions

7.4.1. Pregnancy

Any patient (or patient's partner) who becomes pregnant during the study should be followed through delivery or termination of the pregnancy. In addition, patients who become pregnant during the study must be discontinued from the study treatment immediately.

In pregnancies that progress to term, any congenital abnormalities/birth defects in the offspring of a patient who received study medication should be reported as an SAE. The outcome of the pregnancy and the presence or absence of a congenital abnormality will be documented by completion of a pregnancy questionnaire and a pregnancy-outcome form in accordance with GCP and ICH guidelines and the Sponsor's SOPs.

Female patients should also notify the Investigator if they become pregnant within 30 days after last dose of study medication. Male patients should notify the Investigator if a female partner becomes pregnant within 30 days after last dose of study medication. The Sponsor must be notified of all pregnancies reported to the Investigator (see Section 7.2 for contact information).

8. Statistical Methodology

8.1. Determination of Sample Size

The sample size is derived by satisfying design assumptions for the primary efficacy endpoint. The endpoint per patient is expressed as a rate (change from baseline in the number of BMs per day averaged over the 12-week Treatment Period) and is of the following form:

$$\frac{\sum_{i=1}^k (X_i - \bar{X})}{\sum_{i=1}^k I_i}$$

Where:

X_i = number of BMs recorded on the i th day,

\bar{X} = number of BMs per day averaged over baseline (Run-in Period), and

I_i = an indicator function that takes on a value of 1 if a study day contributes a valid score to the numerator and 0 otherwise.

These per patient quantities are derived across $i = 1$ to k time points where k is the last Treatment Period day with a valid, non-missing record of the number of BMs. Alternatively, they can be derived across the planned duration of the Treatment Period (84 days) and for early terminating patients, a value of 0 will be assigned to the numerator and denominator for those days occurring after the last valid assessment of BMs.

Assume that the population mean rates are expressed as μ_{500} , μ_{250} , μ_{pla} for the 500 mg tid, 250 mg tid, and placebo groups, respectively. The family of treatment comparisons to be tested are $\Delta_{500} = \mu_{500} - \mu_{pla}$ and $\Delta_{250} = \mu_{250} - \mu_{pla}$. The null (H_0) and alternative (H_1) hypotheses for each comparison are:

$$500 \text{ mg tid} - (H_0: \Delta_{500} = 0 | H_1: \Delta_{500} \neq 0),$$

$$250 \text{ mg tid} - (H_0: \Delta_{250} = 0 | H_1: \Delta_{250} \neq 0)$$

The statistical testing strategy is to find 1 or more telotristat etiprate groups that differ from placebo. This strategy results in multiple comparisons and will require a statistical adjustment to assure that the Type I error rate does not exceed the pre-stated level.

A blocked Wilcoxon rank sum (WRS) statistic will be used as the primary method to test each of the treatment comparisons. To derive the sample size, the single step Bonferroni multiple comparison procedure (MCP) will be applied to the blocked WRS in order to have strong control of the Type I error rate for the primary endpoint hypotheses under test. The family wise Type I error rate for the single step Bonferroni MCP is $\alpha_1 = 0.05$. The subscript value of "1" denotes that the single stage Bonferroni test is applied in the first stage of a 2-stage testing procedure; the second stage is used to test the secondary efficacy endpoints. See Section 8.3.1 for more details. To maintain the Type 1 error probability for Stage 1, the per comparison Type I error rates are $\alpha_1^* = 0.025$. The value of α_1^* will be used to derive the sample size. These considerations, together with the following assumptions, are used in the calculation:

- The minimum difference to detect between the treatment group mean rates is -1.5 BM/day (telotristat etiprate minus placebo; more negative values indicate a more favorable result in BM reduction)
- The common standard deviation of the difference in mean rates is 1.0 BM/day
- The standard effect size of -1.5 corresponds to a WRS effect size under H1 of 0.856
- The statistical tests are 2-sided and powered at 96%
- Patients will be randomized among the treatment groups with equal assignment probability (1:1:1 ratio)

Use of these values results in a sample size estimate of 22 patients per treatment group. A 20% dropout rate is expected over the Treatment Period. Assuming that dropouts occur uniformly across the treatment groups and that the dropped telotristat etiprate patients respond in manner similar to the placebo patients, the sample size is adjusted to 35 patients per treatment group. This calculation results in a total sample size requirement of 105 patients. This requirement is specific to only those patients on a stable-dose of FDA approved SSA therapy indicated for the treatment of CS.

8.2. Analysis Populations

The primary comparative analyses will be based on those patients taking a stable-dose of FDA approved SSA therapy indicated for the treatment of CS at study entry. Supplemental analyses of the same data will be performed for all randomized patients, regardless of the type of SSA therapy observed at study entry. For both of these analysis populations, the following datasets will be defined.

Intent to Treat (ITT): Patients will be included in intent-to-treat ITT dataset based on their randomized treatment assignment. All randomized patients will be included in the ITT analyses.

Per-protocol: A per-protocol population will consist of those ITT patients that receive study treatment and have no major protocol violation that would interfere with the collection or interpretation of the efficacy data. Determination of the per-protocol dataset will be made before database lock.

The primary analyses of efficacy will be based on the ITT population using their observed data; the per-protocol population will be used in a supplemental manner.

Safety: The safety population consists of all patients receiving any fraction of a dose of study drug.

Pharmacokinetic: The PK population will be made up of all patients treated with study drug and who have adequate samples taken to reliably estimate the parameters of interest.

The per-protocol, safety, and PK populations will classify patients in the treatment groups per the study drug received on Day 1.

8.3. Statistical Methods

Descriptive and inferential statistics will be used to summarize the data. Continuous variables will be summarized by n, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by patient counts and related percentages. Estimates of treatment effect will be based on use of maximum likelihood methods where applicable. All statistical tests will be 2-sided and have an associated α -level=0.05 unless mentioned otherwise. Confidence limits will be 2-sided and calculated with 95% confidence coefficient.

The main focus of the study will be on the population of patients not adequately controlled by FDA approved (for treatment of CS) SSA therapy. The overall success of the study will be determined by the primary endpoint in this population. Secondary and other endpoints will also be analyzed in this population. These analyses will be limited to the double-blind portion of the study.

All endpoints (primary, secondary, and other) will also be examined in the overall population, regardless of the type of SSA therapy at study entry.

All data will be provided in individual by-patient listings.

A more detailed description of the analysis and reporting of data will be provided in a Statistical Analysis Plan. An overview of the main analysis strategy is provided in the following sections.

8.3.1. Efficacy Analyses

Statistical testing of the primary endpoint and secondary endpoint hypotheses will use a 2-stage procedure. This procedure will test in the following manner:

- Stage 1: Test the primary endpoint null hypotheses using the single stage Bonferroni MCP at $\alpha_1 = 0.05$. The per comparison Type I error rate is $\alpha_1^* = 0.025$ since there are 2

treatment contrasts of interest: each telotristat etiprate dose group versus placebo. If at least 1 null hypothesis is rejected, proceed to Stage 2.

- Stage 2: Test the secondary endpoint null hypotheses using a hierarchical procedure. The α -level for the Stage 2 test is $\alpha_2^* = 0.025$. Within each treatment group contrast that is significant at Stage 1, the order of testing the secondary endpoints is as follows:
 - Change from baseline 5-HIAA levels in urine at Week 12
 - Change from baseline in the number of daily cutaneous flushing episodes averaged across all time points
 - Change from baseline in abdominal pain averaged across all time points

Once a test of these secondary endpoints is not significant at the 0.025 α -level, testing will stop within that hierarchy and no other endpoints at or below that test will be assessed for significance.

Analysis of the other efficacy endpoints will be made using statistical tests each with a 2-sided α -level = 0.05. The p-values used in this manner will be descriptive.

Count data measured as the number of occurrences of an event for a particular variable, including the primary efficacy endpoint, will use a blocked 2-sample WRS statistic (ie, van Elteren test) to evaluate treatment group differences. This will serve as the primary analysis method for these data. The test will be blocked by baseline urinary 5-HIAA levels used in stratifying the randomization. Prior to performing these tests, each variable will be derived as a rate that is calculated as the number of outcomes observed per day minus the baseline outcome mean rate divided by the number of Treatment Period days that the outcome is counted. See Section 8.1 for the generic formula used to derive these rates. The Hodges-Lehmann estimator will be used as a measure of treatment group differences. Differences in arithmetic means will be calculated as supplemental measure of treatment effect.

Since the blocked WRS statistic lacks flexibility in modeling the impact of other variables on the test of treatment effect, a supplemental analysis will be performed by use of a generalized linear mixed model based on the negative binomial distribution. This model will treat the dependent variable as a raw event count and will be parameterized to include fixed effects of treatment, a function of the dependent variable measured at baseline, the baseline variable used to stratify the randomization, and an offset term to account for variable exposure times among the patients. This model may be expanded to include other baseline covariates of prognostic interest that improves interpretation of treatment differences.

Treatment effects for variables measured on at least an ordinal scale (and not a function of counts) will be tested by use of a linear mixed model, primarily analysis of covariance (ANCOVA) fitted for repeated measures as needed. Each model will include a fixed effect of treatment, a covariate that is the baseline measurement of the dependent variable, a term for the variable used to stratify the randomization, a repeated measure for time, and a treatment-by-time interaction. The model will provide a test of treatment group differences based on an average response (derived from repeated measures) and a test of treatment effects at each individual time point. The difference in least squares (LS) adjusted means will serve as the measure of treatment effect. Residual plots will be used to examine the appropriateness of fitting the ANCOVA models to the data. A linear rank analog model will be applied to test the overall effects should the data be grossly non-normal in their distribution. The blocked WRS statistic will be used as a supplemental test for evaluating treatment group differences at each study week. The blocking will be performed based on the baseline urinary 5-HIAA strata used in the randomization process. The measure of treatment effect in this case will be the Hodges-Lehmann statistic, with differences in arithmetic group means used as a supplemental measure.

Use of the ANCOVA models and blocked WRS statistic will also be used to test treatment group difference for variables measured as the proportion of days for a certain outcome (eg, proportion of days in urgency to defecate). The proportion of patients with a certain outcome at each study week will be tested for treatment effects using logistic regression statistics, and as a supplemental analysis, Pearson's chi square statistic. Fisher's exact test will be used as needed. Time to event endpoints will use the stratified logrank test to evaluate treatment differences. Tests based on subdistribution functions of the Kaplan-Meier estimator and other probability measures may be used to test treatment differences in the presence of competing risks. Cox's proportional hazards regression model will be used to evaluate treatment effects in the presence of pertinent baseline covariates.

Regression models will be used to assess the type and magnitude of associations between urinary and plasma 5-HIAA, 5-HIAA changes and clinical outcomes, and the change in BM and other measures of clinical efficacy.

Primary analyses of the data will be based on observed cases using the ITT patient population. Sensitivity analyses of the primary efficacy endpoint will be performed to test the robustness of inferences from the planned analyses. They will include ITT patients. Mean baseline score will be assigned to missing observations. Additional imputation algorithms may be used to supplement the primary results. The primary efficacy endpoint and some of

the secondary endpoints will be adjusted for the use of rescue short-acting SSA therapy. Statistical models based on repeated measurements and using general estimating equations or pattern mixture techniques may be applied after considering the extent/reasons for missing observations.

Subgroup analyses using baseline prognostic variables may be performed, but will serve as exploratory assessments of treatment efficacy.

8.3.2. Safety Analyses

Safety analysis will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Summaries will be prepared by treatment group, and as needed, by study day. All safety data will be listed.

TEAE summaries will include the overall incidence (by system organ class and preferred term), events by maximum intensity, event by relationship to study treatment, events leading to discontinuation of study drug, and SAEs.

Vital signs, ECG, and laboratory parameters (hematology, chemistry) will be summarized descriptively at each time point. Actual and change from baseline data will be calculated and summarized. In addition, shift table analysis will be applied to the laboratory data. Subgroup safety analyses (eg, adverse events, vital signs, ECG, and any other relevant parameters) may be performed for patients treated concomitantly with SSRIs or other serotonergic drugs (eg., SNRIs, tricyclic antidepressants, monoamine oxidase inhibitors, triptans, lithium, mirtazapine, buspirone St. John's Wort, tramadol, linezolid, methylene blue, or others).

8.3.2.1. Adverse Events

All AEs will be coded and listed by body system and preferred term based on the Medical Dictionary for Regulatory Activities (MedDRA). Summaries using descriptive statistics will be provided for treatment-emergent AEs, drug-related AEs and AEs by intensity. Treatment-emergent AEs are those events not present at baseline, but occurring after the start of study drug, or if existing at baseline, increasing in intensity after initiation study drug. Summaries made by intensity will select the event with the highest intensity when multiple occurrences of the same event are reported for the same patient. In a similar manner, summaries prepared by drug relationship will select the event with the greatest degree of relationship when a study reports multiple occurrences of the same event. On-study deaths will be reported for deaths occurring during the active phase of the treatment period and 30 days

after stopping study drug. Also, deaths occurring outside the 30-day window, but secondary to an AE reported within the 30-day post treatment period, will be reported as well.

Listings will be provided for deaths, SAEs, and discontinuations due to AEs. Additional summaries or listings of AEs may also be provided.

8.3.2.2. Clinical Laboratory Parameters

Laboratory results will be reported in conventional units in all tables, figures, and listings. Laboratory results falling out of the normal range will be marked as high or low in the listings. Actual and changes from baseline (Day 1) in clinical laboratory results will be summarized by treatment, and time point using descriptive statistics. Summaries of shifts from baseline to abnormal clinical laboratory results will also be provided.

8.3.2.3. Vital Sign Measurements

Actual an

d changes from baseline (Day 1) in vital signs results will be summarized by treatment and time point using descriptive statistics.

8.3.2.4. Electrocardiograms

Clinically significant changes in ECGs compared to baseline, as determined by the Investigator, will be summarized by treatment and time point using descriptive statistics. Actual and change from baseline (predose values) to each time point in corrected QT interval (QTcF) will be summarized as well.

8.3.3. Pharmacokinetic and Pharmacodynamic Analyses

PK data will be summarized by n, mean, standard deviation, median, minimum, and maximum values at various time points. Regression models may be used to evaluate the type and magnitude of associations between trough concentration of LX1606 and LP-778902 (active moiety) at selected time.

Based on intensive PK sampling from a subset of study patients and sparse PK sampling (eg, trough concentrations) from the study population, Population PK analyses will explore the effects of covariates including, but not limited to, age, sex, race, BMI, renal impairment, hepatic impairment on the systemic exposure to LX1606 and LP-778902 (active moiety). PK data from this study may be integrated with PK data from other clinical trials to further enhance the population PK analysis. Details of population PK analysis plan will be prepared in a separate document.

Results from the population (overall) PK analysis will be documented in a separate report.

8.3.4. Baseline Characteristics and Other Summaries

Treatment group differences will be summarized descriptively for demographic data, prior and concomitant medications, treatment compliance, and final disposition.

Protocol deviations will be provided as listings.

8.3.5. Interim Analysis

An independent DSMB will be charged with reviewing interim safety data and reporting its recommendations to Lexicon Pharmaceuticals, Inc. Appropriate procedures will be detailed in a DSMB Charter that defines accessibility and disclosure of the interim study results.

The study will be analyzed and reported in 2 phases. The first report will summarize data obtained from all patients providing information for the Run-In and Treatment phases of the study (ie, through Week 12 endpoint). The second report will update the initial report by including data from the 36-week Extension Period. The first reporting of the data may be taken as an interim analysis in terms of the procedural efforts needed to summarize these data, but it will not serve as a means to modify the analysis/study conduct of the Extension Period.