Official Title: A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)

NCT Number: NCT02026063

Document Dates: Protocol Amendment/Version 4: 02 November 2015 (North America only)

Protocol Amendment/Version 3: 06 May 2015 (Germany and UK sites only)

Protocol Amendment/Version 2: 08 October 2014

Protocol Amendment/Version 1: 31 January 2014

16. APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol and protocol amendments

Protocol Amendment 4 dated 02Nov2015 (North America sites only)
Summary of Changes for Protocol Amendment 4

Protocol Amendment 3 dated 06May2015 (Germany and UK sites only)
Summary of Changes for Protocol Amendment 3

Protocol Amendment 2 dated 08Oct2014
Protocol Amendment 2 dated 21Jan2015 (France only)
Summary of Changes for Protocol Amendment 2

Protocol Amendment 1 dated 31Jan2014
Protocol Amendment 1 dated 30Dec2014 (France only)
Protocol Amendment 1 Addendum dated 13Apr2015 (the Netherlands only)
Summary of Changes for Protocol Amendment 1

Original Protocol dated 14Jun2013

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CLINICAL STUDY PROTOCOL

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
EudraCT Number	2013-002596-18
Investigational Phase:	3
Protocol Title:	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Study Name:	TELEPATH (**Tel**otristat **E**tiprate – Expanded Treatment for **Pat**ients wit**h** Carcinoid Syndrome)
Amendment 4 Date:	02 November 2015 (North America only)
Amendment 3 Date:	06 May 2015 (Germany and UK sites only)
Amendment 2 Date:	08 October 2014
Amendment 1 Date:	31 January 2014
Original Version Date:	14 June 2013
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Investigator Signature Page

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
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By my signature below, I hereby attest that I have read and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol and will conduct the study in accordance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance.

Additionally, I will not initiate this study without written and dated approval from the appropriate Institutional Review Board (IRB)/ Ethic Review Committee (ERC), and I understand that any changes in the protocol must be approved in writing by the Sponsor, the IRB/ERC, and, in certain cases the Food and Drug Administration (FDA) or other applicable regulatory agencies, before they can be implemented, except where necessary to eliminate hazards to patients.

Principal Investigator's Signature — Date

Principal Investigator's Name (Print)

Lexicon [redacted] – [redacted] (Signature) — Date

[redacted] M.D.

Lexicon [redacted] – [redacted] (Printed Name)

1. Synopsis

Name of Study Drug	Telotristat etiprate
Protocol Number	LX1606.1-302-CS LX1606.302 (Abbreviated number)
Protocol Title	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Primary Objective	The primary objective of this study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate
Secondary Objective	To evaluate changes in patients' quality of life (QOL) through Week 84
Phase of Development	3
Methodology	The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate. Patients currently participating in any LX1606 Phase 2 carcinoid syndrome (CS) study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original study to LX1606.1-302-CS. Following confirmation of eligibility, patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label study drug at the same dose level and regimen as identified in their original study. Downward dose adjustment will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. Patients may return to the previous dosing at the discretion of the Investigator and in consultation with the Medical Monitor. Upon completion or early withdrawal from treatment, all patients will be required to complete a 14-day Follow-up Period, during which no study drug will be administered.

	A Data Safety Monitoring Board (DSMB) will review safety data quarterly throughout the study.
Number of Patients	Up to 130 patients are expected to participate in this study.
Patients	Eligible patients are defined as those that are currently participating in a Phase 2 or Phase 3 telotristat etiprate carcinoid syndrome study.
Number of Study Sites	Approximately 50 sites
Treatments	Telotristat etiprate, 250-mg tablet, administered at the same dose level and regimen identified in the patient's original study
Route of Administration	Oral
Duration of Participation	All patients will participate in the Treatment Period until such time telotristat etiprate has received regulatory approval to be marketed and is available via prescription or 31 March 2017, whichever occurs first. Based upon the expected dates for eligible patients' entry into this study, overall duration of participation will last up to 169 weeks including the Treatment Period and Follow-up Period.
Inclusion Criteria	Patients must meet all of the following criteria to be considered eligible to participate in the study: 1. Ongoing participation in a Phase 2 study (ie, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 study (ie, LX1606.1-301-CS, LX1606.1-303-CS) 2. 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 entry are confirmatory in the absence of a clear postmenopausal

	history. 3. Ability and willingness to provide written informed consent prior to participation in any study-related procedure
Exclusion Criteria	Patients who meet any of the following criteria will be excluded from participating in the study: 1. Major protocol violations in regard to dosing compliance or telotristat etiprate tolerability concerns in a Phase 2 study (ie, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 study (ie, LX1606.1-301-CS, LX1606.1-303-CS) 2. Positive pregnancy test 3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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 4. Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities
Statistical Methods	Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study and combined across all treated patients. Primary analyses of the data will be based on the Safety population which includes all patients treated on Day 1 of this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.
Study Assessments	<u>Safety</u> Safety assessments include monitoring of adverse events, clinical laboratory tests, vital signs measurements, 12-lead electrocardiogram (ECG), and physical examinations. <u>Efficacy</u>

	Efficacy assessments will include patient reported quality of life measures as captured in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and the module specific for gastrointestinal symptoms of carcinoid neuroendocrine tumors (GI.NET21) and subjective global assessment of symptoms associated with CS Pharmacodynamics Pharmacodynamic (PD) assessments include determination of 5-HIAA levels in plasma
Efficacy Data Analysis	All efficacy and PD variables will be summarized descriptively and listed. Statistical tests and estimates of within patient effects for the efficacy and PD measures will be derived from application of a mixed linear model with repeated measures. The form of the model will be specific to measurement properties of the dependent variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model. Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to patients' telotristat etiprate dose level on Day 1 of this study.
Safety Data Analysis	Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group, and as needed, by study visit. Treatment-emergent adverse event 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 serious adverse events. Vital signs, ECG, physical examination findings, and laboratory parameters (hematology, chemistry, and urinalysis) 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.

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2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ALP	alkaline phosphatase
AST	aspartate transaminase
bid	twice daily
BM	bowel movements
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CgA	chromogranin A
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CS	carcinoid syndrome
CT	computed tomography
DSMB	Data Safety Monitoring Board
EC	enterochromaffin
ECG	electrocardiogram
ERC	Ethics Review Committee
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HEENT	head, eyes, ears, nose, and throat
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
IND	Investigational New Drug

Abbreviation	Definition
Continued on the next page	
IRB	Institutional Review Board
ITT	intent-to-treat
IMP	Investigational Medicinal Product
IWRS	interactive web response system
LAR	long-acting release
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MCP	multiple comparison procedure
MRI	magnetic resonance imaging
NET	neuroendocrine tumor
NRS	numeric rating scale
OOR	out-of-range
OTC	over-the-counter
PD	pharmacodynamic
PK	pharmacokinetic
qd	once daily
SAE	serious adverse event
SBS	short bowel syndrome
SOP	standard operating procedure
SSA	somatostatin analog
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
tid	3 times daily
TPH	tryptophan hydroxylase
ULN	upper limit of the normal reference range
WRS	Wilcoxon rank sum

Definitions of Terms

Term	Definition
LX1606 Hippurate	telotristat etiprate
LP-778902	active moiety of LX1606
LX1606	telotristat ethyl: the ethyl-ester prodrug of the active moiety LP-778902; a serotonin synthesis inhibitor being developed by Lexicon Pharmaceuticals, Inc.
QTcF	corrected QT interval using Fredericia's formula

3. Introduction

3.1 Background on Telotristat Etiprate (LX1606) and Disease

Serotonin (5-HT) plays a critical role in regulating several major physiological processes of the gastrointestinal tract, including aspects of secretion, motility, inflammation and sensation. Enterochromaffin (EC) cells release 5-HT when the intestinal wall is stimulated by intraluminal pressure or chemicals. Through multiple classes of receptors, 5-HT is believed to initiate directly, or facilitate, peristaltic and secretory reflexes. 5-HT is also reportedly involved in the pathophysiology of various types of functional gastrointestinal (GI) disorders, valvular heart disease, and may play a role in the pathophysiology of inflammatory bowel disease (IBD).

Carcinoid tumors are mostly derived from EC cells of the midgut, and often produce and release large amounts of 5-HT. Such excess of 5-HT is believed to be responsible for the severe diarrhea and eventual valvular heart damage and mesenteric fibrosis in patients with carcinoid syndrome (CS).[1-3] Inhibition of tryptophan hydroxylase (TPH) activity in carcinoid tumors should lead to a reduction of peripheral 5-HT in afflicted patients and thus an amelioration of the pathophysiology and symptomology of CS. A peripheral TPH inhibitor, such as telotristat etiprate, should alleviate the symptoms due to excess 5-HT in carcinoid patients without central nervous system (CNS)-related adverse events (AEs).

Approximately 90% of the body's 5-HT is found in the EC cells of the GI tract, with the remainder distributed between the platelets and CNS.[4] TPH catalyzes the biopterin-dependent monooxygenation of tryptophan to 5-hydroxytryptophan, which is subsequently decarboxylated to form 5-HT. Expression of TPH is limited to a few specialized tissues: raphe neurons, pinealocytes, mast cells, mononuclear leukocytes, beta cells of the islets of Langerhans, and intestinal and pancreatic EC cells.[5] Two isoforms of the enzyme exist, TPH1 and TPH2. TPH1 is exclusively located in the EC cells of the GI tract and pineal gland and is the rate limiting enzyme responsible for the majority of systemic 5-HT production and is also responsible for 5-HT synthesis in carcinoid tumors. TPH2 is located in the central and enteric nervous systems and is the rate-limiting enzyme in the production of neuronal 5-HT.

The oral TPH inhibitor, telotristat etiprate, represents a novel approach to potentially lessen the pathophysiology of CS by reducing 5-HT levels via inhibition of TPH. Telotristat etiprate was designed specifically as a prodrug in order to gain greater systemic exposure, opening the potential application for indications in which hyperserotonemia is thought to contribute to the disorder, such as CS. Preclinical pharmacology studies of telotristat etiprate were designed to evaluate the compound’s mechanism of action and effects in vivo. Telotristat etiprate is the ethyl-ester prodrug of the active moiety LP-778902. Telotristat etiprate was

designed as a prodrug in order to enhance peripheral exposure without crossing the blood-brain barrier. In vivo, telotristat etiprate is readily converted through esterase activity to its corresponding acid, LP-778902. LP-778902 has an in vitro potency of 0.028 µM on purified human TPH1 enzyme and 0.032 µM on purified human TPH2 enzyme. Therefore, telotristat etiprate is a robust inhibitor of TPH both in vitro and in vivo and has been shown in Phase 2 studies to provide clinical benefit to patients with carcinoid tumors and associated CS.

Telotristat etiprate is being developed to manage GI symptoms and possibly other symptoms associated with CS. Currently, the standard of care for patients with CS is symptom management using somatostatin analogs (SSA), which are available in both short- and long-acting release (LAR) formulations. Somatostatin analogs such as octreotide are indicated for the control of flushing, diarrhea, and other symptoms associated with CS. Common side effects of the long-acting depot form of the drug are pain at the site of the injection, reported in as many as 30 to 50% of carcinoid patients at the 20 and 30 mg dose levels, and less commonly, stomach cramps, nausea, vomiting, headaches, dizziness, and fatigue.[6] Other side effects identified in the product labeling include biliary tract abnormalities (gallstones, sludge, and dilatation), hypothyroidism, dietary fat malabsorption, and hyper or hypoglycemia.[7] In addition to the morbidity associated with parenterally administered agents, tachyphylaxis will occur in the majority of patients, resulting in recurrent symptoms.

There are currently no specific oral treatments indicated for the management of symptoms associated with CS. As a result of the morbidity associated with SSAs and the associated tachyphylaxis, there is an unmet medical need to provide symptom management and modify the pathophysiology of patients with metastatic CS. Inhibition of the excessive 5-HT produced by these tumors with an orally delivered agent such as telotristat etiprate could provide significant benefit as an additional treatment option for patients and clinicians.

3.2 Clinical Trials of Telotristat Etiprate (LX1606) in Humans

Telotristat etiprate has been studied in single/multiple doses in Phase 1 studies, approximately 259 healthy volunteers participated in Phase 1 trials with 237 subjects receiving telotristat etiprate. In Phase 2, 38 patients with CS and 49 patients with ulcerative colitis received telotristat etiprate during the evaluation of 3 clinical studies. Additionally, over 200 patients with carcinoid syndrome have been enrolled and are being evaluated in ongoing Phase 3 studies.

3.2.1 Phase 1 Studies

Telotristat etiprate has been evaluated in 9 completed Phase 1 clinical studies to date. A single ascending dose tolerability study explored a dose range of 50 to 1500 mg (LX1606.1-101-NRM), and a multiple ascending dose tolerability study explored a dose range of 100 mg (qd)

to 1500 mg (500 mg tid) over 14 days (LX1606.1-102-NRM). Both studies were conducted in healthy, normal volunteers in a randomized, double-blind, placebo controlled fashion, utilizing whole blood 5-HT and 24-hour urinary 5-HIAA levels as biomarkers of pharmacologic response. A two-way crossover study of 2 oral formulations of 250 mg given as a single dose (LX1606.1-103-NRM) was conducted in healthy, normal volunteers as a randomized, open-label study, utilizing PK parameters as a marker of comparability of the capsule versus tablet formulation. A study designed to evaluate the pharmacokinetics, metabolism, and routes and extent of elimination of LX1606 telotristat etiprate and its primary metabolite (LP-778902) after a single oral dose of 500 mg 14C-LX1606 was conducted in 8 healthy male volunteers (LX1606.1-104-NRM). A thorough QT study (LX1606.1-105-NRM), a food-effect study (LX1606.1-107-NRM), and 3 drug-drug interaction studies (LX1606.1-106-NRM; LX1606.1-108-NRM; LX1606.1-109-NRM) were also all conducted in healthy, normal volunteers. Telotristat etiprate was well tolerated with drug-related GI AEs (primarily nausea) becoming dose-limiting at the 1500 mg single dose level. Multiple doses of telotristat etiprate over 14 days are well tolerated up to 1500 mg daily dose, administered as 500 mg tid. Telotristat etiprate is readily converted to the active metabolite LP-778902. At the doses evaluated, extremely low levels of telotristat etiprate are present in circulation, with most samples containing ≤ 10 ng/mL of the prodrug and many samples being below the limit of quantitation (0.5 ng/mL). Urinary 5-HIAA levels showed a statistically significant reduction of approximately 50-60% relative to placebo over 14 days at dose levels ≥ 500 mg telotristat etiprate. Similarly whole blood 5-HT declined in a dose-dependent fashion over 14 days. The results of the thorough QT study clearly demonstrated that telotristat etiprate is negative for QT prolongation as defined by the ICH E14 guidance. The results of LX1606.1-106-NRM suggest that telotristat etiprate is not a P-glycoprotein 1 (P-gp) inhibitor as per FDA Guidance for Industry – Drug Interaction Studies (February 2012), where P-gp inhibitors are defined as those drugs that increase the AUC of fexofenadine by ≥1.25 fold. However, telotristat etiprate did exhibit a lower level of P-gp inhibition that is unlikely to be clinically meaningful. LX1606.1-107-NRM confirms a food effect is seen with telotristat etiprate such that systemic exposure to telotristat ethyl and metabolite LP-778902 is significantly increased following administration in the fed state compared to the fasted state. Results of LX1606.1-108-NRM do not support inhibitory activity of steady-state telotristat ethyl concentrations on CYP3A4; however, systemic exposure to midazolam was significantly lower when midazolam was coadministered with telotristat etiprate. It is believed this observation is the result of a reduction in midazolam absorption. Coadministration of octreotide acetate with telotristat etiprate is addressed in LX1606.1-109-NRM. Systemic exposure to both telotristat ethyl and metabolite LP-778902 is significantly reduced compared to administration of telotristat etiprate alone, thereby

suggesting a drug-drug interaction. However, it is not known whether the long-acting depot formulation of octreotide acetate would exhibit a similar interaction with telotristat etiprate as what was seen with the subcutaneous injections of octreotide acetate used in this study.

3.2.2 Phase 2 Studies

In Phase 2 studies in patients with CS, dose levels of 150, 250, 350, or 500 mg tid telotristat etiprate were evaluated. All dose levels were generally well tolerated. The Phase 2 clinical trial results indicated that treatment using telotristat etiprate in patients with CS may lead to improvements in BM frequency, stool consistency, urgency to defecate, abdominal pain, diarrhea, flushing, and reductions in 5-HIAA.

LX1606.1-202-CS was a randomized, double-blind, placebo-controlled, multiple ascending dose study conducted in 2 parts in order to evaluate a total of 23 patients at a dose range of 450 to 1500 mg given as 150, 250, 350, or 500 mg tid (telotristat etiprate or matching placebo) on a background therapy of octreotide. In Part 1, 16 patients were randomly assigned 3:1 into 4 sequential cohorts. Each cohort evaluated 1 of the following daily doses given as 150, 250, 350, or 500 mg tid over a course of 4 weeks. During the study, all patients continued on a stable-dose background therapy of octreotide. In Part 2, an additional 7 patients were randomly assigned 3:1 in order to evaluate 500 mg tid, the highest tolerated dose as determined in Part 1. Upon completion of the initial 4-week double-blind, placebo-controlled portion (the Core Phase), eligible patients had the option to continue into an open-label Extension Period (the Extension Phase).

For the LX1606-treated patients combined (n=18) in the randomized placebo-controlled LX1606.1-202-CS study, 5 patients (33.3%) experienced a reduction in BM frequency of at least 30% versus no patients (0.0%) for the placebo group (n=5). A complete biochemical response, defined as at least a 50% reduction from Baseline in urinary 5-HIAA (mg/24 hours) or normalization post-Baseline urinary 5-HIAA (mg/24 hours) value <ULN for cases where the Baseline value was elevated, was achieved by 9 of 16 patients (56.3%) versus no patients (0.0%) on placebo.

LX1606 was well tolerated by patients enrolled in this study. Across both the Core Phase and the Extension Phase, greater than half (73.9% and 52.6%, respectively) of the TEAEs reported were mild or moderate in intensity. TEAEs were reported most frequently within the GI disorders class, the most frequently reported TEAE was diarrhea, followed by nausea. No clinically significant changes from baseline in laboratory parameters, vital signs, physical examination findings, or ECG results were observed throughout the study, except for alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) levels. Mean ALP and GGT

levels remained elevated compared with Baseline during both study periods, but no relevant clinical outcomes were observed.

During the Core Phase, no dose-response relationship was observed in frequencies of any TEAEs, severe TEAEs or related TEAEs among the treatment groups that received placebo or various dosages of LX1606. One patient each in the placebo arm (20.0%) and the active treatment arm (5.6%) discontinued the study drug due to TEAEs. There were no fatal SAEs during the Core Phase. One patient in the LX1606 350 mg tid group experienced 2 SAEs (severe nausea and vomiting) that were reported as possibly related to study drug; both events resolved after symptomatic treatment.

During the Extension Phase, eight patients experienced a total of 20 SAEs. One patient experienced 4 TEAEs that led to discontinuation. There was 1 fatal SAE of disease progression. None of the SAEs were reported as related to study drug.

LX1606.1-203-CS was an open-label, serial ascending, multiple dose, individual titration study that evaluated the same dose ranges as the LX1606.1-202-CS study in a total of 15 patients. Patients were serially escalated to the next dose level every 2 weeks until a maximally tolerated dose (MTD) or 500 mg tid was reached. Once a MTD had been determined, the patient would remain on the dose for an additional 4 weeks. Patients then had the option to continue into an Extension Period.

In this open-label study, there was evidence of clinically meaningful improvement in the GI-related symptoms associated with carcinoid syndrome, reflected by decreases in BM frequency, improvements in stool consistency, reductions in urgency to defecate, and reductions in flushing. Patients reported adequate relief of their symptoms, and physicians reported global clinical improvement. Reductions in u5-HIAA were observed. Most patients continued into the long-term Extension Period, with no evidence of loss of efficacy over time.

Most patients reached the 500 mg tid dose level during this study. No MTD was identified. Adverse events were those expected for the patient population under treatment, and no clinically significant trends in laboratory values, vital sign measurements, ECG results, or physical examination findings were observed. There was 1 fatal SAE of neoplasm progression; no SAE was reported as related to study drug.

LX1606.1-204-UC evaluated patients with acute, mild to moderate ulcerative colitis experiencing active flares were enrolled in a randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of telotristat etiprate. Patients were maintained on a stable-dose of aminosalicylate therapy for 8 weeks and randomly assigned to receive 1 of 2 dosages of telotristat etiprate (500 mg once daily or 500 mg tid) or placebo; 59 patients were enrolled in the study. Adverse events were those expected for the ulcerative

colitis patient population and no clinically significant trends in laboratory values, vital sign measurements, ECG results, or physical examination findings were observed.

Although results from the study provide a clear signal of activity of the mechanism of action of telotristat etiprate in this patient population, they were not accompanied by other findings that would indicate a large impact on disease modification. Detailed information regarding the completed clinical studies can be found in the Investigator Brochure.[8]

3.2.3 Ongoing Studies

LX1606.1-301-CS is intended to evaluate patients who are currently on a background of SSA therapy and still experiencing breakthrough symptoms such as a frequency of BMs ≥4 per day on average: (1) the efficacy of telotristat etiprate on reducing the number of BMs; (2) the efficacy of telotristat etiprate on a number of clinically relevant secondary endpoints; and, (3) the safety of telotristat etiprate over the 12-week double-blind portion (Treatment Period) of the study. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period.

LX1606.1-303-CS is intended to evaluate patients with carcinoid syndrome whose primary symptoms are not GI related and may be naïve to SSA therapy: (1) the safety of telotristat etiprate over the 12-week double-blind portion (Treatment Period) of the study; (2) percent (%) change from Baseline in 24-hour u5-HIAA levels at Week 12; (3) the effects of telotristat etiprate on a number of clinically relevant secondary endpoints. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period.

Detailed information regarding the ongoing clinical studies can be found in the Investigator Brochure.[8]

3.3 Rationale for Current Study

3.3.1 Rationale for Selection of Dose

The dose levels of telotristat etiprate selected for this study are consistent with prior clinical study experience and based upon clinical safety and pharmacodynamic (PD) data from 2 Phase 2 multiple ascending-dose studies in patients with symptomatic CS (LX1606.1-202-CS and LX1606.1-203-CS).

Based upon observations noted in Section 3.2, it is anticipated that the doses to be utilized in this protocol will be safe and well tolerated and may provide clinical benefit to patients with CS.

3.3.2 Benefit/Risk Assessment

Clinical experience with telotristat etiprate (treated subjects) consists of completed single and multiple ascending dose studies in 259 normal subjects, 2 Phase 2 studies (38 patients with symptomatic CS) and ongoing Phase 3 studies in patients with symptomatic CS.

In healthy volunteer studies, single doses up to 1000 mg were found to be generally well tolerated, while at the 1500 mg dose level GI-related adverse events increased. A similar adverse event profile was observed after multiple dose administration over 14 days with GI events predominating. Mild, dose-dependent increases in hepatic transaminase levels (≤2 x ULN) were observed with increased frequency in relation to dose, with 1 subject requiring withdrawal from therapy at the 500 mg bid dose level. Most subjects that were observed to have increased transaminase levels did not exceed >2 x ULN. No abnormalities in total bilirubin were observed at any dose level. GI events have been the most commonly observed events to date. The adverse event profile in normal subjects may differ significantly from what is observed in patients with hyperserotonemia. All adverse events resolved without sequelae. In addition, there were no significant changes in vital signs or ECG. No physical examination abnormalities were noted in studies to date. There were no serious adverse events reported in healthy volunteers.

In patients with CS, dose escalations have proceeded up to and including 500 mg tid. To date, there has been no evidence of dose-limiting intolerability. Dose levels have been generally well tolerated.

Phase 3 clinical trials are currently underway to provide further data to support the Phase 2 study results. Currently 210 patients have been randomized to the placebo-controlled trials (LX1606.1-301-CS and LX1606.1-303-CS). After completing participation in 1 of the Phase 2 or Phase 3 studies, eligible patients with CS will have the option of continuing treatment with the study drug in this long-term, open-label Extension study (LX1606.1-302-CS).

Based upon observations from preclinical and clinical studies conducted to date, it is anticipated that orally administered telotristat etiprate will be well tolerated at dose levels required to influence peripheral 5-HT production. Potential adverse events primarily involve the GI tract, and could include alterations in gut motility that may result in nausea, vomiting, diarrhea, and constipation. Regular and ongoing clinical and laboratory assessments should detect any of these events, and depending on the type of event, further dose adjustment or discontinuation from the trial would occur. Central nervous system effects are not anticipated at dose levels planned for evaluation, but careful monitoring for any such effect has been included in the study. As elevations in hepatic transaminase levels were observed with

multiple dosing in normal subjects, monitoring clinical laboratory tests of hepatic function will be incorporated into clinical trials conducted in CS patients.

The Phase 2 clinical trial results indicated that treatment may lead to improvements in BM frequency, stool consistency, urgency to defecate, abdominal pain, diarrhea, flushing, and reductions in 5-HIAA. These potential benefits relate to a unique mechanism of action. Symptomatic improvement may lead to a better quality of life (QOL) for patients with few treatment options available, and a reduction in serotonin may help reduce the risk of carcinoid heart disease. Overall, the benefit/risk profile of telotristat etiprate is expected to be favorable for participation in this clinical study.

3.4 Rationale for Study Design and Control Groups

Currently, no approved therapy exists for the treatment of symptoms driven by underlying serotonin pathophysiology of CS in patients whose disease is refractory to SSA therapy or for those patients who are unable to tolerate SSA therapy or who are unwilling to take SSA therapy.

This study will allow for continued access to telotristat etiprate after patients have completed the required study visits in ongoing Phase 2 and Phase 3 studies. Continuation of CS patients into this study will allow for the collection of additional long-term safety and efficacy data, while providing access to patients who may be receiving benefit. The treatment duration is supported by results of chronic toxicology studies (6-month rat and 9-month dog) and the current safety profile from completed and ongoing clinical trials.

4. Study Objectives

4.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

4.2 Secondary Objective(s)

The secondary objective of this study is to evaluate changes in patients' QOL through Week 84.

4.3 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, physical examinations, and ECG findings.

5. Investigational Plan

5.1 Overall Study Design

The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate.

Patients currently participating in any LX1606 Phase 2 CS study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original protocol to LX1606.1-302-CS.

Following confirmation of eligibility, patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label LX1606 at the same dose level identified in the original study.

All patients will receive telotristat etiprate for at least 52 weeks and may continue treatment in the trial until such time telotristat etiprate has received regulatory approval to be marketed and is available via prescription or until 31 March 2017, whichever occurs first. Patients who reach this timeline event will be deemed to have completed the Treatment Period and will advance to the End-of-Study (EOS) visit as identified in Appendix A – Schedule of Events, regardless of where they are in the visit schedule and when their last study visit occurred.

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

Downward dose adjustment will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. Patients may return to the previous dosing at the discretion of the Investigator and in consultation with the Medical Monitor.

A Data Safety Monitoring Board (DSMB) will review safety data quarterly throughout the study.

6. Study Population

Adult patients who are currently participating in ongoing Phase 2 or Phase 3 telotristat etiprate CS clinical protocols will be enrolled into the study. Up to 130 patients are expected to enroll in this study. Approximately 50 sites worldwide will participate in the study. Patients

may continue allowed medications as background therapy provided they remain on stable-doses throughout the Treatment Period.

6.1 Inclusion Criteria

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

1. Ongoing participation in a Phase 2 study (ie, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 study (ie, LX1606.1-301-CS, LX1606.1-303-CS)
2. 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 Baseline Day 1 are confirmatory in the absence of a clear postmenopausal history.
3. Ability and willingness to provide written informed consent prior to participation in any study-related procedure.

6.2 Exclusion Criteria

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

1. Major protocol violations in regard to dosing compliance or telotristat etiprate tolerability concerns in a Phase 2 study (ie, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 study (ie, LX1606.1-301-CS, LX1606.1-303-CS)
2. Positive pregnancy test
3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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

4. Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities

6.3 Criteria for Stopping Treatment/Study Withdrawal

A patient may also be discontinued from the study for the following medical or administrative reasons:

- Withdrawal of consent by the patient or legal guardian
- Noncompliance, including refusal of the study medication and/or failure to adhere to the study requirements as in the study protocol
- Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study
- The Sponsor terminates the study (Section 6.4)
- Pregnancy (Section 9.4.1)

Note: If patients voluntarily withdraw or are discontinued from study treatment before completing the entire duration of the Treatment Period, 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 Appendix A – Schedule of Events and agree to report any SAEs (Section 9.2) that occur within 30 days following the last dose of telotristat etiprate.

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 Case Report Form (CRF).

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.

6.4 Criteria for Termination of the Study

If the 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 carcinoid syndrome or any other indication 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; and,
- Insufficient adherence to protocol requirements.

Study termination and Follow-up would be performed in compliance with applicable governing body regulations.

6.5 Clinical Stopping Rules

Criteria for individual patient withdrawal or study termination are summarized in Sections 6.3 and 6.4, respectively.

6.6 Method of Assigning Patients to Treatment

Patients will enter the study at the same dose level and regimen as identified in the prior Phase 2 or Phase 3 CS study. Randomization will not be used to assign patients to study treatments.

6.7 Blinding and Unblinding of Study Medication

This is an open-label study.

6.8 Replacement of Patients

Patients who do not complete the study will not be replaced.

7. Treatment

7.1.1 Telotristat Etiprate (LX1606)

7.1.1.1 Identity

Telotristat etiprate (LX1606 Hippurate) is the salt form of the drug substance. LX1606 Hippurate is a crystalline white to off-white to tan solid with a melting point of 147°C. LX1606 is insoluble in water within the pH range of 5 to 9 (≤2 mg/L). It undergoes hydrolysis under strongly basic or strongly acidic conditions.

Study drug dosage form consists of white coated debossed oval tablets containing 250 mg LX1606.

7.1.1.2 Packaging, Labeling, and Storage

Patients will receive 250-mg telotristat etiprate tablets packaged in 100 cc high density polyethylene bottles with child-resistant polypropylene screw caps and heat-induction seal liners.

Telotristat etiprate should be stored between 15 to 25°C (59 to 77°F), with excursions allowed up to 30°C.

7.2 Prior and Concomitant Medications

7.2.1 Prior Medications

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

7.2.2 Concomitant Medications

All concomitant medications taken by patients during the study will be recorded on the CRF. Treatment with prescription or over-the-counter (OTC) antidiarrheal therapy, bile acid sequestrants, or pancreatic enzyme is permitted; however, the use of these concomitant therapies should be associated with a documented history of disease (eg, fat malabsorption, bile acid malabsorption, or steatorrhea).

Medical management of patients and their concomitant medications is allowed at the discretion of the Investigator. However, should the need arise to modify/adjust a patient's therapy due to a concern for patient safety and/or tolerability 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.

7.2.3 Prohibited Medications or Concomitant Therapy

None

7.3 Administration of Study Medication

All patients will be instructed to take the study medication with food. “With food” means taking telotristat etiprate 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.

Study medication and instructions will be dispensed to patients at each visit as described in the schedule of study procedures (Appendix A).

7.3.1 Treatment Compliance

Patients will be asked to bring their unused or unopened study medication to each visit (Appendix A). At each visit and in the presence of the patient, study site personnel will count returned tablets and reconcile the counts against planned number of doses for that interval. Site personnel will clarify any discrepancy and record this information within the CRF.

Patients must maintain at least 75% compliance in dosing to be deemed as compliant. In the event of a missed or vomited dose, patients will take their subsequent dose of study drug at the next scheduled time point, following the tid dosing regimen of approximately every 6 hours. A dose outside of a 3-hour window should be considered missed. Missed or vomited doses will not be made up.

7.4 Dose Adjustment

Downward dose adjustment of telotristat etiprate will be permitted if evidence of intolerability emerges. After a period at the lowered dose level, patients may resume the previous dosing level at the discretion of the Investigator after consultation with the Medical Monitor. Patients who experience intolerability at the 250 mg tid dose level **must** be discontinued from study treatment. Interruptions or delays in dosing throughout the entire study may be permitted after consultation with the Medical Monitor, at which time the patient will be reassessed for study continuation, dosage reduction, or discontinuation.

8. Study Procedures

A schedule of study assessments is provided in Appendix A.

8.1 Restrictions during Study

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

8.2 Description of Study Assessments

8.2.1 Efficacy Assessments

Efficacy assessments include the patient reported QOL measures; EORTC QLQ-C30 (Appendix C) & GI.NET21 (Appendix D) questionnaires and subjective global assessment of symptoms associated with CS.

A description of the efficacy assessments is provided below.

8.2.1.1 EORTC QLQ-C30 & GI.NET21

Patients will complete the questionnaires during each visit as indicated in Appendix A.

8.2.1.2 Subjective Global Assessment

A subjective global assessment of symptoms associated with CS will be evaluated using 2 methods at each visit as indicated in Appendix A.

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."

8.2.2 Clinical Laboratory Assessment

Clinical laboratory assessments will consist of hematology (complete blood count [CBC] with differential and platelet counts), blood chemistry (complete metabolic panel and liver function tests), and urinalysis. 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 9.1 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.

8.2.2.1 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 >3 x 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 >3 x ULN (in patients with previous abnormal liver-test results)

OR

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

For any such event, the Investigator should discuss the Follow-up approach with the 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 function test values 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 continued study participation.

8.2.3 Pharmacodynamic Assessments

8.2.3.1 Plasma 5-HIAA

Fasting blood samples (≥6 hours) 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.

8.2.4 Safety Assessments

In addition to the clinical laboratory assessments described in Section 8.2.2, monitoring of AEs is also considered a safety assessment and is described in detail in Section 9. Clinically significant changes compared with Baseline findings for these variables should be reported as AEs on the CRF. Clinically significant changes compared with Baseline values, which are determined to be AEs, 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.

8.2.4.1 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 with 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. All measurements should be 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 Appendix A.

8.2.4.2 Physical Examinations

Complete physical examinations will be performed as outlined in Appendix A. 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, weight will be captured during each physical examination. Efforts should be made to standardize 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.

8.2.4.3 Electrocardiograms

Electrocardiograms (12-lead ECGs) will be performed as specified in Appendix A.

8.2.4.4 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.

8.2.4.4.1 Central Nervous System Events

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

8.2.4.4.1.1 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 evaluated by the Investigator in order to assess if the response is clinically significant. Positive responses assessed as clinically significant prior to Day 1 dosing will be captured on the medical history CRF page. Positive responses following the first dose will be evaluated by the Investigator in order to assess if an AE has occurred. Positive responses assessed to be an AE will be followed as an AE of special interest.

8.3 Other Assessments

8.3.1 Chromogranin A (CgA)

Blood samples for measurement of chromogranin A (CgA) levels will be collected as indicated in Appendix A.

8.3.2 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 (eg, PET, CAT, MRI scans of tumor), or Investigator assessment of disease status, while the patient is enrolled in the study.

8.3.3 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.

8.4 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.

8.4.1 Blood Collection

An attempt should be made to collect all samples as per the schedule outlined in Appendix A. Any portion of samples remaining after the required tests for this study have been completed will be destroyed.

The estimated amount of blood scheduled for collection per patient, over the course of the study, may be found in Appendix B.

9. Safety Reporting

Medical queries should be addressed to the Medical Monitor responsible for the region.

Sites in North America:

[redacted], MD
[redacted]
INC Research
[redacted]
Phone: [redacted]

Sites outside North America:

[redacted], MD, PhD
[redacted]
INC Research
[redacted]
The Netherlands
Phone: [redacted]
Mobile: [redacted]

[redacted], MD, PhD
Medical Monitor
INC Research, LLC
[redacted]
Czech Republic
Phone: [redacted]
Fax: [redacted]

After-hours 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. **Note**: These calls are not toll-free.

9.1 Adverse Events

It is the responsibility of the Investigator to document all AEs that occur during the study.

Adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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 considered related to the study medication. This definition includes an exacerbation of preexisting 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 9.2) 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 study drug 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
  - Event is reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment; there is no reasonable causal link that drug caused the event.

  Unlikely related:

  - Temporal sequence from administration of the study drug to event onset suggests a doubtful or improbable causal relationship
  - Alternative explanation (including underlying disease, complications, concomitant drugs, or concurrent treatment) is plausible and more likely

  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

9.2 Serious Adverse Events (SAEs)

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

1. Death
2. A life-threatening adverse event;
3. Inpatient hospitalization or prolonging of an existing hospitalization (see Section 9.2.1 for information on hospitalization as an SAE);

4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
5. A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

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

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: [redacted]
Belgium: [redacted]
Brazil: [redacted]
France: [redacted]
Germany: [redacted]
Israel: [redacted]
Italy: [redacted]
Netherlands: [redacted]
Spain: [redacted]
Sweden: [redacted]
United Kingdom: [redacted]

Email Address (in case of fax failure): [redacted]

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.

9.2.1 Hospitalization as an SAE

Hospitalization is defined as any in-patient overnight stay in a hospital. A hospitalization in and of itself does not constitute an SAE. The condition which caused the hospitalization must be evaluated and determined to be an AE. Although an AE which results in hospitalization is an SAE, patients are hospitalized for a variety of reasons which may not be associated with or considered an SAE (eg, convenience, logistics, preference, etc). Therefore, each case of hospitalization must be evaluated separately.

For example, the following would not be considered SAEs:

- Hospitalization for a preexisting condition which did not worsen (eg, cataract surgery)
- Hospitalization solely for a procedure or treatment that was not performed to treat an AE
- Hospitalization for a condition that does not normally require treatment, but electively done (eg, cosmetic surgery)
- Hospitalization strictly for convenience reasons or observations (eg, procedures only performed in a hospital because of the distance the subject lives from the hospital)

9.3 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.

9.4 Precautions

9.4.1 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 9.2 for contact information).

10. Statistical Methodology

10.1 Determination of Sample Size

No formal sample size calculation was made. The number of patients expected to participate in this study was calculated from estimated enrollment rates from other carcinoid cancer trials employed in the LX1606 clinical program.

10.2 Analysis Populations

Per protocol: A Per Protocol population will consist of those patients that receive study treatment and have no major protocol violation that would interfere with the collection or interpretation of the efficacy data. The primary analyses of efficacy will be based on the safety population; 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 during this study.

10.3 Study Endpoints

10.3.1 Primary and Secondary Endpoints

The primary endpoint is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

The secondary endpoint is to evaluate changes in patients' QOL over 84 weeks of therapy.

10.3.2 Safety Endpoints

Safety endpoints are as follows:

- Incidence of TEAEs, suspected adverse reaction, AEs leading to discontinuation from the study, SAEs, and deaths
- Actual and change from Baseline in clinical laboratory results
- Actual and change from Baseline in vital signs results
- Actual and change from Baseline in physical examinations
- Actual and change from Baseline in ECG findings

10.4 Statistical Methods

Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study, where appropriate, and combined across all treated patients. All data will be listed.

Primary analyses of the data will be based on the Safety population which includes all patients treated with any fraction of study drug during this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. This dataset will include the Safety population, but limited to those patients that have at least one assessment post Day 1 and do

not have any protocol violations that would interfere with collection or interpretation of the data. The Per Protocol analysis will be applied to the QOL measures, subjective global assessment, and plasma 5-HIAA values.

Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.

10.4.1 Efficacy Analyses

All efficacy and PD variables will be summarized descriptively and listed.

Statistical tests and estimates of within patient effects for these measures will be derived from application of a mixed linear model with repeated measures. The model will be generalized to handle missing data and specific to the measurement properties of the dependent variable. There is no plan to impute data for missing observations for any variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model.

Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to how patients were dosed on Day 1 of this study.

10.4.2 Safety Analyses

Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group (corresponding to the LX1606 dose given on Day 1), pooled across all patients, and as needed, by study visit. All safety data will be listed.

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

Vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) 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 and summarized.

10.4.2.1 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.

10.4.2.2 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 using descriptive statistics. Summaries of shifts from Baseline to abnormal clinical laboratory results will also be provided. Actual and change from Baseline in chromogranin A levels will be summarized descriptively as well.

10.4.2.3 Vital Sign Measurements

Actual and changes from Baseline (Day 1) in vital signs results will be summarized by using descriptive statistics.

10.4.2.4 Electrocardiograms

Clinically significant changes in ECGs compared to Baseline, as determined by the Investigator, will be summarized by using descriptive statistics. Actual and change from Baseline (Day 1 predose values) to each time point in corrected QT interval (QTcF) will be summarized as well.

10.4.3 Pharmacodynamic Analyses

Analysis and summarization of the plasma 5-HIAA data are described in Section 10.4.1.

10.4.4 Baseline Characteristics and Other Summaries

Treatment group differences will be summarized descriptively for demographic data, prior and concomitant medications, treatment compliance, and final disposition. Data collected from assessments of tumor status, when available, will be listed.

Protocol deviations will provided as listings.

10.4.5 Interim Analysis

An independent DSMB will be charged with reviewing interim safety data on a quarterly basis 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 may be analyzed and reported in multiple phases. The first report will summarize data obtained from all patients providing information up to a specified data cut-off point. The following reports will update the initial report by including data from the remaining portion of the study. 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 study conduct or the final analysis.

11. Study Management

The Investigator is responsible for completing and maintaining adequate and accurate CRFs and source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, and discharge summaries.

All data on the CRF must be recorded in accordance with the CRF guidelines. If a correction is necessary, it should be made by the Investigator or a designated qualified individual as specified within the guideline. All CRFs should be completed in their entirety and stored in a secure location. The Investigator must sign the Investigator's statement in each patient's CRF indicating that the data reported are accurate.

At the study site, clinical research associates will verify 100% of CRFs in their entirety against source documentation. Computer programmed edit checks will be run against the database to check for discrepancies and reasonableness of the data, and the safety database will be reconciled with the clinical database. All issues resulting from the computer generated checks and the safety database reconciliation will be resolved according to standard data management practices in conjunction with the Sponsor, clinical study personnel, and the study Investigators.

11.1 Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the

Sponsor's study monitors will contact the study site via visits to the site, telephone calls, and/or letters in order to review study progress, CRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of patients, patient recruitment, patient compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by patients, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

The Investigator must make study data accessible to the clinical monitor, to other authorized representatives of the Sponsor, and to regulatory inspectors

11.2 Audits and Inspections

The Sponsor, regulatory authority, or IRB/ERC may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a Sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

11.3 Amendments

Any amendments to the protocol will be written and approved by the Sponsor. All amendments must be submitted to the IRB/ERC for approval prior to implementing the changes. In some instances, an amendment may require changes to the informed consent form, which also must be submitted for IRB/ERC approval prior to administration to patients. If any changes to the CRF are required, the Sponsor will issue supplemental or revised CRF pages.

11.4 Record Keeping

11.4.1 Drug Accountability

The Investigator must maintain accurate records of receipt of study drug, dispensing information (date, lot, and dose for each patient), and the prompt return or destruction of unused supplies. If the Investigator cannot account for all clinical supplies at the termination of the study, a written explanation must be provided.

11.4.2 Health Insurance Portability Accountability Act of 1996 and Subsequent Updates

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 Code of Federal Regulations (CFR) Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation and any applicable updates). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

11.4.3 Financial Disclosure

The Investigator shall provide to the Sponsor sufficient accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the FDA and/or other applicable regulatory agencies. The Investigator shall promptly update this information if any relevant changes occur in the course of the study or for 1 year following completion of the study.

11.4.4 Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 11) to ensure data integrity. “Original” in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

11.4.5 Retention of Study Documents

According to 21 CFR Part 312.62 and ICH E6, study-related records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor.

The Investigator must not destroy any study-related records without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor must be contacted to arrange alternative record storage options.

12. Administrative Structure of the Study

The study will be monitored by Sponsor personnel or Sponsor representative. The following functions for this study will be performed by organizations designated by the Sponsor: data management and statistical analysis, including PD analysis and reporting.

13. Appendix A – Schedule of Events

Procedure	Treatment Period[6]															EOS[4]	2-Week Follow-up
	Baseline Day 1[1]	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108	Week 120	Week 132	Week 144	Week 156	Week 168		
Tolerance (days)	NA	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	+ 21	± 5
Inclusion/Exclusion criteria	X																
Medical history	X																
Physical examination incl. weight	X	X[3]	X[3]	X[3]	X	X[3]	X[3]	X	X[3]	X[3]	X[3]	X	X[3]	X[3]	X[3]	X	X[5]
Urine pregnancy test[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology, Blood chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
Urinalysis	X				X			X				X				X	X[5]
Chromogranin A	X				X			X				X				X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X				X			X				X				X	X[5]
Subjective Global Assessment	X	X	X	X	X	X	X	X									
EORTC QLQ-C30 & GI.NET21	X		X		X		X	X									
Sleep and Depression Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma 5-HIAA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispensation of LX1606	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	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	X	X	X

[1]Eligibility will be determined at last visit of the original protocol; Day 1 will replace the next scheduled visit in the original protocol schedule. Visits should coincide with LAR injections for those patients receiving SSA therapy. [2]Females of child-bearing potential only. [3]Brief physical examination only (symptom-oriented, including weight). [4]Visit to be performed for subjects who withdraw early and will not return for a 2-week follow-up visit; in all other cases the End-of-Study (EOS) visit should be performed followed by the follow-up visit 2 weeks after the final dose. [5]To be performed only if evaluation at EOS is abnormal. [6]All patients will receive LX1606 for at least 52 weeks and may continue treatment in the trial until such time telotristat etiprate has received regulatory approval to be marketed and is available via prescription or until 31 March 2017, whichever occurs first. Patients who reach this timeline event will be deemed to have completed the Treatment Period and will advance to the EOS visit, regardless of where they are in the visit schedule and when their last study visit occurred. The EOS visit should be performed within 21 calendar days following the completion of the Treatment Period.

14. Appendix B – Amount of Blood to be Collected from Each Patient

Assessment		Sample volume (mL)	Number of samples*	Estimated total volume (mL)
Safety	Hematology	2	17	34
	Blood chemistry	6	17	102
Other	CgA	2	5	10
Pharmacodynamic	Plasma 5-HIAA	4	17	68
			Total	214
*Maximum number of samples is indicated				

15. Appendix C – EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Lexicon

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

16. Appendix D – EORTC QLQ - GI.NET21

ENGLISH

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31. Did you have hot flushes?		1	2	3	4
32. Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33. Did you have night sweats?		1	2	3	4
34. Did you have abdominal discomfort?		1	2	3	4
35. Did you have a bloated feeling in your abdomen?		1	2	3	4
36. Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37. Have you had acid indigestion or heartburn?		1	2	3	4
38. Have you had difficulties with eating?		1	2	3	4
39. Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40. Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41. Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42. Were you concerned about disruption of home life?		1	2	3	4
43. Have you worried about your health in the future?		1	2	3	4
44. How distressing has your illness or treatment been to those close to you?		1	2	3	4
45. Has weight loss been a problem for you?		1	2	3	4
46. Has weight gain been a problem for you?		1	2	3	4
47. Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48. Have you had aches or pains in your muscles or bones?		1	2	3	4
49. Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:					
50. Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51. Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

17. Appendix E – Ethical Standards

Ethics and Regulatory Considerations

This study will be conducted according to GCP, 21 CFR Part 50, (Protection of Human Subjects), 21 CFR Part 56 (Institutional Review Boards), International Conference on Harmonisation Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

General Instructions

The FDA regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to GCP regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- Current FDA Guideline for the Monitoring of Clinical Investigations
- Current Guidance for Institutional Review Boards and Clinical Investigators
- ICH E6 – Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

Studies conducted in the European Union are also regulated by Volume 10 of the publications "The rules governing medicinal products in the European Union".

Copies of these materials are available from the Sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- the study is conducted with diligence and in conformance with the protocol in such a way as to insure the integrity of the findings;
- the potential benefits of the research justify the risks.

Lexicon Pharmaceuticals, Inc. is the Sponsor of the IND. The Sponsor is responsible for the following:

- selecting qualified Investigators,
- providing Investigators with the information they need to properly conduct an investigation,
- ensuring proper monitoring of the investigation,
- ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- maintaining the IND, and
- ensuring that regulatory authorities and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied
- ensuring the study is conducted in accordance to FDA and ICH guidelines and all applicable regulations

18. Appendix F – Investigator Obligations

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56 and ICH E6, the study protocol and the final version of the subject informed consent form will be approved by the IRB/ERC before enrollment of any subjects. The opinion of the IRB/ERC will be dated and given in writing. A copy of the letter of approval from the IRB/ERC and a copy of the approved informed consent form will be received by the Sponsor prior to shipment of study medication supplies to the Investigator.

The Investigator will ensure that the IRB/ERC will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to subjects. The Investigator will also ensure that no changes will be made to the protocol without IRB/ERC approval.

As a part of the IRB/ERC requirement for continuing review of approved research, the Investigator will be responsible for submitting periodic progress reports to the IRB/ERC at intervals appropriate to the degree of subject risk involved, but no less than once per year.

Written informed consent must be given freely and obtained from every subject prior to clinical trial participation. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

As described in GCP guidelines, study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (eg, loss of medical licensure, debarment). Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

Principal Investigators must provide Lexicon with a fully executed Form FDA 1572 (statement of Investigator) and all updates on a new fully executed Form FDA 1572.

Principal Investigators must provide Lexicon with his/her own curriculum vitae and current curriculum vitae for each sub-Investigator listed on Form FDA 1572.

Protection of Human Subjects (21 CFR Part 50 and ICH E6)

Informed consent must be obtained from every subject before entry into a clinical study. It must be given freely and not under duress. Consent must be documented by use of an IRB/ERC-approved consent form and signed by the subject or the subject's legally authorized representative. The US Department of Health and Human Services suggests that when minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent, his signature should also be included. Non-English-speaking subjects must be presented with

a consent form written in a language that they understand. A copy of the signed consent form must be given to the subject signing it. Another copy must be kept in the Investigator's files and made available to regulatory authority representatives upon request. If, for any reason, subject risk is increased as the study progresses, a revised, IRB/ERC-approved consent form must be signed by the subject. Before the study begins, a sample of the consent form must be provided to the Sponsor for review. The FDA and/or other applicable regulatory agencies may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all subjects.

Only in the case of a life-threatening incident may an investigational product be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the Investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB/ERC within 5 working days. In this situation, the Investigator may not administer any subsequent product to that subject until informed consent and IRB/ERC approval are obtained.

Informed Consent

Written informed consent must be obtained from each subject prior to entry in the study. One copy of the signed informed consent document will be given to the subject, and another will be retained by the Investigator. Additionally, the subject must be allowed adequate time to consider the potential risks and benefits associated with his/her participation in the study.

In situations where the subject is not legally competent to provide consent (ie, mentally incapacitated), written consent must be obtained from a parent, legal guardian, or legal representative. In these situations, the consent must be signed and dated by a witness.

The informed consent document must have been reviewed and approved by the Sponsor and by the Investigator's IRB/ERC prior to the initiation of the study. The document must contain the 8 basic elements of informed consent and may contain the 6 additional elements described in 21 CFR Part 50. Every consent form must include the following 8 elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the subject

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility that the FDA and/or other applicable regulatory authority representatives may inspect the records
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available, or a statement describing where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research related injury
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

When appropriate, 1 or more of the following elements of information shall also be included in the consent form:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent
- Any additional costs the subject may incur from participation in the research
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject
- The approximate number of subjects involved in the study

The Declaration of Helsinki includes further details regarding the specific requirements for informed consent.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states, such as California and Oregon, require further action on the Investigator's part concerning subject consent.

Study Documentation

IRB/ERC Review/Approval

The protocol and informed consent for this study, including advertisements used to recruit subjects, must be reviewed and approved by an appropriate IRB/ERC prior to enrollment of subjects in the study. It is the responsibility of the Investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, ICH, GCP, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB/ERC approval which specifically identifies the study/protocol and a list of the committee members must be received by the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

A progress report with a request for re-evaluation and re-approval will be submitted by the Investigator to the IRB/ERC at intervals required by the IRB/ERC, and not less than annually. A copy of the report will be sent to the Sponsor.

When the Sponsor provides the Investigator with a Safety Report, the Investigator must promptly forward a copy to the IRB/ERC.

After completion or termination of the study, the Investigator will submit a final report to the IRB/ERC and to the Sponsor, if required. This report should include: deviations from the protocol, the number and types of subjects evaluated, the number of subjects who discontinued (with reasons), results of the study, if known, and significant AEs, including deaths.

Study Files

The Investigator is required to maintain complete and accurate study documentation in compliance with current Good Clinical Practice standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study. Study documents include, but are not limited to, the Investigator's Brochure, drug accountability records, Sponsor/Investigator correspondence, IRB/ERC correspondence, protocol and amendments, information regarding monitoring activities, subject exclusion records, CRFs, and data queries.

Confidentiality

The anonymity of subjects must be maintained. Patients will be identified by their initials and an assigned subject number on CRFs and other documents submitted to the clinical monitor. Documents that will be submitted to the clinical monitor and that identify the subject (eg, the signed informed consent document) must be maintained in strict confidence by the Principal Investigator, except to the extent necessary to allow auditing by regulatory authorities, the clinical monitor, or Sponsor personnel.

All information regarding the nature of the proposed investigation provided by the Sponsor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB/ERC, the subject, or the regulatory authority) must be kept in confidence by the Investigator.

Drug Accountability

The Investigator or designee is responsible for accountability of the investigational product at the site. The Investigator or designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and return to the Sponsor or alternative disposition of any unused product. These records must include dates, quantities, batch/serial/lot numbers, and expiration dates (if applicable).

The Investigator should ensure that the investigational product is used only in accordance with the protocol

19. References

1. Bhattacharyya S, Toumpanakis C, Chilkunda D, Caplin ME, Davar J. Risk factors for the development and progression of carcinoid heart disease. Am J Cardiol. 2011; 107(8):1221-6. Epub 2011 Feb 4.
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5. Cote F, et al. Disruption of the nonneuronal tph 1 gene demonstrates the importance of peripheral serotonin in cardiac function. Proc Natl Acad Sci. 2003;100(23):13525-30.
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8. Investigator Brochure LX1606, Lexicon Pharmaceuticals, Inc.
9. Dmitrienko A, Tamhane A, Wiens B. General multistage gatekeeping procedures. Biometrical Journal. 2008;50:667-77

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CLINICAL PROTOCOL AMENDMENT 4
STUDY LX1606.302

A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)

PROTOCOL NO.:	**LX1606.1-302-CS** **LX1606.302** (Abbreviated number)
EudraCT Number:	2013-002596-18
INVESTIGATIONAL PHASE:	3
SPONSOR:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: 001 (281) 863-3000 Safety Hotline: 001 (877) 372-3597 Safety Data Facsimile: 001 (832) 442-5917
PROTOCOL AMENDMENT 4 DATE:	02 November 2015 (North America only)
PROTOCOL AMENDMENT 3 DATE:	06 May 2015 (Germany and UK sites only)
PROTOCOL AMENDMENT 2 DATE:	08 October 2014
PROTOCOL AMENDMENT 1 DATE:	31 January 2014
ORIGINAL VERSION DATE:	14 June 2013

Amendment Changes

Rationale

A protocol amendment is proposed to provide additional continued access to telotristat etiprate for patients who are enrolled in the LX1606.1-302-CS study. This amendment will allow treatment with telotristat etiprate until such time telotristat etiprate has received regulatory approval to be marketed and is available via prescription or 31 March 2017, whichever occurs first. Based upon the expected dates for eligible patients' entry into this study, overall duration of participation will last up to 169 weeks including the Treatment Period and Follow-up Period.

As a result of the extended duration of the study, the protocol has been modified to reflect that patient reported quality of life (QOL) measures will be analyzed through Week 84 of the study. These QOL assessments include the EORTC QLQ-C30 & GI.NET21 questionnaires and the subjective global assessment of symptoms associated with carcinoid syndrome (CS).

In addition, modifications have been made to: (1) revise the number of patients expected to participate; (2) decrease the number of study sites anticipated to participate; (3) clarify the nature of major protocol violations in the lead-in study that would meet exclusion criteria under this study; (4) update the clinical trial experience and safety information based on completed Phase 1 and Phase 2 studies; (5) correct errant language that unintentionally associates the term "efficacy" with the primary objectives of the protocol; (6) clarify the upper limit of allowable temperature excursion for the storage of study drug; (7) clarify the manner in which responses to questions designed to detect early signs of depression are managed; (8) clarify the definition of AEs not related to study drug; (9) include a fifth classification for AEs, "unlikely related"; (10) revise the description of safety analyses; (11) update Schedule of Events to reflect new assessments; and (12) update the amount of blood to be collected.

The following administrative changes have also been made:

- Minor formatting, capitalization, punctuation, abbreviation, grammatical, and spelling errors have been corrected
- Definition of Terms has been updated to define telotristat etiprate as the hippurate salt form of the LX1606 drug substance
- Due to the revision of some section headings, renumbering has occurred as appropriate
- The Table of Contents has been updated as appropriate

In response to these changes, the following sections have been revised as follows (changes are indicated in *italics*):

1. **SYNOPSIS – Secondary Objective, page 3 – This section was modified to reflect that patient reported QOL data will be collected and evaluated through Week 84. The revised section now reads:**

"To evaluate changes in patients' quality of life (QOL) *through Week 84*"

2. **SYNOPSIS – Number of Patients, page 4 – This section was modified to update the anticipated study enrollment. The revised section now reads:**

"Up to *130* patients are expected to participate in this study."

3. **SYNOPSIS – Number of Study Sites, page 4 – This section was modified to decrease the number of study sites expected to participate. The revised section now reads:**

"Approximately *50* sites"

4. **SYNOPSIS – Duration of Participation, page 4 – This section was modified to reflect the further extension of the study Treatment Period. The revised section now reads:**

"*All patients will participate in the Treatment Period until such time telotristat etiprate has received regulatory approval to be marketed and is available via prescription or 31 March 2017, whichever occurs first. Based upon the expected dates for eligible patients' entry into this study, overall duration of participation will last up to 169 weeks including the Treatment Period and Follow-up Period.*"

5. **SYNOPSIS – Exclusion Criteria, page 5 and STUDY POPULATION – Exclusion Criteria, Section 6.2, pages 22, Criterion #1 – This criterion has been modified to clarify the nature of major protocol violations in the lead-in study that would meet exclusion criteria under this study. The revised criterion now reads:**

"Major protocol violations *in regard to dosing compliance* or telotristat etiprate tolerability concerns in a Phase 2 *study (ie*, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 *study (ie*, LX1606.1-301-CS, LX1606.1-303-CS)"

6. **INTRODUCTION – Clinical Trials of Telotristat Etiprate (LX1606) in Humans, Section 3.2, page 14 – This section was revised to reflect the total number of healthy volunteers and patients with either carcinoid syndrome or ulcerative colitis that have participated in completed Phase 1 and Phase 2 trials. The revised section now reads:**

"Telotristat etiprate has been studied in single/multiple doses in Phase 1 studies, approximately *259* healthy volunteers participated in Phase 1 trials with *237* subjects receiving telotristat etiprate. In *Phase 2, 38* patients with CS *and 49 patients with ulcerative colitis* received telotristat etiprate during the *evaluation of 3* clinical *studies. Additionally, over 200* patients

with *carcinoid syndrome* have been enrolled *and are being evaluated in* ongoing Phase *3 studies*."

7. **INTRODUCTION – Section 3.2.1 Phase 1 Studies, pages 14-16 – This section was revised in its entirety to update the clinical trial experience and safety information based on completed Phase 1 studies. The revised section now reads:**

"Telotristat etiprate has been evaluated in 9 completed Phase 1 clinical studies to date. A single ascending dose tolerability study explored a dose range of 50 to 1500 mg (LX1606.1-101-NRM), and a multiple ascending dose tolerability study explored a dose range of 100 mg (qd) to 1500 mg (500 mg tid) over 14 days (LX1606.1-102-NRM). Both studies were conducted in healthy, normal volunteers in a randomized, double-blind, placebo controlled fashion, utilizing whole blood 5-HT and 24-hour urinary 5-HIAA levels as biomarkers of pharmacologic response. A two-way crossover study of 2 oral formulations of 250 mg given as a single dose (LX1606.1-103-NRM) was conducted in healthy, normal volunteers as a randomized, open-label study, utilizing PK parameters as a marker of comparability of the capsule versus tablet formulation. A study designed to evaluate the pharmacokinetics, metabolism, and routes and extent of elimination of LX1606 telotristat etiprate and its primary metabolite (LP-778902) after a single oral dose of 500 mg 14C-LX1606 was conducted in 8 healthy male volunteers (LX1606.1-104-NRM). A thorough QT study (LX1606.1-105-NRM), a food-effect study (LX1606.1-107-NRM), and 3 drug-drug interaction studies (LX1606.1-106-NRM; LX1606.1-108-NRM; LX1606.1-109-NRM) were also all conducted in healthy, normal volunteers. Telotristat etiprate was well tolerated with drug-related GI AEs (primarily nausea) becoming dose-limiting at the 1500 mg single dose level. Multiple doses of telotristat etiprate over 14 days are well tolerated up to 1500 mg daily dose, administered as 500 mg tid. Telotristat etiprate is readily converted to the active metabolite LP-778902. At the doses evaluated, extremely low levels of telotristat etiprate are present in circulation, with most samples containing ≤ 10 ng/mL of the prodrug and many samples being below the limit of quantitation (0.5 ng/mL). Urinary 5-HIAA levels showed a statistically significant reduction of approximately 50-60% relative to placebo over 14 days at dose levels ≥ 500 mg telotristat etiprate. Similarly whole blood 5-HT declined in a dose-dependent fashion over 14 days. The results of the thorough QT study clearly demonstrated that telotristat etiprate is negative for QT prolongation as defined by the ICH E14 guidance. The results of LX1606.1-106-NRM suggest that telotristat etiprate is not a P-glycoprotein 1 (P-gp) inhibitor as per FDA Guidance for Industry – Drug Interaction Studies (February 2012), where P-gp inhibitors are defined as those drugs that increase the AUC of fexofenadine by ≥1.25 fold. However, telotristat etiprate did exhibit a lower level of P-gp inhibition that is unlikely to be clinically meaningful. LX1606.1-107-NRM confirms a food effect is seen with telotristat etiprate such that systemic exposure to telotristat ethyl and metabolite LP-778902 is significantly increased following administration in the fed state compared to the fasted state. Results of LX1606.1-108-NRM do

not support inhibitory activity of steady-state telotristat ethyl concentrations on CYP3A4; however, systemic exposure to midazolam was significantly lower when midazolam was coadministered with telotristat etiprate. It is believed this observation is the result of a reduction in midazolam absorption. Coadministration of octreotide acetate with telotristat etiprate is addressed in LX1606.1-109-NRM. Systemic exposure to both telotristat ethyl and metabolite LP-778902 is significantly reduced compared to administration of telotristat etiprate alone, thereby suggesting a drug-drug interaction. However, it is not known whether the long-acting depot formulation of octreotide acetate would exhibit a similar interaction with telotristat etiprate as what was seen with the subcutaneous injections of octreotide acetate used in this study.

8. **INTRODUCTION – Section 3.2.2 Phase 2 Studies, pages 16-18 – This section was revised to update the clinical trial experience and safety information based on completed Phase 2 studies. The revised section now reads:**

"In Phase 2 studies in patients with CS, dose levels of 150, 250, 350, or 500 mg tid telotristat etiprate were evaluated. All dose levels were generally well tolerated. The Phase 2 clinical trial results indicated that treatment using telotristat etiprate in patients with CS may lead to improvements in BM frequency, stool consistency, urgency to defecate, abdominal pain, diarrhea, flushing, and reductions in 5-HIAA.

LX1606.1-202-CS was a randomized, double-blind, placebo-controlled, multiple ascending dose study conducted in 2 parts in order to evaluate a total of 23 patients at a dose range of 450 to 1500 mg given as 150, 250, 350, or 500 mg tid (telotristat etiprate or matching placebo) on a background therapy of octreotide. In Part 1, 16 patients were randomly assigned 3:1 into 4 sequential cohorts. Each cohort evaluated 1 of the following daily doses given as 150, 250, 350, or 500 mg tid over a course of 4 weeks. During the study, all patients continued on a stable-dose background therapy of octreotide. In Part 2, an additional 7 patients were randomly assigned 3:1 in order to evaluate 500 mg tid, the highest tolerated dose as determined in Part 1. Upon completion of the initial 4-week *double-blind, placebo-controlled* portion *(the Core Phase),* eligible patients had the option to continue into an open-label Extension Period *(the Extension Phase).*

For the LX1606-*treated* patients *combined (n=18) in the randomized placebo-controlled LX1606.1-202*-CS *study, 5 patients (33.3%) experienced a reduction in BM frequency of at least 30% versus no patients (0.0%) for the placebo group (n=5). A complete* biochemical response, defined as at least a 50% reduction *from Baseline in urinary 5-HIAA (mg/24 hours)* or normalization *post-Baseline urinary 5-HIAA (mg/24 hours) value <ULN for cases where the Baseline value was elevated, was achieved by 9 of 16 patients (56.3%) versus no patients (0.0%) on placebo.*

LX1606 was well tolerated by patients enrolled in this study. Across both the Core Phase and the Extension Phase, greater than half (73.9% and 52.6%, respectively) of the TEAEs reported were mild or moderate in intensity. TEAEs were reported most frequently within the GI disorders class, the most frequently reported TEAE was diarrhea, followed by nausea. No clinically significant changes from baseline in laboratory parameters, vital signs, physical examination findings, or ECG results were observed throughout the study, except for alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) levels. Mean ALP and GGT levels remained elevated compared with Baseline during both study periods, but no relevant clinical outcomes were observed.

During the Core Phase, no dose-response relationship was observed in frequencies of any TEAEs, severe TEAEs or related TEAEs among the treatment groups that received placebo or various dosages of LX1606. One patient each in the placebo arm (20.0%) and the active treatment arm (5.6%) discontinued the study drug due to TEAEs. There were no fatal SAEs during the Core Phase. One patient in the LX1606 350 mg tid group experienced 2 SAEs (severe nausea and vomiting) that were reported as possibly related to study drug; both events resolved after symptomatic treatment.

During the Extension Phase, eight patients experienced a total of 20 SAEs. One patient experienced 4 TEAEs that led to discontinuation. There was 1 fatal SAE of disease progression. None of the SAEs were reported as related to study drug.

LX1606.1-203-*CS* was an open-label, serial ascending, multiple dose, individual titration study that evaluated the same dose ranges as the LX1606.1-202-CS study in a total of 15 patients. Patients were serially escalated to the next dose level every 2 weeks until a maximally tolerated dose *(MTD)* or 500 mg tid was reached. Once a *MTD* had been determined, the patient would remain on the dose for an additional 4 weeks. Patients then had the option to continue into an Extension Period.

In this open-label study*, there was evidence* of *clinically meaningful* improvement in *the* GI-*related* symptoms associated with carcinoid syndrome*, reflected by* decreases in *BM frequency, improvements in stool consistency, reductions in urgency to defecate, and reductions in* flushing. *Patients reported adequate relief of their symptoms, and physicians reported global clinical improvement. Reductions* in u5-HIAA *were observed. Most patients continued into the long-term Extension Period, with no evidence of loss of efficacy over* time.

Most patients reached the 500 mg tid dose level during this study. No MTD was identified. Adverse events were those expected for the patient population under treatment, and no clinically significant trends in laboratory values, vital sign measurements, ECG results, or physical examination findings were observed. There was 1 fatal SAE of neoplasm progression; no SAE was reported as related to study drug.

LX1606.1-204-UC evaluated patients with *acute, mild to moderate* ulcerative colitis *experiencing active flares were enrolled in a randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of telotristat etiprate. Patients were maintained on a stable-dose of aminosalicylate therapy for 8 weeks and randomly assigned to receive 1 of 2 dosages of telotristat etiprate (*500 mg once daily *or* 500 mg tid*) or* placebo; 59 patients were enrolled *in the study. Adverse events were those expected for the ulcerative colitis patient population and no clinically significant trends in laboratory values, vital sign measurements, ECG results, or physical examination findings were observed.*

Although results from the study provide a clear signal of activity of the mechanism of action of telotristat etiprate in this patient population, they were not accompanied by other findings that would indicate a large impact on disease modification. Detailed information regarding the completed clinical studies can be found in the Investigator Brochure.[8]"

9. **INTRODUCTION – Ongoing Studies, Section 3.2.3, page 18 – This section was revised to reference the Investigator Brochure. The following paragraph has been inserted at the end of this section:**

"Detailed information regarding the ongoing clinical studies can be found in the Investigator Brochure.[8]"

10. **INTRODUCTION – Benefit/Risk Assessment, Section 3.3.2, pages 19-20 – This section was revised to reflect the total number of subjects that have been exposed to telotristat etiprate in Phase 1, Phase 2, and Phase 3 studies. In addition, some textual clarifications were made to better reflect the observed and anticipated benefits and risks associated with telotristat etiprate. The revised section now reads:**

"Clinical experience with telotristat etiprate (treated subjects) consists of completed single and multiple ascending dose studies in *259* normal subjects, 2 Phase 2 studies (*38* patients with symptomatic CS) and ongoing Phase 3 studies in patients with symptomatic CS.

In healthy volunteer studies, single doses up to 1000 mg were found to be generally well tolerated, while at the 1500 mg dose level GI-related adverse events increased. A similar adverse event profile was observed after multiple dose administration over 14 days with GI events predominating. Mild, dose-dependent increases in hepatic transaminase levels (≤2 x ULN) were observed with increased frequency in relation to dose, with 1 subject requiring withdrawal from therapy at the 500 mg bid dose level. Most subjects that were observed to have increased transaminase levels did not exceed >2 x ULN. No abnormalities in total bilirubin were observed at any dose level. GI events have been the most commonly observed events to date. The adverse event profile in normal subjects may differ significantly from what is observed in patients with hyperserotonemia. All adverse events resolved without sequelae. In addition, there were no

significant changes in vital signs or ECG. No physical examination abnormalities were noted in studies to date. There were no serious adverse events reported in healthy volunteers.

In patients with CS, dose escalations have proceeded up to and including 500 mg tid. To date, there has been no evidence of dose-limiting intolerability. Dose levels have been generally well tolerated.

Phase 3 clinical trials are currently underway to *provide further data to support the Phase 2 study results. Currently 210 patients have been randomized to the placebo-controlled trials (LX1606.1-301-CS and LX1606.1-303-CS). After completing participation* in *1 of the Phase 2 or Phase 3 studies, eligible patients with CS will have the option of continuing treatment with the study drug in this long-term, open-label Extension study (LX1606.1-302-CS)*.

Based upon observations from preclinical and clinical studies conducted to date, it is anticipated that orally administered telotristat etiprate will be well tolerated at dose levels required to influence peripheral 5-HT production. Potential adverse events primarily involve the GI tract, and could include alterations in gut motility *that may result in* nausea, vomiting, diarrhea, *and* constipation. Regular and ongoing clinical and laboratory assessments should detect any of these events, and depending on the type of event, further dose adjustment or discontinuation from the trial would occur. *Central nervous system* effects are not anticipated at dose levels planned for evaluation, *but careful monitoring for* any *such effect has been included in the study*. As elevations in hepatic transaminase levels were observed with multiple dosing in normal subjects, monitoring clinical laboratory tests of hepatic function will be incorporated into clinical trials conducted in CS patients.

The Phase 2 clinical trial results indicated that treatment may lead to improvements in BM frequency, stool consistency, urgency *to defecate*, abdominal pain, diarrhea, flushing, and reductions in 5-HIAA. These potential benefits relate to a unique mechanism of action. Symptomatic improvement may lead to a better quality of life (QOL) for patients with few treatment options available, and a reduction in serotonin may help reduce the risk of carcinoid heart disease. Overall the benefit/risk profile of telotristat etiprate is expected to be favorable for participation in this clinical study."

11. **STUDY OBJECTIVES – Efficacy Objectives, Section 4.1, page 20 – This section header was deleted to correct errant language that unintentionally associates the term "efficacy" with the primary objectives of the protocol. As a result of the deletion, section headers for Primary Objective, Section 4.1.1, page 20, Secondary Objective(s), Section 4.1.2, page 20, and Safety Objectives, Section 4.2, page 20 were updated. The revised section headers now read as in the following comparison table:**

Section	Previous Headings (Amendment 2, dated 31 January 2014) with Revisions Marked in Track Change Mode	New Headings (Amendment 4, dated 02 November 2015) as Revised
Section 4./ Study Objectives (page 20)	**4. Study Objectives** **~~4. 1 Efficacy Objectives~~** **4.1~~.1~~ Primary Objective** **4.~~1.~~2 Secondary Objective(s)** **4.~~2~~3 Safety Objectives**	**4. Study Objectives** ***4.1*** **Primary Objective** ***4.2*** **Secondary Objective(s)** ***4.3*** **Safety Objectives**
added text / ~~deleted text~~		

12. STUDY OBJECTIVES – Secondary Objective(s), Section 4.2, page 20 – This section was modified to reflect that patient reported QOL data will be collected and evaluated through Week 84. The revised section now reads:

"The secondary objective of this study is to evaluate changes in patients' QOL *through Week 84*."

13. INVESTIGATIONAL PLAN – Overall Study Design, Section 5.1, paragraphs 3 and 4, page 21 - This section was revised to insert paragraph 3 describing the minimum treatment duration of 52 weeks, which may continue to the earlier of marketing approval with prescription availability or 31 March 2017. The inserted text also defines the completion of the Treatment Period. The paragraph describing the patients' completion of a Follow-up Period was moved to immediately follow the inserted text and revised to address only patients who complete the Treatment Period since the management of discontinued patients is already described elsewhere in the protocol. The following paragraph was been inserted, followed by the relocated paragraph:

"*All patients will receive telotristat etiprate for at least 52 weeks and may continue treatment in the trial until such time telotristat etiprate has received regulatory approval to be marketed and is available via prescription or until 31 March 2017, whichever occurs first. Patients who reach this timeline event will be deemed to have completed the Treatment Period and will advance to the End-of-Study (EOS) visit as identified in Appendix A – Schedule of Events, regardless of where they are in the visit schedule and when their last study visit occurred.*

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

14. STUDY POPULATION – Section 6, pages 21-22 – This section was revised to update both the number of patients and the number of study sites expected to participate in the study. The revised section now reads:

"Adult patients who are currently participating in ongoing Phase 2 or Phase 3 telotristat etiprate CS clinical protocols will be enrolled into the study. Up to *130* patients are expected to enroll in

this study. Approximately *50* sites worldwide will participate in the study. Patients may continue allowed medications as background therapy provided they remain on stable- doses throughout the Treatment Period."

15. **TREATMENT – Packaging, Labeling, and Storage, Section 7.1.1.2, page 25, paragraph 2 – This paragraph was revised to clarify the upper limit of allowable temperature excursion for the storage of study drug. The revised paragraph now reads:**

"Telotristat etiprate should be stored between 15 to 25°C (59 to 77°F)*, with excursions allowed up to 30°C.*"

16. **STUDY PROCEDURES – Efficacy Assessments, Section 8.2.1, pages 26-27, paragraph – This paragraph was revised to correct parenthetic references to protocol appendices. The paragraph now reads:**

"Efficacy assessments include the patient reported QOL measures; EORTC QLQ-C30 (Appendix *C*) & GI.NET21 (Appendix *D*) questionnaires and subjective global assessment of symptoms associated with CS."

17. **STUDY PROCEDURES – Subjective Global Assessment, Section 8.2.1.2, page 26 – This section was revised to reference Appendix A – Schedule of Events, which reflects that the Subjective Global Assessment will be conducted through Week 84. The following paragraph now reads:**

"A subjective global assessment of symptoms associated with CS will be evaluated using 2 methods at each visit *as indicated in Appendix A*."

18. **STUDY PROCEDURES – Depression Detection, Section 8.2.4.4.1.1, pages 30-31 – This section has been modified to clarify how responses to the questions should be assessed and documented. The section now reads:**

"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 evaluated by the Investigator in order to assess if the response is clinically significant. Positive responses assessed as clinically significant* prior to Day 1 dosing will be captured on the medical history CRF page. Positive responses following the first dose will be *evaluated by the Investigator in order to assess if* an AE *has occurred. Positive responses assessed to be an AE will be followed as an AE* of special interest."

19. SAFETY REPORTING – Adverse Events, Section 9.1, Relationship to Study Drug, page 34 – This section has been modified to provide clarification on categorizing events that are not related. In addition, a 5th classification "unlikely related" has been added. The revised and added text reads:

"Not related:

- Does not follow a reasonable temporal sequence from administration of the drug
- *Event is* reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment; *there is no reasonable causal link that drug caused the event.*

Unlikely related:

- *Temporal sequence from administration of the study drug to event onset suggests a doubtful or improbable causal relationship*
- *Alternative explanation (including underlying disease, complications, concomitant drugs, or concurrent treatment) is plausible and more likely*"

20. STATISTICAL METHODOLOGY – Efficacy Endpoints, Section 10.3.1, page 39 – This section was renamed to correct errant language that unintentionally associates the term "efficacy" with the primary objectives of the protocol. In addition, the second paragraph was revised to more precisely reflect the study period over which patient reported QOL data will be evaluated. The revised section now reads as in the following comparison table:

Section	Previous Section Heading and Content (Amendment 2, dated 31 January 2014) with Revisions Marked in Track Change Mode	New Section Heading and Content (Amendment 4, dated 02 November 2015) as Revised
Section 10.3.1/ Efficacy Endpoints (page 39)	**10.3.1 ~~Efficacy~~ Primary and Secondary Endpoints** The primary ~~efficacy~~ endpoint is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate. ~~Secondary~~ ~~efficacy~~ The secondary endpoint is to evaluate changes in patients' QOL over ~~multiple years~~ 84 weeks of therapy.	**10.3.1 Primary and Secondary Endpoints** The primary endpoint is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate. *The secondary* endpoint is to evaluate changes in patients' QOL over *84 weeks* of therapy.
added text / ~~deleted text~~		

21. STATISTICAL METHODOLOGY – Safety Analyses, Section 10.4.2, page 40, paragraph 2 – This paragraph was updated to better reflect what treatment-emergent adverse event summaries will include. The revised paragraph now reads:

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

22. APPENDIX A – Schedule of Events, Section 13, page 45 – The Schedule of Events has been updated to reflect the following changes:

- Addition of Week 96, Week 108, Week 120, Week 132, Week 144, Week 156, and Week 168 visits
- Addition of dispensation of LX1606 at Week 84
- Separation of EOS visit from Week 84 as a stand-alone visit
- Revision of the table footnote to clarify the conduct of the EOS visit and reflect the management of the Treatment Period for patients who reach the timeline event of marketing approval with prescription availability or 31 March 2017, whichever occurs first
- Renaming of Extension Period to Treatment Period to be consistent with the protocol

Changes are indicated by highlighted cells in 'Revised Appendix A – Schedule of Events' table below.

Revised Appendix A – Schedule of Events

Procedure	~~Extension~~ Treatment Period[6]														EOS[4]	2-Week Follow-up[4]
	Baseline Day 1[1]	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84 / ~~EOS~~	Week 96	Week 108	Week 120	Week 132	Week 144	Week 156	Week 168	
Tolerance (days)	NA	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	~~± 5~~ + 21	± 5
Inclusion/Exclusion criteria	X																
Medical history	X																
Physical examination incl. weight	X	X[3]	X[3]	X[3]	X	X[3]	X[3]	X	X[3]	X[3]	X[3]	X	X[3]	X[3]	X[3]	X	X[5]
Urine pregnancy test[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology, Blood chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
Urinalysis	X				X			X				X				X	X[5]
Chromogranin A	X				X			X				X				X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X				X			X				X				X	X[5]
Subjective Global Assessment	X	X	X	X	X	X	X	X									
EORTC QLQ-C30 & GI.NET21	X		X		X		X	X									
Sleep and Depression Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma 5-HIAA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispensation of LX1606	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	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	X	X	X

[1]Eligibility will be determined at last visit of the original protocol; Day 1 will replace the next scheduled visit in the original protocol schedule. Visits should coincide with LAR injections for those patients receiving SSA therapy. [2]Females of child-bearing potential only. [3]Brief physical examination only (symptom-oriented, including weight). [4]Visit to be performed for subjects who withdraw early and will not return for a 2-week follow-up visit; in all other cases the End-of-Study (EOS) visit should be performed followed by the follow-up visit 2 weeks ~~postdose~~after the final dose. [5]To be performed only if evaluation at ~~Week 84/~~EOS is abnormal. [6]All patients will receive LX1606 for at least 52 weeks and may continue treatment in the trial until such time telotristat etiprate has received regulatory approval to be marketed and is available via prescription or until 31 March 2017, whichever occurs first. Patients who reach this timeline event will be deemed to have completed the Treatment Period and will advance to the EOS visit, regardless of where they are in the visit schedule and when their last study visit occurred. The EOS visit should be performed within 21 calendar days following the completion of the Treatment Period.

added text / ~~deleted text~~

23. APPENDIX B – Amount of Blood to be Collected from Each Patient, Section 14, page 46 – This section has been modified to reflect the maximum estimated volume of blood that may be collected from each patient based upon changes reflected in Appendix A. Changes are indicated by highlighted cells. The revised table now reads:

Assessment		Sample volume (mL)	Number of samples*	Estimated total volume (mL)
Safety	Hematology	2	17	34
	Blood chemistry	6	17	102
Other	CgA	2	5	10
Pharmacodynamic	Plasma 5-HIAA	4	17	68
			Total	214
*Maximum number of samples is indicated				

Lexicon Pharmaceuticals, Inc.
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The Woodlands, TX 77381-1160

CLINICAL STUDY PROTOCOL

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
EudraCT Number	2013-002596-18
Investigational Phase:	3
Protocol Title:	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Study Name:	TELEPATH (**Tel**otristat **E**tiprate – Expanded Treatment for **Pat**ients wit**h** Carcinoid Syndrome)
Amendment 3 Date:	06 May 2015 (Germany and UK sites only)
Amendment 2 Date:	08 October 2014
Amendment 1 Date:	31 January 2014
Original Version Date:	14 June 2013
Sponsor:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: 001 (281) 863-3000 Safety Hotline: 001 (877) 372-3597 Safety Data Facsimile: 001 (832) 442-5917

Lexicon Pharmaceuticals, Inc.
8800 Technology Forest Pl.
The Woodlands, TX 77381-1160

Investigator Signature Page

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
Protocol Title:	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
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By my signature below, I hereby attest that I have read and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol and will conduct the study in accordance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance.

Additionally, I will not initiate this study without written and dated approval from the appropriate Institutional Review Board (IRB)/ Ethic Review Committee (ERC), and I understand that any changes in the protocol must be approved in writing by the Sponsor, the IRB/ERC, and, in certain cases the Food and Drug Administration (FDA) or other applicable regulatory agencies, before they can be implemented, except where necessary to eliminate hazards to patients.

Principal Investigator's Signature — Date

Principal Investigator's Name (Print)

[redacted]

Lexicon [redacted] (Signature) — Date [redacted]

[redacted] M.D

Lexicon [redacted] (Printed Name)

1. Synopsis

Name of Study Drug	Telotristat etiprate
Protocol Number	LX1606.1-302-CS LX1606.302 (Abbreviated number)
Protocol Title	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Primary Objective	The primary objective of this study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate
Secondary Objective	To evaluate changes in patients' quality of life (QOL) through Week 84
Phase of Development	3
Methodology	The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate. Patients currently participating in any LX1606 Phase 2 carcinoid syndrome (CS) study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original study to LX1060.1-302-CS. Following confirmation of eligibility, patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label study drug at the same dose level and regimen as identified in their original study. Downward dose adjustment will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. Patients may return to the previous dosing at the discretion of the Investigator and in consultation with the Medical Monitor. Upon completion or early withdrawal from treatment, all patients will be required to complete a 14-day Follow-up Period, during which no study drug will be administered.

	A Data Safety Monitoring Board (DSMB) will review safety data quarterly throughout the study.
Number of Patients	Up to 100 patients are expected to participate in this study.
Patients	Eligible patients are defined as those that are currently participating in a Phase 2 or Phase 3 telotristat etiprate carcinoid syndrome study.
Number of Study Sites	Approximately 70 sites
Treatments	Telotristat etiprate, 250-mg tablet, administered at the same dose level and regimen identified in the patient's original study
Route of Administration	Oral
Duration of Participation	All patients will participate for at least 86 weeks including Treatment and Follow-up. Patients who are scheduled to complete the Treatment Period prior to 31 March 2016 will have the option to extend the Treatment Period until 31 March 2016.
Inclusion Criteria	Patients must meet all of the following criteria to be considered eligible to participate in the study: 1. Ongoing participation in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study 2. 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 entry are confirmatory in the absence of a clear postmenopausal history.

	3. Ability and willingness to provide written informed consent prior to participation in any study-related procedure
Exclusion Criteria	Patients who meet any of the following criteria will be excluded from participating in the study: 1. Major protocol violations or telotristat etiprate tolerability concerns in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study 2. Positive pregnancy test 3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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 4. Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities
Statistical Methods	Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study and combined across all treated patients. Primary analyses of the data will be based on the Safety population which includes all patients treated on Day 1 of this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.
Study Assessments	<u>Safety</u> Safety assessments include monitoring of adverse events, clinical laboratory tests, vital signs measurements, 12-lead ECG, and physical examinations <u>Efficacy</u>

	Efficacy assessments will include patient reported quality of life measures as captured in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and the module specific for gastrointestinal symptoms of carcinoid neuroendocrine tumors (GI.NET21) and subjective global assessment of symptoms associated with CS Pharmacodynamics Pharmacodynamic (PD) assessments include determination of 5-HIAA levels in plasma
Efficacy Data Analysis	All efficacy and PD variables will be summarized descriptively and listed. Statistical tests and estimates of within patient effects for the efficacy and PD measures will be derived from application of a mixed linear model with repeated measures. The form of the model will be specific to measurement properties of the dependent variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model. Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to patients' telotristat etiprate dose level on Day 1 of this study.
Safety Data Analysis	Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group, and as needed, by study visit. Treatment-emergent adverse event 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 serious adverse events. Vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) 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.

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2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ALP	alkaline phosphatase
AST	aspartate transaminase
bid	twice daily
BM	bowel movements
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CgA	chromogranin A
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CS	carcinoid syndrome
CT	computed tomography
DSMB	Data Safety Monitoring Board
EC	enterochromaffin
ECG	electrocardiogram
ERC	Ethic Review Committee
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HEENT	head, eyes, ears, nose, and throat
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
IND	Investigational New Drug

Continued on the next page

Abbreviation	Definition
IRB	Institutional Review Board
ITT	intent-to-treat
IMP	Investigational Medicinal Product
IWRS	interactive web response system
LAR	long-acting release
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MCP	multiple comparison procedure
MRI	magnetic resonance imaging
NET	neuroendocrine tumor
NRS	numeric rating scale
OOR	out-of-range
OTC	over-the-counter
PD	pharmacodynamic
PK	pharmacokinetic
qd	once daily
SAE	serious adverse event
SBS	short bowel syndrome
SOP	standard operating procedure
SSA	somatostatin analog
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse events
tid	3 times daily
TPH	tryptophan hydroxylase
ULN	upper limit of the normal reference range
WRS	Wilcoxon rank sum

Definitions of Terms

Term	Definition
LP-778902	active moiety of LX1606
LX1606	telotristat ethyl: the ethyl-ester prodrug of the active moiety LP-778902; a serotonin synthesis inhibitor being developed by Lexicon Pharmaceuticals, Inc.
QTcF	corrected QT interval using Fredericia's formula

3. Introduction

3.1 Background on Telotristat Etiprate (LX1606) and Disease

Serotonin (5-HT) plays a critical role in regulating several major physiological processes of the gastrointestinal tract, including aspects of secretion, motility, inflammation and sensation. Enterochromaffin (EC) cells release 5-HT when the intestinal wall is stimulated by intraluminal pressure or chemicals. Through multiple classes of receptors, 5-HT is believed to initiate directly, or facilitate, peristaltic and secretory reflexes. 5-HT is also reportedly involved in the pathophysiology of various types of functional gastrointestinal (GI) disorders, valvular heart disease, and may play a role in the pathophysiology of inflammatory bowel disease (IBD).

Carcinoid tumors are mostly derived from EC cells of the midgut, and often produce and release large amounts of 5-HT. Such excess of 5-HT is believed to be responsible for the severe diarrhea and eventual valvular heart damage and mesenteric fibrosis in patients with carcinoid syndrome (CS).[1-3] Inhibition of tryptophan hydroxylase (TPH) activity in carcinoid tumors should lead to a reduction of peripheral 5-HT in afflicted patients and thus an amelioration of the pathophysiology and symptomology of CS. A peripheral TPH inhibitor, such as telotristat etiprate, should alleviate the symptoms due to excess 5-HT in carcinoid patients without central nervous system (CNS)-related adverse events (AEs).

Approximately 90% of the body's 5-HT is found in the EC cells of the GI tract, with the remainder distributed between the platelets and CNS.[4] TPH catalyzes the biopterin-dependent monooxygenation of tryptophan to 5-hydroxytryptophan, which is subsequently decarboxylated to form 5-HT. Expression of TPH is limited to a few specialized tissues: raphe neurons, pinealocytes, mast cells, mononuclear leukocytes, beta cells of the islets of Langerhans, and intestinal and pancreatic EC cells.[5] Two isoforms of the enzyme exist, TPH1 and TPH2. TPH1 is exclusively located in the EC cells of the GI tract and pineal gland and is the rate limiting enzyme responsible for the majority of systemic 5-HT production and is also responsible for 5-HT synthesis in carcinoid tumors. TPH2 is located in the central and enteric nervous systems and is the rate-limiting enzyme in the production of neuronal 5-HT.

The oral TPH inhibitor, telotristat etiprate, represents a novel approach to potentially lessen the pathophysiology of CS by reducing 5-HT levels via inhibition of TPH. Telotristat etiprate was designed specifically as a prodrug in order to gain greater systemic exposure, opening the potential application for indications in which hyperserotonemia is thought to contribute to the disorder, such as CS. Preclinical pharmacology studies of telotristat etiprate were designed to evaluate the compound’s mechanism of action and effects in vivo. Telotristat etiprate is the ethyl-ester prodrug of the active moiety LP-778902. Telotristat etiprate was

designed as a prodrug in order to enhance peripheral exposure without crossing the blood-brain barrier. In vivo, telotristat etiprate is readily converted through esterase activity to its corresponding acid, LP-778902. LP-778902 has an in vitro potency of 0.028 μM on purified human TPH1 enzyme and 0.032 μM on purified human TPH2 enzyme. Therefore, telotristat etiprate is a robust inhibitor of TPH both in vitro and in vivo and has been shown in Phase 2 studies to provide clinical benefit to patients with carcinoid tumors and associated CS.

Telotristat etiprate is being developed to manage GI symptoms and possibly other symptoms associated with CS. Currently, the standard of care for patients with CS is symptom management using somatostatin analogs (SSA), which are available in both short- and long-acting release (LAR) formulations. Somatostatin analogs such as octreotide are indicated for the control of flushing, diarrhea, and other symptoms associated with CS. Common side effects of the long-acting depot form of the drug are pain at the site of the injection, reported in as many as 30 to 50% of carcinoid patients at the 20 and 30 mg dose levels, and less commonly, stomach cramps, nausea, vomiting, headaches, dizziness, and fatigue.[6] Other side effects identified in the product labeling include biliary tract abnormalities (gallstones, sludge, and dilatation), hypothyroidism, dietary fat malabsorption, and hyper or hypoglycemia.[7] In addition to the morbidity associated with parenterally administered agents, tachyphylaxis will occur in the majority of patients, resulting in recurrent symptoms.

There are currently no specific oral treatments indicated for the management of symptoms associated with CS. As a result of the morbidity associated with SSAs and the associated tachyphylaxis, there is an unmet medical need to provide symptom management and modify the pathophysiology of patients with metastatic CS. Inhibition of the excessive 5-HT produced by these tumors with an orally delivered agent such as telotristat etiprate could provide significant benefit as an additional treatment option for patients and clinicians.

3.2 Clinical Trials of Telotristat Etiprate (LX1606) in Humans

Telotristat etiprate has been studied in single/multiple doses in Phase 1 studies, approximately 117 healthy volunteers participated in Phase 1 trials with 96 subjects receiving telotristat etiprate and 21 subjects receiving placebo. In addition, 37 patients with CS have received telotristat etiprate during the clinical development program in Phase 2. An additional 59 patients with ulcerative colitis have been enrolled into an ongoing Phase 2 study to evaluate telotristat etiprate versus placebo in patients with ulcerative colitis experiencing active flares.

3.2.1 Phase 1 Studies

LX1606.1-101-NRM utilized telotristat etiprate as a single oral dose and was noted to be safe and well tolerated up to doses of 1,000 mg. At doses of ≥1,000 mg, an increase in GI AEs was observed, which were assessed as at least possibly related to study drug. These AEs led

to a decision not to escalate the dose beyond 1,500 mg. No serious adverse events (SAEs) or deaths were reported and no patient discontinued due to an AE. Twenty-three patients experienced at least 1 AE. The majority of the AEs were assessed as mild. The most common AEs were diarrhea and nausea. Random out-of-range laboratory values at various time points in several patients occurred without any apparent trend. There were no other clinically significant vital signs, laboratory or physical examination findings.

LX1606.1-102-NRM utilized telotristat etiprate as multiple oral doses over 14 days and was tolerated up to the maximum dose assessed, 500 mg tid; 1,500 mg total dose daily. Most AEs were mild, the most common being nausea and headache; all resolved. Most AEs were at least possibly related to study treatment. Four AEs required treatment with concomitant medication, 3 AEs of constipation and 1 of headache. No deaths or SAEs were reported. One patient was discontinued due to an AE of abnormal liver function. There were no apparent trends or clinically significant findings observed upon review of vital signs and electrocardiogram (ECG) data. There were no clinically significant abnormal physical examination findings.

Overall, in LX1606.1-102-NRM, treatment with telotristat etiprate was associated with mild elevations, generally ≤2x the upper limit of normal (ULN), in alanine transaminase (ALT) and aspartate transaminase (AST), with elevations in values observed earlier in the higher dose cohorts. Results were assessed as clinically significant for only 1 patient, in Cohort 4, who was withdrawn on Day 10. The trend was most pronounced in Cohort 5, in which 5 out of 6 patients who received telotristat etiprate had increases in ALT values which were above normal range and 4 patients had increases in AST values which were above normal range at Day 14. Mean increases in ALT and AST appeared earlier in the study for Cohorts 4 and 5 than in the other cohorts, and were noted for all cohorts by Day 12. All patients had normal ALT and AST values at Baseline and most elevated transaminases returned to normal range within 48 hours after the last dose of study drug. No changes in alkaline phosphatase (ALP) or total bilirubin were observed in any patient.

LX1606.1-103-NRM evaluated 2 oral formulations of telotristat etiprate in an open-label crossover study. Each formulation was given as a single oral dose followed by a 5-day washout and then patients were given a single oral dose of the second formulation. During this study, there were no deaths or SAEs reported and no AEs lead to discontinuation. The most commonly reported AE was diarrhea. No clinically significant observations or changes in other safety parameters (eg, clinical laboratory evaluations, vital signs, physical examinations, ECGs, and AEs) were identified in the patient population during the study conduct.

LX1606.1-104-NRM was designed to evaluate the pharmacokinetics, metabolism, and routes and extent of elimination of telotristat ethyl and its primary metabolite (LP-778902) in 8 healthy male subjects after a single oral dose of 500 mg radio-labeled telotristat etiprate (14C-LX1606). This study has been completed and the results will be discussed in the annual update of the Investigator Brochure.

3.2.2 Phase 2 Studies

LX1606.1-202-CS was a randomized, double-blind, placebo-controlled, multiple ascending dose study conducted in 2 parts in order to evaluate a total of 23 patients at a dose range of 450 to 1500 mg given as 150, 250, 350, or 500 mg tid (telotristat etiprate or matching placebo) on a background therapy of octreotide. In Part 1, 16 patients were randomly assigned 3:1 into 4 sequential cohorts. Each cohort evaluated 1 of the following daily doses given as 150, 250, 350, or 500 mg tid over a course of 4 weeks. During the study, all patients continued on a stable-dose background therapy of octreotide. In Part 2, an additional 7 patients were randomly assigned 3:1 in order to evaluate 500 mg tid, the highest tolerated dose as determined in Part 1. Upon completion of the initial 4-week portion, eligible patients had the option to continue into an open-label Extension Period.

There was 1 treatment emergent SAE assessed as possibly related to study drug which occurred in the 350 mg tid dose group. The patient had a history of nausea and vomiting and was hospitalized for exacerbation of these conditions.

Telotristat etiprate was generally well tolerated with no evidence of dose-limiting tolerability. Adverse events were mostly mild to moderate and with similar frequencies between treatment groups and placebo. No significant changes in vital signs, ECG, or physical exam findings were noted after administration of telotristat etiprate at any dose level. The most common AEs were GI-related and reported as diarrhea, nausea, and abdominal pain, respectively. The modest elevations in transaminases seen in the Phase 1 multiple ascending dose study (LX1606.1-102-NRM) were not apparent in this 4-week study in patients with CS.

Patients that received telotristat etiprate achieved a clinical response (28%) defined as at least a 30% reduction in bowel movements (BMs) for at least 2 weeks; a biochemical response (56%) defined as at least a 50% reduction or normalization of urinary 5-hydroxyindoleacetic acid (5-HIAA); and reported adequate relief at Week 4 (46%) while no placebo patients experienced clinical response, biochemical response, or adequate relief.

LX1606.1-203 was an open-label, serial ascending, multiple dose, individual titration study that evaluated the same dose ranges as the LX1606.1-202-CS study in a total of 15 patients. Patients were serially escalated to the next dose level every 2 weeks until a maximally tolerated dose or 500 mg tid was reached. Once a dose had been determined, the patient

would remain on the dose for an additional 4 weeks. Patients then had the option to continue into an Extension Period.

Telotristat etiprate was generally safe and well-tolerated in subjects with CS in the LX1606.1-203 study. Most AEs were mild to moderate in severity and assessed as unrelated to study drug. Events in the Gastrointestinal Disorders system organ class were common, as is anticipated with the underlying illness.

Statistically significant reductions from Baseline in the mean number of BMs/day were observed in this study throughout the entire dose-escalation and stable-dose phases, as were improvements in stool form. Telotristat etiprate produced an improvement in global assessment of GI symptoms associated with CS in the majority of subjects (12 of 15 subjects, 80%) across the 12-week period. The global assessment of GI symptoms was based on 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 BM, abdominal pain or discomfort?” In addition, subjects experienced statistically significant decreases in the mean daily number of cutaneous flushing episodes.

Thirteen subjects (86.7%) experienced a complete biochemical response (defined as a ≥50% reduction from Baseline in u5-HIAA levels at 1 or more time points). Consistent with the proposed mechanism of action for telotristat etiprate, a complete biochemical response correlated closely with measures of clinical response, such as number of bowel movements per day.

LX1606.1-204-UC evaluated patients with active flares of ulcerative colitis. Doses under evaluation are 500 mg once daily (qd) and 500 mg tid vs. placebo; 59 patients were enrolled for an 8-week treatment period. This study has been completed and the results will be discussed in the annual update of the Investigator Brochure.

Detailed information regarding the completed clinical studies can be found in the Investigator Brochure.[8]

3.2.3 Ongoing Studies

The open-label extension portions in LX1606.1-202-CS and LX1606.1-203-CS remain ongoing.

LX1606.1-301-CS is intended to evaluate patients who are currently on a background of SSA therapy and still experiencing breakthrough symptoms such as an increased frequency of BMs ≥4 per day on average: (1) the efficacy of telotristat etiprate on reducing the number of BMs; (2) the efficacy of telotristat etiprate on a number of clinically relevant secondary endpoints; and, (3) the safety of telotristat etiprate over the 12-week double-blind portion

(Treatment Period) of the study. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period (Extension Period).

LX1606.1-303-CS is intended to evaluate patients with carcinoid syndrome whose primary symptoms are not GI related and may be naïve to SSA therapy: (1) the safety of telotristat etiprate over the 12-week double-blind portion (Treatment Period) of the study; (2) percent (%) change from Baseline in 24-hour u5-HIAA levels at Week 12; (3) the effects of telotristat etiprate on a number of clinically relevant secondary endpoints. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period.

3.3 Rationale for Current Study

3.3.1 Rationale for Selection of Dose

The dose levels of telotristat etiprate selected for this study are consistent with prior clinical study experience and based upon clinical safety and pharmacodynamic (PD) data from 2 Phase 2 multiple ascending-dose studies in patients with symptomatic CS (LX1606.1-202-CS and LX1606.1-203-CS).

Based upon observations noted in Section 3.2, it is anticipated that the doses to be utilized in this protocol will be safe and well tolerated and may provide clinical benefit to patients with CS.

3.3.2 Benefit/Risk Assessment

Clinical experience with telotristat etiprate (treated subjects) consists of completed single and multiple ascending dose studies in 96 normal subjects (44 in single dose studies and 52 in the multiple dose study), 2 Phase 2 studies (37 patients with symptomatic CS) and 2 ongoing Phase 3 studies in patients with symptomatic CS.

In healthy volunteer studies, single doses up to 1000 mg were found to be generally well tolerated, while at the 1500 mg dose level GI-related adverse events increased. A similar adverse event profile was observed after multiple dose administration over 14 days with GI events predominating. Mild, dose-dependent increases in hepatic transaminase levels (≤2 x ULN) were observed with increased frequency in relation to dose, with 1 subject requiring withdrawal from therapy at the 500 mg bid dose level. Most subjects that were observed to have increased transaminase levels did not exceed >2 x ULN. No abnormalities in total bilirubin were observed at any dose level. GI events have been the most commonly observed events to date. The adverse event profile in normal subjects may differ significantly from what is observed in patients with hyperserotonemia. All adverse events resolved without sequelae. In addition, there were no significant changes in vital signs or ECG. No physical

examination abnormalities were noted in studies to date. There were no serious adverse events reported in healthy volunteers.

In patients with CS, dose escalations have proceeded up to and including 500 mg tid. To date, there has been no evidence of dose-limiting intolerability. Dose levels have been generally well tolerated with no evidence to suggest elevations in hepatic transaminase levels. Based upon observations from preclinical and clinical studies conducted to date, it is anticipated that orally administered telotristat etiprate will be well tolerated at dose levels required to influence peripheral 5-HT production in patients with symptomatic CS. Potential adverse events primarily involve the GI tract, and could include alterations in gut motility, nausea, vomiting, diarrhea, constipation, abdominal bloating, and/or pain. Regular and ongoing clinical and laboratory assessments should detect any of these events, and depending on the type of event, further dose adjustment or discontinuation from the trial would occur. Although CNS effects are not anticipated at dose levels planned for evaluation, standard adverse event questioning and/or physical examination should reveal any subtle CNS findings. As elevations in hepatic transaminase levels were observed with multiple dosing in normal subjects, monitoring clinical laboratory tests of hepatic function will be incorporated into clinical trials conducted in CS patients.

Treatment has the potential to improve several signs and symptoms of CS. The Phase 2 clinical trial results indicated that treatment may lead to improvements in BM frequency, stool consistency, urgency, abdominal pain, diarrhea, flushing, and reductions in 5-HIAA. These potential benefits relate to a unique mechanism of action. Symptomatic improvement may lead to a better quality of life (QOL) for patients with few treatment options available, and a reduction in serotonin may help reduce the risk of carcinoid heart disease. Overall the benefit/risk profile of telotristat etiprate is expected to be favorable for participation in this clinical study.

3.4 Rationale for Study Design and Control Groups

Currently, no approved therapy exists for the treatment of symptoms driven by underlying serotonin pathophysiology of CS in patients whose disease is refractory to SSA therapy or for those patients who are unable to tolerate SSA therapy or who are unwilling to take SSA therapy.

This study will allow for continued access to telotristat etiprate after patients have completed the required study visits in ongoing Phase 2 and Phase 3 studies. Continuation of CS patients into this study will allow for the collection of additional long-term safety and efficacy data, while providing access to patients who may be receiving benefit. The treatment duration is

supported by results of chronic toxicology studies (6-month rat and 9-month dog) and the current safety profile from completed and ongoing clinical trials.

4. Study Objectives

4.1 Efficacy Objectives

4.1.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

4.1.2 Secondary Objective(s)

The secondary objective of this study is to evaluate changes in patients' QOL through Week 84.

4.2 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

5. Investigational Plan

5.1 Overall Study Design

The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate.

Patients currently participating in any LX1606 Phase 2 CS study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original protocol to LX1606.1-302-CS.

Following confirmation of eligibility, patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label LX1606 at the same dose level identified in the original study.

All patients will receive telotristat etiprate for at least 84 weeks. However, patients who will complete 84 weeks of treatment prior to 31 March 2016 may continue to receive telotristat etiprate in the trial until 31 March 2016.

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

Downward dose adjustment will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. Patients may return to the previous dosing at the discretion of the Investigator and in consultation with the Medical Monitor.

A Data Safety Monitoring Board (DSMB) will review safety data quarterly throughout the study.

6. Study Population

Adult patients who are currently participating in ongoing Phase 2 or Phase 3 telotristat etiprate CS clinical protocols will be enrolled into the study. Up to 100 patients are expected to enroll in this study. Approximately 70 sites worldwide will participate in the study. Patients may continue allowed medications as background therapy provided they remain on stable-doses throughout the Treatment Period.

6.1 Inclusion Criteria

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

1. Ongoing participation in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study
2. 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 Baseline Day 1 are confirmatory in the absence of a clear postmenopausal history.

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

6.2 Exclusion Criteria

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

1. Major protocol violations or telotristat etiprate tolerability concerns in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study
2. Positive pregnancy test
3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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
4. Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities

6.3 Criteria for Stopping Treatment/Study Withdrawal

A patient may also be discontinued from the study for the following medical or administrative reasons:

- Withdrawal of consent by the patient or legal guardian
- Noncompliance, including refusal of the study medication and/or failure to adhere to the study requirements as in the study protocol
- Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study
- The Sponsor terminates the study (Section 6.4)
- Pregnancy (Section 9.4.1)

Note: If a patients voluntarily withdraws or is discontinued from study treatment before completing the entire duration of the Treatment Period, 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 Appendix A – Schedule of Events and agree to report any SAEs (Section 9.2) that occur within 30 days following the last dose of telotristat etiprate.

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 Case Report Form (CRF).

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.

6.4 Criteria for Termination of the Study

If the 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 carcinoid syndrome or any other indication 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; and,
- Insufficient adherence to protocol requirements.

Study termination and Follow-up would be performed in compliance with applicable governing body regulations.

6.5 Clinical Stopping Rules

Criteria for individual patient withdrawal or study termination are summarized in Sections 6.3 and 6.4, respectively.

6.6 Method of Assigning Patients to Treatment

Patients will enter the study at the same dose level and regimen as identified in the prior Phase 2 or Phase 3 CS study. Randomization will not be used to assign patients to study treatments.

6.7 Blinding and Unblinding of Study Medication

This is an open-label study.

6.8 Replacement of Patients

Patients who do not complete the study will not be replaced.

7. Treatment

7.1.1 Telotristat Etiprate (LX1606)

7.1.1.1 Identity

Telotristat etiprate (LX1606 hippurate) is the salt form of the drug substance. LX1606 hippurate is a crystalline white to off-white to tan solid with a melting point of 147°C. LX1606 is insoluble in water within the pH range of 5 to 9 (≤2 mg/L). It undergoes hydrolysis under strongly basic or strongly acidic conditions. The solubility of LX1606 hippurate in water is about 22 mg/L at 25°C.

Study drug dosage form consists of white coated debossed oval tablets containing 250 mg LX1606.

7.1.1.2 Packaging, Labeling, and Storage

Patients will receive 250-mg telotristat etiprate tablets packaged in 100 cc high density polyethylene bottles with child-resistant polypropylene screw caps and heat-induction seal liners.

Telotristat etiprate should be stored between 15 to 25°C (59 to 77°F).

7.2 Prior and Concomitant Medications

7.2.1 Prior Medications

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

7.2.2 Concomitant Medications

All concomitant medications taken by patients during the study will be recorded on the CRF. Treatment with prescription or over-the-counter (OTC) antidiarrheal therapy, bile acid sequestrants, or pancreatic enzyme is permitted; however, the use of these concomitant therapies should be associated with a documented history of disease (eg, fat malabsorption, bile acid malabsorption, or steatorrhea).

Medical management of patients and their concomitant medications is allowed at the discretion of the Investigator. However, should the need arise to modify/adjust a patient's therapy due to a concern for patient safety and/or tolerability 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.

7.2.3 Prohibited Medications or Concomitant Therapy

None

7.3 Administration of Study Medication

All patients will be instructed to take the study medication with food. "With food" means taking telotristat etiprate 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.

Study medication and instructions will be dispensed to patients at each visit as described in the schedule of study procedures (Appendix A).

7.3.1 Treatment Compliance

Patients will be asked to bring their unused or unopened study medication to each visit (Appendix A). At each visit and in the presence of the patient, study site personnel will count returned tablets and reconcile the counts against planned number of doses for that interval. Site personnel will clarify any discrepancy and record this information within the CRF.

Patients must maintain at least 75% compliance in dosing to be deemed as compliant. In the event of a missed or vomited dose, patients will take their subsequent dose of study drug at the next scheduled time point, following the tid dosing regimen of approximately every 6 hours. A dose outside of a 3-hour window should be considered missed. Missed or vomited doses will not be made up.

7.4 Dose Adjustment

Downward dose adjustment of telotristat etiprate will be permitted if evidence of intolerability emerges. After a period at the lowered dose level, patients may resume the previous dosing level at the discretion of the Investigator after consultation with the Medical Monitor. Patients who experience intolerability at the 250 mg tid dose level **must** be discontinued from study treatment. Interruptions or delays in dosing throughout the entire study may be permitted after consultation with the Medical Monitor, at which time the patient will be reassessed for study continuation, dosage reduction, or discontinuation.

8. Study Procedures

A schedule of study assessments is provided in Appendix A.

8.1 Restrictions during Study

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

8.2 Description of Study Assessments

8.2.1 Efficacy Assessments

Efficacy assessments include the patient reported QOL measures; EORTC QLQ-C30 (Appendix D) & GI.NET21 (Appendix E) questionnaires and subjective global assessment of symptoms associated with CS.

A description of the efficacy assessments is provided below.

8.2.1.1 EORTC QLQ-C30 & GI.NET21

Patients will complete the questionnaires during each visit as indicated in Appendix A.

8.2.1.2 Subjective Global Assessment

A subjective global assessment of symptoms associated with CS will be evaluated using 2 methods at each visit as indicated in Appendix A.

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."

8.2.2 Clinical Laboratory Assessment

Clinical laboratory assessments will consist of hematology (complete blood count [CBC] with differential and platelet counts), blood chemistry (complete metabolic panel and liver function tests), and urinalysis. 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 9.1 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.

8.2.2.1 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 >3 x 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 >3 x ULN (in patients with previous abnormal liver-test results)

OR

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

For any such event, the Investigator should discuss the Follow-up approach with the 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 function test values 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 continued study participation.

8.2.3 Pharmacodynamic Assessments

8.2.3.1 Plasma 5-HIAA

Fasting blood samples (≥6 hours) 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.

8.2.4 Safety Assessments

In addition to the clinical laboratory assessments described in Section 8.2.2, monitoring of AEs is also considered a safety assessment and is described in detail in Section 9. Clinically significant changes compared with Baseline findings for these variables should be reported as AEs on the CRF. Clinically significant changes compared with Baseline values, which are determined to be AEs, 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.

8.2.4.1 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 with 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. All measurements should be 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 Appendix A.

8.2.4.2 Physical Examinations

Complete physical examinations will be performed as outlined in Appendix A. 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, weight will be captured during each physical examination. Efforts should be made to standardize 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.

8.2.4.3 Electrocardiograms

Electrocardiograms (12-lead ECGs) will be performed as specified in Appendix A.

8.2.4.4 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.

8.2.4.4.1 Central Nervous System Events

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

8.2.4.4.1.1 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.

8.3 Other Assessments

8.3.1 Chromogranin A (CgA)

Blood samples for measurement of chromogranin A (CgA) levels will be collected as indicated in Appendix A.

8.3.2 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 (eg, PET, CAT, MRI scans of tumor), or Investigator assessment of disease status, while the patient is enrolled in the study.

8.3.3 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.

8.4 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.

8.4.1 Blood Collection

An attempt should be made to collect all samples as per the schedule outlined in Appendix A. Any portion of samples remaining after the required tests for this study have been completed will be destroyed.

The estimated amount of blood scheduled for collection per patient, over the course of the study, may be found in Appendix B.

9. Safety Reporting

Medical queries should be addressed to the Medical Monitor responsible for the region.

Sites in North America:

[redacted], MD
[redacted]
INC Research
[redacted]
Phone: [redacted]

Sites outside North America:

[redacted], MD, PhD
[redacted]
INC Research
[redacted]

[redacted]
The Netherlands
Phone: [redacted]
Mobile: [redacted]

[redacted], MD, PhD
Medical Monitor
INC Research, LLC
[redacted]
Czech Republic
Phone: [redacted]
Fax: [redacted]

After-hours 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. **Note**: These calls are not toll-free.

9.1 Adverse Events

It is the responsibility of the Investigator to document all AEs that occur during the study.

Adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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 considered related to the study medication. This definition includes an exacerbation of preexisting 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 9.2) 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 study drug 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

9.2 Serious Adverse Events (SAEs)

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

1. Death
2. A life-threatening adverse event;
3. Inpatient hospitalization or prolonging of an existing hospitalization (see Section 9.2.1 for information on hospitalization as an SAE);
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
5. A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

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: [redacted]
Belgium: [redacted]
Brazil: [redacted]
France: [redacted]
Germany: [redacted]
Israel: [redacted]
Italy: [redacted]
Netherlands: [redacted]

Spain: [redacted]
Sweden: [redacted]
United Kingdom: [redacted]

Email Address (in case of fax failure): [redacted]

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.

9.2.1 Hospitalization as an SAE

Hospitalization is defined as any in-patient overnight stay in a hospital. A hospitalization in and of itself does not constitute an SAE. The condition which caused the hospitalization must be evaluated and determined to be an AE. Although an AE which results in hospitalization is an SAE, patients are hospitalized for a variety of reasons which may not be associated with or considered an SAE (eg, convenience, logistics, preference, etc). Therefore, each case of hospitalization must be evaluated separately.

For example, the following would not be considered SAEs:

- Hospitalization for a preexisting condition which did not worsen (eg, cataract surgery)
- Hospitalization solely for a procedure or treatment that was not performed to treat an AE
- Hospitalization for a condition that does not normally require treatment, but electively done (eg, cosmetic surgery)
- Hospitalization strictly for convenience reasons or observations (eg, procedures only performed in a hospital because of the distance the subject lives from the hospital)

9.3 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.

9.4 Precautions

9.4.1 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 9.2 for contact information).

10. Statistical Methodology

10.1 Determination of Sample Size

No formal sample size calculation was made. The number of patients expected to participate in this study was calculated from estimated enrollment rates from other carcinoid cancer trials employed in the LX1606 clinical program.

10.2 Analysis Populations

Per protocol: A Per Protocol population will consist of those patients that receive study treatment and have no major protocol violation that would interfere with the collection or interpretation of the efficacy data. The primary analyses of efficacy will be based on the safety population; 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 during this study.

10.3 Study Endpoints

10.3.1 Efficacy Endpoints

The primary efficacy endpoint is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

Secondary efficacy endpoint is to evaluate changes in patients' QOL over 84 weeks of therapy.

10.3.2 Safety Endpoints

Safety endpoints are as follows:

- Incidence of TEAEs, suspected adverse reaction, AEs leading to discontinuation from the study, SAEs, and deaths
- Actual and change from Baseline in clinical laboratory results
- Actual and change from Baseline in vital signs results
- Actual and change from Baseline in physical examinations

- Actual and change from Baseline in ECG findings

10.4 Statistical Methods

Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study and combined across all treated patients. All data will be listed.

Primary analyses of the data will be based on the Safety population which includes all patients treated with any fraction of study drug during this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. This dataset will include the Safety population, but limited to those patients that have at least one assessment post Day 1 and do not have any protocol violations that would interfere with collection or interpretation of the data. The Per Protocol analysis will be applied to the QOL measures, subjective global assessment, and plasma 5-HIAA values.

Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.

10.4.1 Efficacy Analyses

All efficacy and PD variables will be summarized descriptively and listed.

Statistical tests and estimates of within patient effects for these measures will be derived from application of a mixed linear model with repeated measures. The model will be generalized to handle missing data and specific to the measurement properties of the dependent variable. There is no plan to impute data for missing observations for any variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model.

Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to how patients were dosed on Day 1 of this study.

10.4.2 Safety Analyses

Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group (corresponding to the LX1606 dose given on Day 1), pooled across all patients, and as needed, by study visit. All safety data will be listed.

Treatment-emergent adverse event 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 serious adverse events.

Vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) 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 and summarized.

10.4.2.1 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.

10.4.2.2 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 using descriptive statistics. Summaries of shifts from Baseline to abnormal clinical laboratory results will also be provided. Actual and change from Baseline in chromogranin A levels will be summarized descriptively as well.

10.4.2.3 Vital Sign Measurements

Actual and changes from Baseline (Day 1) in vital signs results will be summarized by using descriptive statistics.

10.4.2.4 Electrocardiograms

Clinically significant changes in ECGs compared to Baseline, as determined by the Investigator, will be summarized by using descriptive statistics. Actual and change from Baseline (Day 1 predose values) to each time point in corrected QT interval (QTcF) will be summarized as well.

10.4.3 Pharmacodynamic Analyses

Analysis and summarization of the plasma 5-HIAA data are described in Section 10.4.1.

10.4.4 Baseline Characteristics and Other Summaries

Treatment group differences will be summarized descriptively for demographic data, prior and concomitant medications, treatment compliance, and final disposition. Data collected from assessments of tumor status, when available, will be listed.

Protocol deviations will provided as listings.

10.4.5 Interim Analysis

An independent DSMB will be charged with reviewing interim safety data on a quarterly basis 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 may be analyzed and reported in multiple phases. The first report will summarize data obtained from all patients providing information up to a specified data cut-off point. The following reports will update the initial report by including data from the remaining portion of the study. 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.

11. Study Management

The Investigator is responsible for completing and maintaining adequate and accurate CRFs and source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, and discharge summaries.

All data on the CRF must be recorded in accordance with the CRF guidelines. If a correction is necessary, it should be made by the Investigator or a designated qualified individual as specified within the guideline. All CRFs should be completed in their entirety and stored in a

secure location. The Investigator must sign the Investigator's statement in each patient's CRF indicating that the data reported are accurate.

At the study site, clinical research associates will verify 100% of CRFs in their entirety against source documentation. Computer programmed edit checks will be run against the database to check for discrepancies and reasonableness of the data, and the safety database will be reconciled with the clinical database. All issues resulting from the computer generated checks and the safety database reconciliation will be resolved according to standard data management practices in conjunction with the Sponsor, clinical study personnel, and the study Investigators.

11.1 Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the Sponsor's study monitors will contact the study site via visits to the site, telephone calls, and/or letters in order to review study progress, CRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of patients, patient recruitment, patient compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by patients, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

The Investigator must make study data accessible to the clinical monitor, to other authorized representatives of the Sponsor, and to regulatory inspectors

11.2 Audits and Inspections

The Sponsor, regulatory authority, or IRB/ERC may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a Sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

11.3 Amendments

Any amendments to the protocol will be written and approved by the Sponsor. All amendments must be submitted to the IRB/ERC for approval prior to implementing the changes. In some instances, an amendment may require changes to the informed consent

form, which also must be submitted for IRB/ERC approval prior to administration to patients. If any changes to the CRF are required, the Sponsor will issue supplemental or revised CRF pages.

11.4 Record Keeping

11.4.1 Drug Accountability

The Investigator must maintain accurate records of receipt of study drug, dispensing information (date, lot, and dose for each patient), and the prompt return or destruction of unused supplies. If the Investigator cannot account for all clinical supplies at the termination of the study, a written explanation must be provided.

11.4.2 Health Insurance Portability Accountability Act of 1996 and Subsequent Updates

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 Code of Federal Regulations (CFR) Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation and any applicable updates). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

11.4.3 Financial Disclosure

The Investigator shall provide to the Sponsor sufficient accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the FDA and/or other applicable regulatory agencies. The Investigator shall promptly update this information if any relevant changes occur in the course of the study or for 1 year following completion of the study.

11.4.4 Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 11) to ensure data integrity. “Original” in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

11.4.5 Retention of Study Documents

According to 21 CFR Part 312.62 and ICH E6, study-related records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor.

The Investigator must not destroy any study-related records without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor must be contacted to arrange alternative record storage options.

12. Administrative Structure of the Study

The study will be monitored by Sponsor personnel or Sponsor representative. The following functions for this study will be performed by organizations designated by the Sponsor: data management and statistical analysis, including PD analysis and reporting.

13. Appendix A – Schedule of Events

Procedure	Extension Period								Optional Extension		2-Week Follow-up[4]
	Baseline Day 1[1]	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84 / EOS	Week 96[6]	Week 108[6]	
Tolerance (days)	NA	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5
Inclusion/Exclusion criteria	X										
Medical history	X										
Physical examination incl. weight	X	X[3]	X[3]	X[3]	X	X[3]	X[3]	X	X[3]	X[3]	X[5]
Urine pregnancy test[2]	X	X	X	X	X	X	X	X	X	X	X
Hematology, Blood chemistry	X	X	X	X	X	X	X	X	X	X	X[5]
Urinalysis	X				X			X			X[5]
Chromogranin A	X				X			X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X
ECG	X				X			X			X[5]
Subjective Global Assessment	X	X	X	X	X	X	X	X			X
EORTC QLQ-C30 & GI.NET21	X		X		X		X	X			
Sleep and Depression Assessment	X	X	X	X	X	X	X	X	X	X	X
Plasma 5-HIAA	X	X	X	X	X	X	X	X	X	X	X
Dispensation of LX1606	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

[1]Eligibility will be determined at last visit of the original protocol; Day 1 will replace the next scheduled visit in the original protocol schedule. Visits should coincide with LAR injections for those patients receiving SSA therapy. [2]Females of child-bearing potential only. [3]Brief physical examination only (symptom-oriented, including weight). [4]Visit 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. [5]To be performed only if evaluation at Week 84/EOS is abnormal. [6]Week 96 and Week 108 visits may be performed up until 31 March 2016 for patients who would otherwise complete 84 weeks of treatment in the study prior to 31 March 2016.

14. Appendix B – Amount of Blood to be Collected from Each Patient

Assessment		Sample volume (mL)	Number of samples*	Estimated total volume (mL)
Safety	Hematology	2	11	22
	Blood chemistry	6	11	66
Other	CgA	2	3	6
Pharmacodynamic	Plasma 5-HIAA	4	11	44
			Total	138
*Maximum number of samples is indicated				

15. Appendix C – EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Lexicon

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

16. Appendix D – EORTC QLQ - GI.NET21

ENGL2S1

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31. Did you have hot flushes?		1	2	3	4
32. Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33. Did you have night sweats?		1	2	3	4
34. Did you have abdominal discomfort?		1	2	3	4
35. Did you have a bloated feeling in your abdomen?		1	2	3	4
36. Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37. Have you had acid indigestion or heartburn?		1	2	3	4
38. Have you had difficulties with eating?		1	2	3	4
39. Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40. Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41. Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42. Were you concerned about disruption of home life?		1	2	3	4
43. Have you worried about your health in the future?		1	2	3	4
44. How distressing has your illness or treatment been to those close to you?		1	2	3	4
45. Has weight loss been a problem for you?		1	2	3	4
46. Has weight gain been a problem for you?		1	2	3	4
47. Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48. Have you had aches or pains in your muscles or bones?		1	2	3	4
49. Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:					
50. Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51. Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

17. Appendix E – Ethical Standards

Ethics and Regulatory Considerations

This study will be conducted according to GCP, 21 CFR Part 50, (Protection of Human Subjects), 21 CFR Part 56 (Institutional Review Boards), International Conference on Harmonisation Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

General Instructions

The FDA regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to GCP regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- Current FDA Guideline for the Monitoring of Clinical Investigations
- Current Guidance for Institutional Review Boards and Clinical Investigators
- ICH E6 – Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

Studies conducted in the European Union are also regulated by Volume 10 of the publications "The rules governing medicinal products in the European Union".

Copies of these materials are available from the Sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- the study is conducted with diligence and in conformance with the protocol in such a way as to insure the integrity of the findings;
- the potential benefits of the research justify the risks.

Lexicon Pharmaceuticals, Inc. is the Sponsor of the IND. The Sponsor is responsible for the following:

- selecting qualified Investigators,
- providing Investigators with the information they need to properly conduct an investigation,
- ensuring proper monitoring of the investigation,
- ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- maintaining the IND, and
- ensuring that regulatory authorities and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied
- ensuring the study is conducted in accordance to FDA and ICH guidelines and all applicable regulations

18. Appendix F – Investigator Obligations

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56 and ICH E6, the study protocol and the final version of the subject informed consent form will be approved by the IRB/ERC before enrollment of any subjects. The opinion of the IRB/ERC will be dated and given in writing. A copy of the letter of approval from the IRB/ERC and a copy of the approved informed consent form will be received by the Sponsor prior to shipment of study medication supplies to the Investigator.

The Investigator will ensure that the IRB/ERC will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to subjects. The Investigator will also ensure that no changes will be made to the protocol without IRB/ERC approval.

As a part of the IRB/ERC requirement for continuing review of approved research, the Investigator will be responsible for submitting periodic progress reports to the IRB/ERC at intervals appropriate to the degree of subject risk involved, but no less than once per year.

Written informed consent must be given freely and obtained from every subject prior to clinical trial participation. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

As described in GCP guidelines, study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (eg, loss of medical licensure, debarment). Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

Principal Investigators must provide Lexicon with a fully executed Form FDA 1572 (statement of Investigator) and all updates on a new fully executed Form FDA 1572.

Principal Investigators must provide Lexicon with his/her own curriculum vitae and current curriculum vitae for each sub-Investigator listed on Form FDA 1572.

Protection of Human Subjects (21 CFR Part 50 and ICH E6)

Informed consent must be obtained from every subject before entry into a clinical study. It must be given freely and not under duress. Consent must be documented by use of an IRB/ERC-approved consent form and signed by the subject or the subject's legally authorized representative. The US Department of Health and Human Services suggests that when minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent, his signature should also be included. Non-English-speaking subjects must be presented with

a consent form written in a language that they understand. A copy of the signed consent form must be given to the subject signing it. Another copy must be kept in the Investigator's files and made available to regulatory authority representatives upon request. If, for any reason, subject risk is increased as the study progresses, a revised, IRB/ERC-approved consent form must be signed by the subject. Before the study begins, a sample of the consent form must be provided to the Sponsor for review. The FDA and/or other applicable regulatory agencies may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all subjects.

Only in the case of a life-threatening incident may an investigational product be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the Investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB/ERC within 5 working days. In this situation, the Investigator may not administer any subsequent product to that subject until informed consent and IRB/ERC approval are obtained.

Informed Consent

Written informed consent must be obtained from each subject prior to entry in the study. One copy of the signed informed consent document will be given to the subject, and another will be retained by the Investigator. Additionally, the subject must be allowed adequate time to consider the potential risks and benefits associated with his/her participation in the study.

In situations where the subject is not legally competent to provide consent (ie, mentally incapacitated), written consent must be obtained from a parent, legal guardian, or legal representative. In these situations, the consent must be signed and dated by a witness.

The informed consent document must have been reviewed and approved by the Sponsor and by the Investigator's IRB/ERC prior to the initiation of the study. The document must contain the 8 basic elements of informed consent and may contain the 6 additional elements described in 21 CFR Part 50. Every consent form must include the following 8 elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the subject

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility that the FDA and/or other applicable regulatory authority representatives may inspect the records
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available, or a statement describing where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research related injury
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

When appropriate, 1 or more of the following elements of information shall also be included in the consent form:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent
- Any additional costs the subject may incur from participation in the research
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject
- The approximate number of subjects involved in the study

The Declaration of Helsinki includes further details regarding the specific requirements for informed consent.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states, such as California and Oregon, require further action on the Investigator's part concerning subject consent.

Study Documentation

IRB/ERC Review/Approval

The protocol and informed consent for this study, including advertisements used to recruit subjects, must be reviewed and approved by an appropriate IRB/ERC prior to enrollment of subjects in the study. It is the responsibility of the Investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, ICH, GCP, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB/ERC approval which specifically identifies the study/protocol and a list of the committee members must be received by the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

A progress report with a request for re-evaluation and re-approval will be submitted by the Investigator to the IRB/ERC at intervals required by the IRB/ERC, and not less than annually. A copy of the report will be sent to the Sponsor.

When the Sponsor provides the Investigator with a Safety Report, the Investigator must promptly forward a copy to the IRB/ERC.

After completion or termination of the study, the Investigator will submit a final report to the IRB/ERC and to the Sponsor, if required. This report should include: deviations from the protocol, the number and types of subjects evaluated, the number of subjects who discontinued (with reasons), results of the study, if known, and significant AEs, including deaths.

Study Files

The Investigator is required to maintain complete and accurate study documentation in compliance with current Good Clinical Practice standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study. Study documents include, but are not limited to, the Investigator's Brochure, drug accountability records, Sponsor/Investigator correspondence, IRB/ERC correspondence, protocol and amendments, information regarding monitoring activities, subject exclusion records, CRFs, and data queries.

Confidentiality

The anonymity of subjects must be maintained. Patients will be identified by their initials and an assigned subject number on CRFs and other documents submitted to the clinical monitor. Documents that will be submitted to the clinical monitor and that identify the subject (eg, the signed informed consent document) must be maintained in strict confidence by the Principal Investigator, except to the extent necessary to allow auditing by regulatory authorities, the clinical monitor, or Sponsor personnel.

All information regarding the nature of the proposed investigation provided by the Sponsor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB/ERC, the subject, or the regulatory authority) must be kept in confidence by the Investigator.

Drug Accountability

The Investigator or designee is responsible for accountability of the investigational product at the site. The Investigator or designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and return to the Sponsor or alternative disposition of any unused product. These records must include dates, quantities, batch/serial/lot numbers, and expiration dates (if applicable).

The Investigator should ensure that the investigational product is used only in accordance with the protocol

19. References

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8. Investigator Brochure LX1606, Lexicon Pharmaceuticals, Inc.
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CLINICAL PROTOCOL AMENDMENT 3
STUDY LX1606.302

A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)

PROTOCOL NO.:	**LX1606.1-302-CS** **LX1606.302** (Abbreviated number)
EudraCT Number:	2013-002596-18
INVESTIGATIONAL PHASE:	3
SPONSOR:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: 001 (281) 863-3000 Safety Hotline: 001 (877) 372-3597 Safety Data Facsimile: 001 (832) 442-5917
PROTOCOL AMENDMENT 3 DATE:	06 May 2015 (Germany and UK sites only)
PROTOCOL AMENDMENT 2 DATE:	08 October 2014
PROTOCOL AMENDMENT 1 DATE:	31 January 2014
ORIGINAL VERSION DATE:	14 June 2013

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Amendment Changes

Rationale

Data readout from an interim analysis of the placebo-controlled, double-blind treatment phase of Lexicon Pharmaceutical, Inc.'s (Lexicon's) pivotal Phase 3 study for telotristat etiprate, LX1606.1-301-CS, is anticipated during the third quarter of 2015, results of which are anticipated to inform and guide decisions regarding the development and regulatory path for telotristat etiprate. During this time, the earliest enrollees of this LX1606.1-302-CS study are scheduled to complete the protocol-prescribed 84-week Treatment Period. A protocol amendment is proposed to provide additional continued access to telotristat etiprate for patients who are enrolled in the LX1606.1-302-CS study and scheduled to complete the Treatment Period prior to 31 March 2016. This amendment will provide these patients the option to extend the Treatment Period until 31 March 2016.

As a result of the extended duration of study, the protocol has been modified to reflect that patient reported quality of life (QOL) measures will be analyzed through Week 84 of the study. These QOL assessments include the EORTC QLQ-C30 & GI.NET21 questionnaires and the subjective global assessment of symptoms associated with carcinoid syndrome (CS).

Modifications have also been made to: (1) update the Schedule of Events to reflect additional visits required for patients who elect to extend the Treatment Period to 31 March 2016; and (2) revise the maximum amount of blood to be collected from patients who attend the additional visits.

The following administrative changes have also been made:

- Document versioning has been updated to reflect the new amendment number and date
- The Table of Contents has been updated as appropriate

In response to these changes, the following sections have been revised as follows (changes are indicated in *italics*):

1. **SYNOPSIS – Secondary Objective, page 3 – This section was modified to reflect that patient reported QOL data will be collected and evaluated through Week 84. The revised section now reads:**

"To evaluate changes in patients' quality of life (QOL) *through Week 84*"

2. **SYNOPSIS – Duration of Participation, page 4 – This section has been modified to reflect the minimum study duration of 86 weeks for all patients and the optional**

extended Treatment Period for patients who are scheduled to complete the Treatment Period prior to 31 March 2016. The revised section now reads:

"*All patients will participate for at least* 86 weeks including Treatment and Follow-up. *Patients who are scheduled to complete the Treatment Period prior to 31 March 2016 will have the option to extend the Treatment Period until 31 March 2016.*"

3. **STUDY OBJECTIVES – Secondary Objective(s), Section 4.1.2, page 13 – This section was modified to reflect that patient reported QOL data will be collected and evaluated through Week 84. The revised section now reads:**

"The secondary objective of this study is to evaluate changes in patients' QOL *through Week 84*."

4. **INVESTIGATIONAL PLAN – Overall Study Design, Section 5.1, page 21 – This section was revised to reflect the minimum treatment duration of 84 weeks for all patients and the option for patients who are scheduled to complete the Treatment Period prior to 31 March 2016 to continue to receive study drug until 31 March 2016. The paragraph describing the patients' completion of a Follow-up Period was moved to immediately follow the inserted text. The following paragraph has been inserted, followed by the relocated paragraph:**

"*All patients will receive telotristat etiprate for at least 84 weeks. However, patients who will complete 84 weeks of treatment prior to 31 March 2016 may continue to receive telotristat etiprate in the trial until 31 March 2016.*

Upon completion or early withdrawal from treatment, all patients will be required to complete a 14-day Follow-up Period, during which no study drug will be administered."

5. **STUDY PROCEDURES – Subjective Global Assessment, Section 8.2.1.2, page 26 – This section was revised to reference Appendix A – Schedule of Events, which reflects that the Subjective Global Assessment will be conducted through Week 84. The following paragraph now reads:**

"A subjective global assessment of symptoms associated with CS will be evaluated using 2 methods at each visit *as indicated in Appendix A*."

6. **STATISTICAL METHODOLOGY – Efficacy Endpoints, Section 10.3.1, page 38 – This section was revised to more precisely reflect the study period over which patient reported QOL data will be evaluated. The following paragraph now reads:**

"Secondary efficacy endpoint is to evaluate changes in patients' QOL over *84 weeks* of therapy."

7. **APPENDIX A – Schedule of Events, Section 13, page 45 – The Schedule of Events has been updated to reflect the following changes:**

- Addition of Optional Extension Week 96 and Week 108 for patients scheduled to complete 84 weeks of participation in the study prior to 31 March 2016
- Dispensation of LX1606 at Week 84 and Optional Extension Week 96
- Update footnote to reflect new Optional Extension visits

Changes are indicated by highlighted cells in 'Revised Appendix A – Schedule of Events' table below.

Revised Appendix A – Schedule of Events

Procedure	Extension Period								Optional Extension		2-Week Follow-up[4]
	Baseline Day 1[1]	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84 / EOS	Week 96[6]	Week 108[6]	
Tolerance (days)	NA	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5
Inclusion/Exclusion criteria	X										
Medical history	X										
Physical examination incl. weight	X	X[3]	X[3]	X[3]	X	X[3]	X[3]	X	X[3]	X[3]	X[5]
Urine pregnancy test[2]	X	X	X	X	X	X	X	X	X	X	X
Hematology, Blood chemistry	X	X	X	X	X	X	X	X	X	X	X[5]
Urinalysis	X				X			X			X[5]
Chromogranin A	X				X			X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X
ECG	X				X			X			X[5]
Subjective Global Assessment	X	X	X	X	X	X	X	X			X
EORTC QLQ-C30 & GI.NET21	X		X		X		X	X			
Sleep and Depression Assessment	X	X	X	X	X	X	X	X	X	X	X
Plasma 5-HIAA	X	X	X	X	X	X	X	X	X	X	X
Dispensation of LX1606	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

[1]Eligibility will be determined at last visit of the original protocol; Day 1 will replace the next scheduled visit in the original protocol schedule. Visits should coincide with LAR injections for those patients receiving SSA therapy. [2]Females of child-bearing potential only. [3]Brief physical examination only (symptom-oriented, including weight). [4]Visit 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. [5]To be performed only if evaluation at Week 84/EOS is abnormal. [6]Week 96 and Week 108 visits may be performed up until 31 March 2016 for patients who would otherwise complete 84 weeks of treatment in the study prior to 31 March 2016.

8. Appendix B – Amount of Blood to be Collected from Each Patient, Section 14, page 46 – This section has been modified to reflect estimated volume of blood collected based upon changes reflected in Appendix A. Changes are indicated by highlighted cells. The revised table now reads:

Assessment		Sample volume (mL)	Number of samples*	Estimated total volume (mL)
Safety	Hematology	2	11	22
	Blood chemistry	6	11	66
Other	CgA	2	3	6
Pharmacodynamic	Plasma 5-HIAA	4	11	44
			Total	138
*Maximum number of samples is indicated				

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CLINICAL STUDY PROTOCOL

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
EudraCT Number	2013-002596-18
Investigational Phase:	3
Protocol Title:	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Study Name:	TELEPATH (**Tel**otristat **E**tiprate – Expanded Treatment for **Pat**ients wit**h** Carcinoid Syndrome)
Amendment 2 Date:	08 October 2014
Amendment 1 Date:	31 January 2014
Original Version Date:	14 June 2013
Sponsor:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: 001 (281) 863-3000 Safety Hotline: 001 (877) 372-3597 Safety Data Facsimile: 001 (832) 442-5917

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Investigator Signature Page

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
Protocol Title:	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Amendment 2 Date:	08 October 2014
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By my signature below, I hereby attest that I have read and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol and will conduct the study in accordance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance.

Additionally, I will not initiate this study without written and dated approval from the appropriate Institutional Review Board (IRB)/ Ethic Review Committee (ERC), and I understand that any changes in the protocol must be approved in writing by the Sponsor, the IRB/ERC, and, in certain cases the Food and Drug Administration (FDA) or other applicable regulatory agencies, before they can be implemented, except where necessary to eliminate hazards to patients.

Principal Investigator's Signature — Date

Principal Investigator's Name (Print)

[redacted]

Lexicon [redacted] (Signature) — Date

[redacted] M.D

Lexicon [redacted] (Printed Name)

1. Synopsis

Name of Study Drug	Telotristat etiprate
Protocol Number	LX1606.1-302-CS LX1606.302 (Abbreviated number)
Protocol Title	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Primary Objective	The primary objective of this study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate
Secondary Objective	To evaluate long-term changes in patients' quality of life (QOL)
Phase of Development	3
Methodology	The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate. Patients currently participating in any LX1606 Phase 2 carcinoid syndrome (CS) study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original study to LX1060.1-302-CS. Following confirmation of eligibility, patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label study drug at the same dose level and regimen as identified in their original study. Downward dose adjustment will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. Patients may return to the previous dosing at the discretion of the Investigator and in consultation with the Medical Monitor. Upon completion or early withdrawal from treatment, all patients will be required to complete a 14-day Follow-up Period, during which no study drug will be administered.

	A Data Safety Monitoring Board (DSMB) will review safety data quarterly throughout the study.
Number of Patients	Up to 100 patients are expected to participate in this study.
Patients	Eligible patients are defined as those that are currently participating in a Phase 2 or Phase 3 telotristat etiprate carcinoid syndrome study.
Number of Study Sites	Approximately 70 sites
Treatments	Telotristat etiprate, 250-mg tablet, administered at the same dose level and regimen identified in the patient's original study
Route of Administration	Oral
Duration of Participation	Up to 86 weeks including Treatment and Follow-up
Inclusion Criteria	Patients must meet all of the following criteria to be considered eligible to participate in the study: 1. Ongoing participation in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study 2. 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 entry are confirmatory in the absence of a clear postmenopausal history. 3. Ability and willingness to provide written informed consent prior to participation in any study-related procedure

Exclusion Criteria	Patients who meet any of the following criteria will be excluded from participating in the study: 1. Major protocol violations or telotristat etiprate tolerability concerns in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study 2. Positive pregnancy test 3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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 4. Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities
Statistical Methods	Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study and combined across all treated patients. Primary analyses of the data will be based on the Safety population which includes all patients treated on Day 1 of this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.
Study Assessments	<u>Safety</u> Safety assessments include monitoring of adverse events, clinical laboratory tests, vital signs measurements, 12-lead ECG, and physical examinations <u>Efficacy</u> Efficacy assessments will include patient reported quality of life measures as captured in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and the module specific for gastrointestinal symptoms of

	carcinoid neuroendocrine tumors (GI.NET21) and subjective global assessment of symptoms associated with CS Pharmacodynamics Pharmacodynamic (PD) assessments include determination of 5-HIAA levels in plasma
Efficacy Data Analysis	All efficacy and PD variables will be summarized descriptively and listed. Statistical tests and estimates of within patient effects for the efficacy and PD measures will be derived from application of a mixed linear model with repeated measures. The form of the model will be specific to measurement properties of the dependent variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model. Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to patients' telotristat etiprate dose level on Day 1 of this study.
Safety Data Analysis	Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group, and as needed, by study visit. Treatment-emergent adverse event 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 serious adverse events. Vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) 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.

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2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ALP	alkaline phosphatase
AST	aspartate transaminase
bid	twice daily
BM	bowel movements
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CgA	chromogranin A
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CS	carcinoid syndrome
CT	computed tomography
DSMB	Data Safety Monitoring Board
EC	enterochromaffin
ECG	electrocardiogram
ERC	Ethic Review Committee
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HEENT	head, eyes, ears, nose, and throat
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
IND	Investigational New Drug

Abbreviation	Definition
Continued on the next page	
IRB	Institutional Review Board
ITT	intent-to-treat
IMP	Investigational Medicinal Product
IWRS	interactive web response system
LAR	long-acting release
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MCP	multiple comparison procedure
MRI	magnetic resonance imaging
NET	neuroendocrine tumor
NRS	numeric rating scale
OOR	out-of-range
OTC	over-the-counter
PD	pharmacodynamic
PK	pharmacokinetic
qd	once daily
SAE	serious adverse event
SBS	short bowel syndrome
SOP	standard operating procedure
SSA	somatostatin analog
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse events
tid	3 times daily
TPH	tryptophan hydroxylase
ULN	upper limit of the normal reference range
WRS	Wilcoxon rank sum

Definitions of Terms

Term	Definition
LP-778902	active moiety of LX1606
LX1606	telotristat ethyl: the ethyl-ester prodrug of the active moiety LP-778902; a serotonin synthesis inhibitor being developed by Lexicon Pharmaceuticals, Inc.

Term	Definition
QTcF	corrected QT interval using Fredericia's formula

3. Introduction

3.1 Background on Telotristat Etiprate (LX1606) and Disease

Serotonin (5-HT) plays a critical role in regulating several major physiological processes of the gastrointestinal tract, including aspects of secretion, motility, inflammation and sensation. Enterochromaffin (EC) cells release 5-HT when the intestinal wall is stimulated by intraluminal pressure or chemicals. Through multiple classes of receptors, 5-HT is believed to initiate directly, or facilitate, peristaltic and secretory reflexes. 5-HT is also reportedly involved in the pathophysiology of various types of functional gastrointestinal (GI) disorders, valvular heart disease, and may play a role in the pathophysiology of inflammatory bowel disease (IBD).

Carcinoid tumors are mostly derived from EC cells of the midgut, and often produce and release large amounts of 5-HT. Such excess of 5-HT is believed to be responsible for the severe diarrhea and eventual valvular heart damage and mesenteric fibrosis in patients with carcinoid syndrome (CS).[1-3] Inhibition of tryptophan hydroxylase (TPH) activity in carcinoid tumors should lead to a reduction of peripheral 5-HT in afflicted patients and thus an amelioration of the pathophysiology and symptomology of CS. A peripheral TPH inhibitor, such as telotristat etiprate, should alleviate the symptoms due to excess 5-HT in carcinoid patients without central nervous system (CNS)-related adverse events (AEs).

Approximately 90% of the body's 5-HT is found in the EC cells of the GI tract, with the remainder distributed between the platelets and CNS.[4] TPH catalyzes the biopterin-dependent monooxygenation of tryptophan to 5-hydroxytryptophan, which is subsequently decarboxylated to form 5-HT. Expression of TPH is limited to a few specialized tissues: raphe neurons, pinealocytes, mast cells, mononuclear leukocytes, beta cells of the islets of Langerhans, and intestinal and pancreatic EC cells.[5] Two isoforms of the enzyme exist, TPH1 and TPH2. TPH1 is exclusively located in the EC cells of the GI tract and pineal gland and is the rate limiting enzyme responsible for the majority of systemic 5-HT production and is also responsible for 5-HT synthesis in carcinoid tumors. TPH2 is located in the central and enteric nervous systems and is the rate-limiting enzyme in the production of neuronal 5-HT.

The oral TPH inhibitor, telotristat etiprate, represents a novel approach to potentially lessen the pathophysiology of CS by reducing 5-HT levels via inhibition of TPH. Telotristat etiprate was designed specifically as a prodrug in order to gain greater systemic exposure, opening the potential application for indications in which hyperserotonemia is thought to contribute to the disorder, such as CS. Preclinical pharmacology studies of telotristat etiprate were designed to evaluate the compound’s mechanism of action and effects in vivo. Telotristat etiprate is the ethyl-ester prodrug of the active moiety LP-778902. Telotristat etiprate was

designed as a prodrug in order to enhance peripheral exposure without crossing the blood-brain barrier. In vivo, telotristat etiprate is readily converted through esterase activity to its corresponding acid, LP-778902. LP-778902 has an in vitro potency of 0.028 μM on purified human TPH1 enzyme and 0.032 μM on purified human TPH2 enzyme. Therefore, telotristat etiprate is a robust inhibitor of TPH both in vitro and in vivo and has been shown in Phase 2 studies to provide clinical benefit to patients with carcinoid tumors and associated CS.

Telotristat etiprate is being developed to manage GI symptoms and possibly other symptoms associated with CS. Currently, the standard of care for patients with CS is symptom management using somatostatin analogs (SSA), which are available in both short- and long-acting release (LAR) formulations. Somatostatin analogs such as octreotide are indicated for the control of flushing, diarrhea, and other symptoms associated with CS. Common side effects of the long-acting depot form of the drug are pain at the site of the injection, reported in as many as 30 to 50% of carcinoid patients at the 20 and 30 mg dose levels, and less commonly, stomach cramps, nausea, vomiting, headaches, dizziness, and fatigue.[6] Other side effects identified in the product labeling include biliary tract abnormalities (gallstones, sludge, and dilatation), hypothyroidism, dietary fat malabsorption, and hyper or hypoglycemia.[7] In addition to the morbidity associated with parenterally administered agents, tachyphylaxis will occur in the majority of patients, resulting in recurrent symptoms.

There are currently no specific oral treatments indicated for the management of symptoms associated with CS. As a result of the morbidity associated with SSAs and the associated tachyphylaxis, there is an unmet medical need to provide symptom management and modify the pathophysiology of patients with metastatic CS. Inhibition of the excessive 5-HT produced by these tumors with an orally delivered agent such as telotristat etiprate could provide significant benefit as an additional treatment option for patients and clinicians.

3.2 Clinical Trials of Telotristat Etiprate (LX1606) in Humans

Telotristat etiprate has been studied in single/multiple doses in Phase 1 studies, approximately 117 healthy volunteers participated in Phase 1 trials with 96 subjects receiving telotristat etiprate and 21 subjects receiving placebo. In addition, 37 patients with CS have received telotristat etiprate during the clinical development program in Phase 2. An additional 59 patients with ulcerative colitis have been enrolled into an ongoing Phase 2 study to evaluate telotristat etiprate versus placebo in patients with ulcerative colitis experiencing active flares.

3.2.1 Phase 1 Studies

LX1606.1-101-NRM utilized telotristat etiprate as a single oral dose and was noted to be safe and well tolerated up to doses of 1,000 mg. At doses of ≥1,000 mg, an increase in GI AEs was observed, which were assessed as at least possibly related to study drug. These AEs led

to a decision not to escalate the dose beyond 1,500 mg. No serious adverse events (SAEs) or deaths were reported and no patient discontinued due to an AE. Twenty-three patients experienced at least 1 AE. The majority of the AEs were assessed as mild. The most common AEs were diarrhea and nausea. Random out-of-range laboratory values at various time points in several patients occurred without any apparent trend. There were no other clinically significant vital signs, laboratory or physical examination findings.

LX1606.1-102-NRM utilized telotristat etiprate as multiple oral doses over 14 days and was tolerated up to the maximum dose assessed, 500 mg tid; 1,500 mg total dose daily. Most AEs were mild, the most common being nausea and headache; all resolved. Most AEs were at least possibly related to study treatment. Four AEs required treatment with concomitant medication, 3 AEs of constipation and 1 of headache. No deaths or SAEs were reported. One patient was discontinued due to an AE of abnormal liver function. There were no apparent trends or clinically significant findings observed upon review of vital signs and electrocardiogram (ECG) data. There were no clinically significant abnormal physical examination findings.

Overall, in LX1606.1-102-NRM, treatment with telotristat etiprate was associated with mild elevations, generally ≤2x the upper limit of normal (ULN), in alanine transaminase (ALT) and aspartate transaminase (AST), with elevations in values observed earlier in the higher dose cohorts. Results were assessed as clinically significant for only 1 patient, in Cohort 4, who was withdrawn on Day 10. The trend was most pronounced in Cohort 5, in which 5 out of 6 patients who received telotristat etiprate had increases in ALT values which were above normal range and 4 patients had increases in AST values which were above normal range at Day 14. Mean increases in ALT and AST appeared earlier in the study for Cohorts 4 and 5 than in the other cohorts, and were noted for all cohorts by Day 12. All patients had normal ALT and AST values at Baseline and most elevated transaminases returned to normal range within 48 hours after the last dose of study drug. No changes in alkaline phosphatase (ALP) or total bilirubin were observed in any patient.

LX1606.1-103-NRM evaluated 2 oral formulations of telotristat etiprate in an open-label crossover study. Each formulation was given as a single oral dose followed by a 5-day washout and then patients were given a single oral dose of the second formulation. During this study, there were no deaths or SAEs reported and no AEs lead to discontinuation. The most commonly reported AE was diarrhea. No clinically significant observations or changes in other safety parameters (eg, clinical laboratory evaluations, vital signs, physical examinations, ECGs, and AEs) were identified in the patient population during the study conduct.

LX1606.1-104-NRM was designed to evaluate the pharmacokinetics, metabolism, and routes and extent of elimination of telotristat ethyl and its primary metabolite (LP-778902) in 8 healthy male subjects after a single oral dose of 500 mg radio-labeled telotristat etiprate (14C-LX1606). This study has been completed and the results will be discussed in the annual update of the Investigator Brochure.

3.2.2 Phase 2 Studies

LX1606.1-202-CS was a randomized, double-blind, placebo-controlled, multiple ascending dose study conducted in 2 parts in order to evaluate a total of 23 patients at a dose range of 450 to 1500 mg given as 150, 250, 350, or 500 mg tid (telotristat etiprate or matching placebo) on a background therapy of octreotide. In Part 1, 16 patients were randomly assigned 3:1 into 4 sequential cohorts. Each cohort evaluated 1 of the following daily doses given as 150, 250, 350, or 500 mg tid over a course of 4 weeks. During the study, all patients continued on a stable-dose background therapy of octreotide. In Part 2, an additional 7 patients were randomly assigned 3:1 in order to evaluate 500 mg tid, the highest tolerated dose as determined in Part 1. Upon completion of the initial 4-week portion, eligible patients had the option to continue into an open-label Extension Period.

There was 1 treatment emergent SAE assessed as possibly related to study drug which occurred in the 350 mg tid dose group. The patient had a history of nausea and vomiting and was hospitalized for exacerbation of these conditions.

Telotristat etiprate was generally well tolerated with no evidence of dose-limiting tolerability. Adverse events were mostly mild to moderate and with similar frequencies between treatment groups and placebo. No significant changes in vital signs, ECG, or physical exam findings were noted after administration of telotristat etiprate at any dose level. The most common AEs were GI-related and reported as diarrhea, nausea, and abdominal pain, respectively. The modest elevations in transaminases seen in the Phase 1 multiple ascending dose study (LX1606.1-102-NRM) were not apparent in this 4-week study in patients with CS.

Patients that received telotristat etiprate achieved a clinical response (28%) defined as at least a 30% reduction in bowel movements (BMs) for at least 2 weeks; a biochemical response (56%) defined as at least a 50% reduction or normalization of urinary 5-hydroxyindoleacetic acid (5-HIAA); and reported adequate relief at Week 4 (46%) while no placebo patients experienced clinical response, biochemical response, or adequate relief.

LX1606.1-203 was an open-label, serial ascending, multiple dose, individual titration study that evaluated the same dose ranges as the LX1606.1-202-CS study in a total of 15 patients. Patients were serially escalated to the next dose level every 2 weeks until a maximally tolerated dose or 500 mg tid was reached. Once a dose had been determined, the patient

would remain on the dose for an additional 4 weeks. Patients then had the option to continue into an Extension Period.

Telotristat etiprate was generally safe and well-tolerated in subjects with CS in the LX1606.1-203 study. Most AEs were mild to moderate in severity and assessed as unrelated to study drug. Events in the Gastrointestinal Disorders system organ class were common, as is anticipated with the underlying illness.

Statistically significant reductions from Baseline in the mean number of BMs/day were observed in this study throughout the entire dose-escalation and stable-dose phases, as were improvements in stool form. Telotristat etiprate produced an improvement in global assessment of GI symptoms associated with CS in the majority of subjects (12 of 15 subjects, 80%) across the 12-week period. The global assessment of GI symptoms was based on 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 BM, abdominal pain or discomfort?” In addition, subjects experienced statistically significant decreases in the mean daily number of cutaneous flushing episodes.

Thirteen subjects (86.7%) experienced a complete biochemical response (defined as a ≥50% reduction from Baseline in u5-HIAA levels at 1 or more time points). Consistent with the proposed mechanism of action for telotristat etiprate, a complete biochemical response correlated closely with measures of clinical response, such as number of bowel movements per day.

LX1606.1-204-UC evaluated patients with active flares of ulcerative colitis. Doses under evaluation are 500 mg once daily (qd) and 500 mg tid vs. placebo; 59 patients were enrolled for an 8-week treatment period. This study has been completed and the results will be discussed in the annual update of the Investigator Brochure.

Detailed information regarding the completed clinical studies can be found in the Investigator Brochure.[8]

3.2.3 Ongoing Studies

The open-label extension portions in LX1606.1-202-CS and LX1606.1-203-CS remain ongoing.

LX1606.1-301-CS is intended to evaluate patients who are currently on a background of SSA therapy and still experiencing breakthrough symptoms such as an increased frequency of BMs ≥4 per day on average: (1) the efficacy of telotristat etiprate on reducing the number of BMs; (2) the efficacy of telotristat etiprate on a number of clinically relevant secondary endpoints; and, (3) the safety of telotristat etiprate over the 12-week double-blind portion

(Treatment Period) of the study. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period (Extension Period).

LX1606.1-303-CS is intended to evaluate patients with carcinoid syndrome whose primary symptoms are not GI related and may be naïve to SSA therapy: (1) the safety of telotristat etiprate over the 12-week double-blind portion (Treatment Period) of the study; (2) percent (%) change from Baseline in 24-hour u5-HIAA levels at Week 12; (3) the effects of telotristat etiprate on a number of clinically relevant secondary endpoints. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period.

3.3 Rationale for Current Study

3.3.1 Rationale for Selection of Dose

The dose levels of telotristat etiprate selected for this study are consistent with prior clinical study experience and based upon clinical safety and pharmacodynamic (PD) data from 2 Phase 2 multiple ascending-dose studies in patients with symptomatic CS (LX1606.1-202-CS and LX1606.1-203-CS).

Based upon observations noted in Section 3.2, it is anticipated that the doses to be utilized in this protocol will be safe and well tolerated and may provide clinical benefit to patients with CS.

3.3.2 Benefit/Risk Assessment

Clinical experience with telotristat etiprate (treated subjects) consists of completed single and multiple ascending dose studies in 96 normal subjects (44 in single dose studies and 52 in the multiple dose study), 2 Phase 2 studies (37 patients with symptomatic CS) and 2 ongoing Phase 3 studies in patients with symptomatic CS.

In healthy volunteer studies, single doses up to 1000 mg were found to be generally well tolerated, while at the 1500 mg dose level GI-related adverse events increased. A similar adverse event profile was observed after multiple dose administration over 14 days with GI events predominating. Mild, dose-dependent increases in hepatic transaminase levels (≤2 x ULN) were observed with increased frequency in relation to dose, with 1 subject requiring withdrawal from therapy at the 500 mg bid dose level. Most subjects that were observed to have increased transaminase levels did not exceed >2 x ULN. No abnormalities in total bilirubin were observed at any dose level. GI events have been the most commonly observed events to date. The adverse event profile in normal subjects may differ significantly from what is observed in patients with hyperserotonemia. All adverse events resolved without sequelae. In addition, there were no significant changes in vital signs or ECG. No physical

examination abnormalities were noted in studies to date. There were no serious adverse events reported in healthy volunteers.

In patients with CS, dose escalations have proceeded up to and including 500 mg tid. To date, there has been no evidence of dose-limiting intolerability. Dose levels have been generally well tolerated with no evidence to suggest elevations in hepatic transaminase levels. Based upon observations from preclinical and clinical studies conducted to date, it is anticipated that orally administered telotristat etiprate will be well tolerated at dose levels required to influence peripheral 5-HT production in patients with symptomatic CS. Potential adverse events primarily involve the GI tract, and could include alterations in gut motility, nausea, vomiting, diarrhea, constipation, abdominal bloating, and/or pain. Regular and ongoing clinical and laboratory assessments should detect any of these events, and depending on the type of event, further dose adjustment or discontinuation from the trial would occur. Although CNS effects are not anticipated at dose levels planned for evaluation, standard adverse event questioning and/or physical examination should reveal any subtle CNS findings. As elevations in hepatic transaminase levels were observed with multiple dosing in normal subjects, monitoring clinical laboratory tests of hepatic function will be incorporated into clinical trials conducted in CS patients.

Treatment has the potential to improve several signs and symptoms of CS. The Phase 2 clinical trial results indicated that treatment may lead to improvements in BM frequency, stool consistency, urgency, abdominal pain, diarrhea, flushing, and reductions in 5-HIAA. These potential benefits relate to a unique mechanism of action. Symptomatic improvement may lead to a better quality of life (QOL) for patients with few treatment options available, and a reduction in serotonin may help reduce the risk of carcinoid heart disease. Overall the benefit/risk profile of telotristat etiprate is expected to be favorable for participation in this clinical study.

3.4 Rationale for Study Design and Control Groups

Currently, no approved therapy exists for the treatment of symptoms driven by underlying serotonin pathophysiology of CS in patients whose disease is refractory to SSA therapy or for those patients who are unable to tolerate SSA therapy or who are unwilling to take SSA therapy.

This study will allow for continued access to telotristat etiprate after patients have completed the required study visits in ongoing Phase 2 and Phase 3 studies. Continuation of CS patients into this study will allow for the collection of additional long-term safety and efficacy data, while providing access to patients who may be receiving benefit. The treatment duration is

supported by results of chronic toxicology studies (6-month rat and 9-month dog) and the current safety profile from completed and ongoing clinical trials.

4. Study Objectives

4.1 Efficacy Objectives

4.1.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

4.1.2 Secondary Objective(s)

The secondary objective of this study is to evaluate changes in patients' QOL.

4.2 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

5. Investigational Plan

5.1 Overall Study Design

The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate.

Patients currently participating in any LX1606 Phase 2 CS study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original protocol to LX1060.1-302-CS.

Following confirmation of eligibility, patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label LX1606 at the same dose level identified in the original study.

Downward dose adjustment will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be

discontinued from the study. Patients may return to the previous dosing at the discretion of the Investigator and in consultation with the Medical Monitor.

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

A Data Safety Monitoring Board (DSMB) will review safety data quarterly throughout the study.

6. Study Population

Adult patients who are currently participating in ongoing Phase 2 or Phase 3 telotristat etiprate CS clinical protocols will be enrolled into the study. Up to 100 patients are expected to enroll in this study. Approximately 70 sites worldwide will participate in the study. Patients may continue allowed medications as background therapy provided they remain on stable-doses throughout the Treatment Period.

6.1 Inclusion Criteria

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

1. Ongoing participation in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study
2. 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 Baseline Day 1 are confirmatory in the absence of a clear postmenopausal history.
3. Ability and willingness to provide written informed consent prior to participation in any study-related procedure.

6.2 Exclusion Criteria

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

1. Major protocol violations or telotristat etiprate tolerability concerns in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study
2. Positive pregnancy test
3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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
4. Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities

6.3 Criteria for Stopping Treatment/Study Withdrawal

A patient may also be discontinued from the study for the following medical or administrative reasons:

- Withdrawal of consent by the patient or legal guardian
- Noncompliance, including refusal of the study medication and/or failure to adhere to the study requirements as in the study protocol
- Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study
- The Sponsor terminates the study (Section 6.4)
- Pregnancy (Section 9.4.1)

Note: If a patients voluntarily withdraws or is discontinued from study treatment before completing the entire duration of the Treatment Period, 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 Appendix A – Schedule of Events and agree to report any SAEs (Section 9.2) that occur within 30 days following the last dose of telotristat etiprate.

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 Case Report Form (CRF).

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.

6.4 Criteria for Termination of the Study

If the 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 carcinoid syndrome or any other indication 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; and,
- Insufficient adherence to protocol requirements.

Study termination and Follow-up would be performed in compliance with applicable governing body regulations.

6.5 Clinical Stopping Rules

Criteria for individual patient withdrawal or study termination are summarized in Sections 6.3 and 6.4, respectively.

6.6 Method of Assigning Patients to Treatment

Patients will enter the study at the same dose level and regimen as identified in the prior Phase 2 or Phase 3 CS study. Randomization will not be used to assign patients to study treatments.

6.7 Blinding and Unblinding of Study Medication

This is an open-label study.

6.8 Replacement of Patients

Patients who do not complete the study will not be replaced.

7. Treatment

7.1.1 Telotristat Etiprate (LX1606)

7.1.1.1 Identity

Telotristat etiprate (LX1606 hippurate) is the salt form of the drug substance. LX1606 hippurate is a crystalline white to off-white to tan solid with a melting point of 147°C. LX1606 is insoluble in water within the pH range of 5 to 9 (≤2 mg/L). It undergoes hydrolysis under strongly basic or strongly acidic conditions. The solubility of LX1606 hippurate in water is about 22 mg/L at 25°C.

Study drug dosage form consists of white coated debossed oval tablets containing 250 mg LX1606.

7.1.1.2 Packaging, Labeling, and Storage

Patients will receive 250-mg telotristat etiprate tablets packaged in 100 cc high density polyethylene bottles with child-resistant polypropylene screw caps and heat-induction seal liners.

Telotristat etiprate should be stored between 15 to 25°C (59 to 77°F).

7.2 Prior and Concomitant Medications

7.2.1 Prior Medications

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

7.2.2 Concomitant Medications

All concomitant medications taken by patients during the study will be recorded on the CRF. Treatment with prescription or over-the-counter (OTC) antidiarrheal therapy, bile acid sequestrants, or pancreatic enzyme is permitted; however, the use of these concomitant therapies should be associated with a documented history of disease (eg, fat malabsorption, bile acid malabsorption, or steatorrhea).

Medical management of patients and their concomitant medications is allowed at the discretion of the Investigator. However, should the need arise to modify/adjust a patient's therapy due to a concern for patient safety and/or tolerability 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.

7.2.3 Prohibited Medications or Concomitant Therapy

None

7.3 Administration of Study Medication

All patients will be instructed to take the study medication with food. "With food" means taking telotristat etiprate 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.

Study medication and instructions will be dispensed to patients at each visit as described in the schedule of study procedures (Appendix A).

7.3.1 Treatment Compliance

Patients will be asked to bring their unused or unopened study medication to each visit (Appendix A). At each visit and in the presence of the patient, study site personnel will count returned tablets and reconcile the counts against planned number of doses for that interval. Site personnel will clarify any discrepancy and record this information within the CRF.

Patients must maintain at least 75% compliance in dosing to be deemed as compliant. In the event of a missed or vomited dose, patients will take their subsequent dose of study drug at the next scheduled time point, following the tid dosing regimen of approximately every 6 hours. A dose outside of a 3-hour window should be considered missed. Missed or vomited doses will not be made up.

7.4 Dose Adjustment

Downward dose adjustment of telotristat etiprate will be permitted if evidence of intolerability emerges. After a period at the lowered dose level, patients may resume the previous dosing level at the discretion of the Investigator after consultation with the Medical Monitor. Patients who experience intolerability at the 250 mg tid dose level **must** be discontinued from study treatment. Interruptions or delays in dosing throughout the entire study may be permitted after consultation with the Medical Monitor, at which time the patient will be reassessed for study continuation, dosage reduction, or discontinuation.

8. Study Procedures

A schedule of study assessments is provided in Appendix A.

8.1 Restrictions during Study

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

8.2 Description of Study Assessments

8.2.1 Efficacy Assessments

Efficacy assessments include the patient reported QOL measures; EORTC QLQ-C30 (Appendix D) & GI.NET21 (Appendix E) questionnaires and subjective global assessment of symptoms associated with CS.

A description of the efficacy assessments is provided below.

8.2.1.1 EORTC QLQ-C30 & GI.NET21

Patients will complete the questionnaires during each visit as indicated in Appendix A.

8.2.1.2 Subjective Global Assessment

A subjective global assessment of symptoms associated with CS will be evaluated using 2 methods at each visit.

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.”

8.2.2 Clinical Laboratory Assessment

Clinical laboratory assessments will consist of hematology (complete blood count [CBC] with differential and platelet counts), blood chemistry (complete metabolic panel and liver function tests), and urinalysis. 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 9.1 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.

8.2.2.1 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 >3 x 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 >3 x ULN (in patients with previous abnormal liver-test results)

OR

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

For any such event, the Investigator should discuss the Follow-up approach with the 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 function test values 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 continued study participation.

8.2.3 Pharmacodynamic Assessments

8.2.3.1 Plasma 5-HIAA

Fasting blood samples (≥6 hours) 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.

8.2.4 Safety Assessments

In addition to the clinical laboratory assessments described in Section 8.2.2, monitoring of AEs is also considered a safety assessment and is described in detail in Section 9. Clinically

significant changes compared with Baseline findings for these variables should be reported as AEs on the CRF. Clinically significant changes compared with Baseline values, which are determined to be AEs, 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.

8.2.4.1 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 with 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. All measurements should be 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 Appendix A.

8.2.4.2 Physical Examinations

Complete physical examinations will be performed as outlined in Appendix A. 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, weight will be captured during each physical examination. Efforts should be made to standardize 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.

8.2.4.3 Electrocardiograms

Electrocardiograms (12-lead ECGs) will be performed as specified in Appendix A.

8.2.4.4 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.

8.2.4.4.1 Central Nervous System Events

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

8.2.4.4.1.1 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.

8.3 Other Assessments

8.3.1 Chromogranin A (CgA)

Blood samples for measurement of chromogranin A (CgA) levels will be collected as indicated in Appendix A.

8.3.2 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 (eg, PET, CAT, MRI scans of tumor), or Investigator assessment of disease status, while the patient is enrolled in the study.

8.3.3 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.

8.4 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.

8.4.1 Blood Collection

An attempt should be made to collect all samples as per the schedule outlined in Appendix A. Any portion of samples remaining after the required tests for this study have been completed will be destroyed.

The estimated amount of blood scheduled for collection per patient, over the course of the study, may be found in Appendix B.

9. Safety Reporting

Medical queries should be addressed to the Medical Monitor responsible for the region.

Sites in North America:

[redacted], MD
[redacted]
INC Research
[redacted]
Phone: [redacted]

Sites outside North America:

[redacted], MD, PhD
[redacted]
INC Research
[redacted]
The Netherlands
Phone: [redacted]
Mobile: [redacted]

[redacted], MD, PhD
Medical Monitor
INC Research, LLC
[redacted]
Czech Republic
Phone: [redacted]
Fax: [redacted]

After-hours 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. **Note**: These calls are not toll-free.

9.1 Adverse Events

It is the responsibility of the Investigator to document all AEs that occur during the study.

Adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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 considered related to the study medication. This definition includes an exacerbation of preexisting 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 9.2) 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 study drug 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

9.2 Serious Adverse Events (SAEs)

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

1. Death
2. A life-threatening adverse event;
3. Inpatient hospitalization or prolonging of an existing hospitalization (see Section 9.2.1 for information on hospitalization as an SAE);

4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or

5. A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

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: [redacted]
Belgium: [redacted]
Brazil: [redacted]
France: [redacted]
Germany: [redacted]
Israel: [redacted]
Italy: [redacted]
Netherlands: [redacted]
Spain: [redacted]
Sweden: [redacted]
United Kingdom: [redacted]

Email Address (in case of fax failure): [redacted]

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.

9.2.1 Hospitalization as an SAE

Hospitalization is defined as any in-patient overnight stay in a hospital. A hospitalization in and of itself does not constitute an SAE. The condition which caused the hospitalization must be evaluated and determined to be an AE. Although an AE which results in hospitalization is an SAE, patients are hospitalized for a variety of reasons which may not be associated with or considered an SAE (eg, convenience, logistics, preference, etc). Therefore, each case of hospitalization must be evaluated separately.

For example, the following would not be considered SAEs:

- Hospitalization for a preexisting condition which did not worsen (eg, cataract surgery)
- Hospitalization solely for a procedure or treatment that was not performed to treat an AE
- Hospitalization for a condition that does not normally require treatment, but electively done (eg, cosmetic surgery)
- Hospitalization strictly for convenience reasons or observations (eg, procedures only performed in a hospital because of the distance the subject lives from the hospital)

9.3 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.

9.4 Precautions

9.4.1 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 9.2 for contact information).

10. Statistical Methodology

10.1 Determination of Sample Size

No formal sample size calculation was made. The number of patients expected to participate in this study was calculated from estimated enrollment rates from other carcinoid cancer trials employed in the LX1606 clinical program.

10.2 Analysis Populations

Per protocol: A Per Protocol population will consist of those patients that receive study treatment and have no major protocol violation that would interfere with the collection or interpretation of the efficacy data. The primary analyses of efficacy will be based on the safety population; 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 during this study.

10.3 Study Endpoints

10.3.1 Efficacy Endpoints

The primary efficacy endpoint is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

Secondary efficacy endpoint is to evaluate changes in patients' QOL over multiple years of therapy.

10.3.2 Safety Endpoints

Safety endpoints are as follows:

- Incidence of TEAEs, suspected adverse reaction, AEs leading to discontinuation from the study, SAEs, and deaths
- Actual and change from Baseline in clinical laboratory results
- Actual and change from Baseline in vital signs results
- Actual and change from Baseline in physical examinations
- Actual and change from Baseline in ECG findings

10.4 Statistical Methods

Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study and combined across all treated patients. All data will be listed.

Primary analyses of the data will be based on the Safety population which includes all patients treated with any fraction of study drug during this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. This dataset will include the Safety

population, but limited to those patients that have at least one assessment post Day 1 and do not have any protocol violations that would interfere with collection or interpretation of the data. The Per Protocol analysis will be applied to the QOL measures, subjective global assessment, and plasma 5-HIAA values.

Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.

10.4.1 Efficacy Analyses

All efficacy and PD variables will be summarized descriptively and listed.

Statistical tests and estimates of within patient effects for these measures will be derived from application of a mixed linear model with repeated measures. The model will be generalized to handle missing data and specific to the measurement properties of the dependent variable. There is no plan to impute data for missing observations for any variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model.

Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to how patients were dosed on Day 1 of this study.

10.4.2 Safety Analyses

Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group (corresponding to the LX1606 dose given on Day 1), pooled across all patients, and as needed, by study visit. All safety data will be listed.

Treatment-emergent adverse event 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 serious adverse events.

Vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) 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 and summarized.

10.4.2.1 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.

10.4.2.2 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 using descriptive statistics. Summaries of shifts from Baseline to abnormal clinical laboratory results will also be provided. Actual and change from Baseline in chromogranin A levels will be summarized descriptively as well.

10.4.2.3 Vital Sign Measurements

Actual and changes from Baseline (Day 1) in vital signs results will be summarized by using descriptive statistics.

10.4.2.4 Electrocardiograms

Clinically significant changes in ECGs compared to Baseline, as determined by the Investigator, will be summarized by using descriptive statistics. Actual and change from Baseline (Day 1 predose values) to each time point in corrected QT interval (QTcF) will be summarized as well.

10.4.3 Pharmacodynamic Analyses

Analysis and summarization of the plasma 5-HIAA data are described in Section 10.4.1.

10.4.4 Baseline Characteristics and Other Summaries

Treatment group differences will be summarized descriptively for demographic data, prior and concomitant medications, treatment compliance, and final disposition. Data collected from assessments of tumor status, when available, will be listed.

Protocol deviations will provided as listings.

10.4.5 Interim Analysis

An independent DSMB will be charged with reviewing interim safety data on a quarterly basis 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 may be analyzed and reported in multiple phases. The first report will summarize data obtained from all patients providing information up to a specified data cut-off point. The following reports will update the initial report by including data from the remaining portion of the study. 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.

11. Study Management

The Investigator is responsible for completing and maintaining adequate and accurate CRFs and source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, and discharge summaries.

All data on the CRF must be recorded in accordance with the CRF guidelines. If a correction is necessary, it should be made by the Investigator or a designated qualified individual as specified within the guideline. All CRFs should be completed in their entirety and stored in a secure location. The Investigator must sign the Investigator's statement in each patient's CRF indicating that the data reported are accurate.

At the study site, clinical research associates will verify 100% of CRFs in their entirety against source documentation. Computer programmed edit checks will be run against the database to check for discrepancies and reasonableness of the data, and the safety database will be reconciled with the clinical database. All issues resulting from the computer generated checks and the safety database reconciliation will be resolved according to standard data management practices in conjunction with the Sponsor, clinical study personnel, and the study Investigators.

11.1 Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the

Sponsor's study monitors will contact the study site via visits to the site, telephone calls, and/or letters in order to review study progress, CRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of patients, patient recruitment, patient compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by patients, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

The Investigator must make study data accessible to the clinical monitor, to other authorized representatives of the Sponsor, and to regulatory inspectors

11.2 Audits and Inspections

The Sponsor, regulatory authority, or IRB/ERC may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a Sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

11.3 Amendments

Any amendments to the protocol will be written and approved by the Sponsor. All amendments must be submitted to the IRB/ERC for approval prior to implementing the changes. In some instances, an amendment may require changes to the informed consent form, which also must be submitted for IRB/ERC approval prior to administration to patients. If any changes to the CRF are required, the Sponsor will issue supplemental or revised CRF pages.

11.4 Record Keeping

11.4.1 Drug Accountability

The Investigator must maintain accurate records of receipt of study drug, dispensing information (date, lot, and dose for each patient), and the prompt return or destruction of unused supplies. If the Investigator cannot account for all clinical supplies at the termination of the study, a written explanation must be provided.

11.4.2 Health Insurance Portability Accountability Act of 1996 and Subsequent Updates

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 Code of Federal Regulations (CFR) Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation and any applicable updates). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

11.4.3 Financial Disclosure

The Investigator shall provide to the Sponsor sufficient accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the FDA and/or other applicable regulatory agencies. The Investigator shall promptly update this information if any relevant changes occur in the course of the study or for 1 year following completion of the study.

11.4.4 Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 11) to ensure data integrity. “Original” in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

11.4.5 Retention of Study Documents

According to 21 CFR Part 312.62 and ICH E6, study-related records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor.

The Investigator must not destroy any study-related records without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor must be contacted to arrange alternative record storage options.

12. Administrative Structure of the Study

The study will be monitored by Sponsor personnel or Sponsor representative. The following functions for this study will be performed by organizations designated by the Sponsor: data management and statistical analysis, including PD analysis and reporting.

13. Appendix A – Schedule of Events

Procedure	Extension Period								2-Week Follow-up[4]
	Baseline Day 1[1]	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84 / EOS	
Tolerance (days)	NA	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5
Inclusion/Exclusion criteria	X								
Medical history	X								
Physical examination incl. weight	X	X[3]	X[3]	X[3]	X	X[3]	X[3]	X	X[5]
Urine pregnancy test[2]	X	X	X	X	X	X	X	X	X
Hematology, Blood chemistry	X	X	X	X	X	X	X	X	X[5]
Urinalysis	X				X			X	X[5]
Chromogranin A	X				X			X	
Vital signs	X	X	X	X	X	X	X	X	X
ECG	X				X			X	X[5]
Subjective Global Assessment	X	X	X	X	X	X	X	X	X
EORTC QLQ-C30 & GI.NET21	X		X		X		X	X	
Sleep and Depression Assessment	X	X	X	X	X	X	X	X	X
Plasma 5-HIAA	X	X	X	X	X	X	X	X	X
Dispensation of LX1606	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

[1]Eligibility will be determined at last visit of the original protocol; Day 1 will replace the next scheduled visit in the original protocol schedule. Visits should coincide with LAR injections for those patients receiving SSA therapy. [2]Females of child-bearing potential only. [3]Brief physical examination only (symptom-oriented, including weight). [4]Visit 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. [5]To be performed only if evaluation at Week 84/EOS is abnormal.

14. Appendix B – Amount of Blood to be Collected from Each Patient

Assessment		Sample volume (mL)	Number of samples*	Estimated total volume (mL)
Safety	Hematology	2	9	18
	Blood chemistry	6	9	54
Other	CgA	2	3	6
Pharmacodynamic	Plasma 5-HIAA	4	9	36
			Total	114
*Maximum number of samples is indicated				

15. Appendix C – EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Lexicon

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

16. Appendix D – EORTC QLQ - GI.NET21

ENGL201

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31. Did you have hot flushes?		1	2	3	4
32. Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33. Did you have night sweats?		1	2	3	4
34. Did you have abdominal discomfort?		1	2	3	4
35. Did you have a bloated feeling in your abdomen?		1	2	3	4
36. Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37. Have you had acid indigestion or heartburn?		1	2	3	4
38. Have you had difficulties with eating?		1	2	3	4
39. Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40. Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41. Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42. Were you concerned about disruption of home life?		1	2	3	4
43. Have you worried about your health in the future?		1	2	3	4
44. How distressing has your illness or treatment been to those close to you?		1	2	3	4
45. Has weight loss been a problem for you?		1	2	3	4
46. Has weight gain been a problem for you?		1	2	3	4
47. Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48. Have you had aches or pains in your muscles or bones?		1	2	3	4
49. Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:					
50. Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51. Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

17. Appendix E – Ethical Standards

Ethics and Regulatory Considerations

This study will be conducted according to GCP, 21 CFR Part 50, (Protection of Human Subjects), 21 CFR Part 56 (Institutional Review Boards), International Conference on Harmonisation Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

General Instructions

The FDA regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to GCP regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- Current FDA Guideline for the Monitoring of Clinical Investigations
- Current Guidance for Institutional Review Boards and Clinical Investigators
- ICH E6 – Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

Studies conducted in the European Union are also regulated by Volume 10 of the publications "The rules governing medicinal products in the European Union".

Copies of these materials are available from the Sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- the study is conducted with diligence and in conformance with the protocol in such a way as to insure the integrity of the findings;
- the potential benefits of the research justify the risks.

Lexicon Pharmaceuticals, Inc. is the Sponsor of the IND. The Sponsor is responsible for the following:

- selecting qualified Investigators,
- providing Investigators with the information they need to properly conduct an investigation,
- ensuring proper monitoring of the investigation,
- ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- maintaining the IND, and
- ensuring that regulatory authorities and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied
- ensuring the study is conducted in accordance to FDA and ICH guidelines and all applicable regulations

18. Appendix F – Investigator Obligations

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56 and ICH E6, the study protocol and the final version of the subject informed consent form will be approved by the IRB/ERC before enrollment of any subjects. The opinion of the IRB/ERC will be dated and given in writing. A copy of the letter of approval from the IRB/ERC and a copy of the approved informed consent form will be received by the Sponsor prior to shipment of study medication supplies to the Investigator.

The Investigator will ensure that the IRB/ERC will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to subjects. The Investigator will also ensure that no changes will be made to the protocol without IRB/ERC approval.

As a part of the IRB/ERC requirement for continuing review of approved research, the Investigator will be responsible for submitting periodic progress reports to the IRB/ERC at intervals appropriate to the degree of subject risk involved, but no less than once per year.

Written informed consent must be given freely and obtained from every subject prior to clinical trial participation. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

As described in GCP guidelines, study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (eg, loss of medical licensure, debarment). Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

Principal Investigators must provide Lexicon with a fully executed Form FDA 1572 (statement of Investigator) and all updates on a new fully executed Form FDA 1572.

Principal Investigators must provide Lexicon with his/her own curriculum vitae and current curriculum vitae for each sub-Investigator listed on Form FDA 1572.

Protection of Human Subjects (21 CFR Part 50 and ICH E6)

Informed consent must be obtained from every subject before entry into a clinical study. It must be given freely and not under duress. Consent must be documented by use of an IRB/ERC-approved consent form and signed by the subject or the subject's legally authorized representative. The US Department of Health and Human Services suggests that when minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent, his signature should also be included. Non-English-speaking subjects must be presented with

a consent form written in a language that they understand. A copy of the signed consent form must be given to the subject signing it. Another copy must be kept in the Investigator's files and made available to regulatory authority representatives upon request. If, for any reason, subject risk is increased as the study progresses, a revised, IRB/ERC-approved consent form must be signed by the subject. Before the study begins, a sample of the consent form must be provided to the Sponsor for review. The FDA and/or other applicable regulatory agencies may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all subjects.

Only in the case of a life-threatening incident may an investigational product be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the Investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB/ERC within 5 working days. In this situation, the Investigator may not administer any subsequent product to that subject until informed consent and IRB/ERC approval are obtained.

Informed Consent

Written informed consent must be obtained from each subject prior to entry in the study. One copy of the signed informed consent document will be given to the subject, and another will be retained by the Investigator. Additionally, the subject must be allowed adequate time to consider the potential risks and benefits associated with his/her participation in the study.

In situations where the subject is not legally competent to provide consent (ie, mentally incapacitated), written consent must be obtained from a parent, legal guardian, or legal representative. In these situations, the consent must be signed and dated by a witness.

The informed consent document must have been reviewed and approved by the Sponsor and by the Investigator's IRB/ERC prior to the initiation of the study. The document must contain the 8 basic elements of informed consent and may contain the 6 additional elements described in 21 CFR Part 50. Every consent form must include the following 8 elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the subject

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility that the FDA and/or other applicable regulatory authority representatives may inspect the records
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available, or a statement describing where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research related injury
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

When appropriate, 1 or more of the following elements of information shall also be included in the consent form:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent
- Any additional costs the subject may incur from participation in the research
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject
- The approximate number of subjects involved in the study

The Declaration of Helsinki includes further details regarding the specific requirements for informed consent.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states, such as California and Oregon, require further action on the Investigator's part concerning subject consent.

Study Documentation

IRB/ERC Review/Approval

The protocol and informed consent for this study, including advertisements used to recruit subjects, must be reviewed and approved by an appropriate IRB/ERC prior to enrollment of subjects in the study. It is the responsibility of the Investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, ICH, GCP, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB/ERC approval which specifically identifies the study/protocol and a list of the committee members must be received by the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

A progress report with a request for re-evaluation and re-approval will be submitted by the Investigator to the IRB/ERC at intervals required by the IRB/ERC, and not less than annually. A copy of the report will be sent to the Sponsor.

When the Sponsor provides the Investigator with a Safety Report, the Investigator must promptly forward a copy to the IRB/ERC.

After completion or termination of the study, the Investigator will submit a final report to the IRB/ERC and to the Sponsor, if required. This report should include: deviations from the protocol, the number and types of subjects evaluated, the number of subjects who discontinued (with reasons), results of the study, if known, and significant AEs, including deaths.

Study Files

The Investigator is required to maintain complete and accurate study documentation in compliance with current Good Clinical Practice standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study. Study documents include, but are not limited to, the Investigator's Brochure, drug accountability records, Sponsor/Investigator correspondence, IRB/ERC correspondence, protocol and amendments, information regarding monitoring activities, subject exclusion records, CRFs, and data queries.

Confidentiality

The anonymity of subjects must be maintained. Patients will be identified by their initials and an assigned subject number on CRFs and other documents submitted to the clinical monitor. Documents that will be submitted to the clinical monitor and that identify the subject (eg, the signed informed consent document) must be maintained in strict confidence by the Principal Investigator, except to the extent necessary to allow auditing by regulatory authorities, the clinical monitor, or Sponsor personnel.

All information regarding the nature of the proposed investigation provided by the Sponsor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB/ERC, the subject, or the regulatory authority) must be kept in confidence by the Investigator.

Drug Accountability

The Investigator or designee is responsible for accountability of the investigational product at the site. The Investigator or designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and return to the Sponsor or alternative disposition of any unused product. These records must include dates, quantities, batch/serial/lot numbers, and expiration dates (if applicable).

The Investigator should ensure that the investigational product is used only in accordance with the protocol

19. References

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CLINICAL STUDY PROTOCOL

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
EudraCT Number	2013-002596-18
Investigational Phase:	3
Protocol Title:	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Study Name:	TELEPATH (**Tel**otristat **E**tiprate – Expanded Treatment for **Pat**ients wit**h** Carcinoid Syndrome)
Amendment 2 Date:	21 January 2015 (France only)
Amendment 1 Date:	30 December 2014 (France only)
Original Version Date:	14 June 2013
Sponsor:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: 001 (281) 863-3000 Safety Hotline: 001 (877) 372-3597 Safety Data Facsimile: 001 (832) 442-5917

Lexicon Pharmaceuticals, Inc.
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Investigator Signature Page

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
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By my signature below, I hereby attest that I have read and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol and will conduct the study in accordance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance.

Additionally, I will not initiate this study without written and dated approval from the appropriate Institutional Review Board (IRB)/ Ethic Review Committee (ERC), and I understand that any changes in the protocol must be approved in writing by the Sponsor, the IRB/ERC, and, in certain cases the Food and Drug Administration (FDA) or other applicable regulatory agencies, before they can be implemented, except where necessary to eliminate hazards to patients.

Principal Investigator's Signature — Date

Principal Investigator's Name (Print)
[redacted]

Lexicon [redacted] and [redacted] — Date
(Signature)

[redacted] M.D
Lexicon [redacted] and [redacted]
(Printed Name)

1. Synopsis

Name of Study Drug	Telotristat etiprate
Protocol Number	LX1606.1-302-CS LX1606.302 (Abbreviated number)
Protocol Title	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Primary Objective	The primary objective of this study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate
Secondary Objective	To evaluate long-term changes in patients' quality of life (QOL)
Phase of Development	3
Methodology	The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate. Patients currently participating in any LX1606 Phase 2 carcinoid syndrome (CS) study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original study to LX1060.1-302-CS. Following confirmation of eligibility, patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label study drug at the same dose level and regimen as identified in their original study. Downward dose adjustment will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. Patients may return to the previous dosing at the discretion of the Investigator and in consultation with the Medical Monitor. Upon completion or early withdrawal from treatment, all patients will be required to complete a 14-day Follow-up Period, during which no study drug will be administered.

	A Data Safety Monitoring Board (DSMB) will review safety data quarterly throughout the study.
Number of Patients	Up to 100 patients are expected to participate in this study.
Patients	Eligible patients are defined as those that are currently participating in a Phase 2 or Phase 3 telotristat etiprate carcinoid syndrome study.
Number of Study Sites	Approximately 70 sites
Treatments	Telotristat etiprate, 250-mg tablet, administered at the same dose level and regimen identified in the patient's original study
Route of Administration	Oral
Duration of Participation	Up to 86 weeks including Treatment and Follow-up
Inclusion Criteria	Patients must meet all of the following criteria to be considered eligible to participate in the study: 1. Ongoing participation in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study 2. 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 entry are confirmatory in the absence of a clear postmenopausal history. 3. Ability and willingness to provide written informed consent prior to participation in any study-related procedure

Exclusion Criteria	Patients who meet any of the following criteria will be excluded from participating in the study: 1. Major protocol violations or telotristat etiprate tolerability concerns in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study 2. Positive pregnancy test 3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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 4. Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities
Statistical Methods	Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study and combined across all treated patients. Primary analyses of the data will be based on the Safety population which includes all patients treated on Day 1 of this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.
Study Assessments	<u>Safety</u> Safety assessments include monitoring of adverse events, clinical laboratory tests, vital signs measurements, 12-lead ECG, and physical examinations <u>Efficacy</u> Efficacy assessments will include patient reported quality of life measures as captured in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and the module specific for gastrointestinal symptoms of

	carcinoid neuroendocrine tumors (GI.NET21) and subjective global assessment of symptoms associated with CS Pharmacodynamics Pharmacodynamic (PD) assessments include determination of 5-HIAA levels in plasma
Efficacy Data Analysis	All efficacy and PD variables will be summarized descriptively and listed. Statistical tests and estimates of within patient effects for the efficacy and PD measures will be derived from application of a mixed linear model with repeated measures. The form of the model will be specific to measurement properties of the dependent variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model. Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to patients' telotristat etiprate dose level on Day 1 of this study.
Safety Data Analysis	Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group, and as needed, by study visit. Treatment-emergent adverse event 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 serious adverse events. Vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) 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.

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2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ALP	alkaline phosphatase
AST	aspartate transaminase
bid	twice daily
BM	bowel movements
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CgA	chromogranin A
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CS	carcinoid syndrome
CT	computed tomography
DSMB	Data Safety Monitoring Board
EC	enterochromaffin
ECG	electrocardiogram
ERC	Ethic Review Committee
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HEENT	head, eyes, ears, nose, and throat
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
IND	Investigational New Drug

Continued on the next page

Abbreviation	Definition
IRB	Institutional Review Board
ITT	intent-to-treat
IMP	Investigational Medicinal Product
IWRS	interactive web response system
LAR	long-acting release
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MCP	multiple comparison procedure
MRI	magnetic resonance imaging
NET	neuroendocrine tumor
NRS	numeric rating scale
OOR	out-of-range
OTC	over-the-counter
PD	pharmacodynamic
PK	pharmacokinetic
qd	once daily
SAE	serious adverse event
SBS	short bowel syndrome
SOP	standard operating procedure
SSA	somatostatin analog
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse events
tid	3 times daily
TPH	tryptophan hydroxylase
ULN	upper limit of the normal reference range
WRS	Wilcoxon rank sum

Definitions of Terms

Term	Definition
LP-778902	active moiety of LX1606
LX1606	telotristat ethyl: the ethyl-ester prodrug of the active moiety LP-778902; a serotonin synthesis inhibitor being developed by Lexicon Pharmaceuticals, Inc.
QTcF	corrected QT interval using Fredericia's formula

3. Introduction

3.1 Background on Telotristat Etiprate (LX1606) and Disease

Serotonin (5-HT) plays a critical role in regulating several major physiological processes of the gastrointestinal tract, including aspects of secretion, motility, inflammation and sensation. Enterochromaffin (EC) cells release 5-HT when the intestinal wall is stimulated by intraluminal pressure or chemicals. Through multiple classes of receptors, 5-HT is believed to initiate directly, or facilitate, peristaltic and secretory reflexes. 5-HT is also reportedly involved in the pathophysiology of various types of functional gastrointestinal (GI) disorders, valvular heart disease, and may play a role in the pathophysiology of inflammatory bowel disease (IBD).

Carcinoid tumors are mostly derived from EC cells of the midgut, and often produce and release large amounts of 5-HT. Such excess of 5-HT is believed to be responsible for the severe diarrhea and eventual valvular heart damage and mesenteric fibrosis in patients with carcinoid syndrome (CS).[1-3] Inhibition of tryptophan hydroxylase (TPH) activity in carcinoid tumors should lead to a reduction of peripheral 5-HT in afflicted patients and thus an amelioration of the pathophysiology and symptomology of CS. A peripheral TPH inhibitor, such as telotristat etiprate, should alleviate the symptoms due to excess 5-HT in carcinoid patients without central nervous system (CNS)-related adverse events (AEs).

Approximately 90% of the body's 5-HT is found in the EC cells of the GI tract, with the remainder distributed between the platelets and CNS.[4] TPH catalyzes the biopterin-dependent monooxygenation of tryptophan to 5-hydroxytryptophan, which is subsequently decarboxylated to form 5-HT. Expression of TPH is limited to a few specialized tissues: raphe neurons, pinealocytes, mast cells, mononuclear leukocytes, beta cells of the islets of Langerhans, and intestinal and pancreatic EC cells.[5] Two isoforms of the enzyme exist, TPH1 and TPH2. TPH1 is exclusively located in the EC cells of the GI tract and pineal gland and is the rate limiting enzyme responsible for the majority of systemic 5-HT production and is also responsible for 5-HT synthesis in carcinoid tumors. TPH2 is located in the central and enteric nervous systems and is the rate-limiting enzyme in the production of neuronal 5-HT.

The oral TPH inhibitor, telotristat etiprate, represents a novel approach to potentially lessen the pathophysiology of CS by reducing 5-HT levels via inhibition of TPH. Telotristat etiprate was designed specifically as a prodrug in order to gain greater systemic exposure, opening the potential application for indications in which hyperserotonemia is thought to contribute to the disorder, such as CS. Preclinical pharmacology studies of telotristat etiprate were designed to evaluate the compound’s mechanism of action and effects in vivo. Telotristat etiprate is the ethyl-ester prodrug of the active moiety LP-778902. Telotristat etiprate was

designed as a prodrug in order to enhance peripheral exposure without crossing the blood-brain barrier. In vivo, telotristat etiprate is readily converted through esterase activity to its corresponding acid, LP-778902. LP-778902 has an in vitro potency of 0.028 μM on purified human TPH1 enzyme and 0.032 μM on purified human TPH2 enzyme. Therefore, telotristat etiprate is a robust inhibitor of TPH both in vitro and in vivo and has been shown in Phase 2 studies to provide clinical benefit to patients with carcinoid tumors and associated CS.

Telotristat etiprate is being developed to manage GI symptoms and possibly other symptoms associated with CS. Currently, the standard of care for patients with CS is symptom management using somatostatin analogs (SSA), which are available in both short- and long-acting release (LAR) formulations. Somatostatin analogs such as octreotide are indicated for the control of flushing, diarrhea, and other symptoms associated with CS. Common side effects of the long-acting depot form of the drug are pain at the site of the injection, reported in as many as 30 to 50% of carcinoid patients at the 20 and 30 mg dose levels, and less commonly, stomach cramps, nausea, vomiting, headaches, dizziness, and fatigue.[6] Other side effects identified in the product labeling include biliary tract abnormalities (gallstones, sludge, and dilatation), hypothyroidism, dietary fat malabsorption, and hyper or hypoglycemia.[7] In addition to the morbidity associated with parenterally administered agents, tachyphylaxis will occur in the majority of patients, resulting in recurrent symptoms.

There are currently no specific oral treatments indicated for the management of symptoms associated with CS. As a result of the morbidity associated with SSAs and the associated tachyphylaxis, there is an unmet medical need to provide symptom management and modify the pathophysiology of patients with metastatic CS. Inhibition of the excessive 5-HT produced by these tumors with an orally delivered agent such as telotristat etiprate could provide significant benefit as an additional treatment option for patients and clinicians.

3.2 Clinical Trials of Telotristat Etiprate (LX1606) in Humans

Telotristat etiprate has been studied in single/multiple doses in Phase 1 studies, approximately 117 healthy volunteers participated in Phase 1 trials with 96 subjects receiving telotristat etiprate and 21 subjects receiving placebo. In addition, 37 patients with CS have received telotristat etiprate during the clinical development program in Phase 2. An additional 59 patients with ulcerative colitis have been enrolled into an ongoing Phase 2 study to evaluate telotristat etiprate versus placebo in patients with ulcerative colitis experiencing active flares.

3.2.1 Phase 1 Studies

LX1606.1-101-NRM utilized telotristat etiprate as a single oral dose and was noted to be safe and well tolerated up to doses of 1,000 mg. At doses of ≥1,000 mg, an increase in GI AEs was observed, which were assessed as at least possibly related to study drug. These AEs led

to a decision not to escalate the dose beyond 1,500 mg. No serious adverse events (SAEs) or deaths were reported and no patient discontinued due to an AE. Twenty-three patients experienced at least 1 AE. The majority of the AEs were assessed as mild. The most common AEs were diarrhea and nausea. Random out-of-range laboratory values at various time points in several patients occurred without any apparent trend. There were no other clinically significant vital signs, laboratory or physical examination findings.

LX1606.1-102-NRM utilized telotristat etiprate as multiple oral doses over 14 days and was tolerated up to the maximum dose assessed, 500 mg tid; 1,500 mg total dose daily. Most AEs were mild, the most common being nausea and headache; all resolved. Most AEs were at least possibly related to study treatment. Four AEs required treatment with concomitant medication, 3 AEs of constipation and 1 of headache. No deaths or SAEs were reported. One patient was discontinued due to an AE of abnormal liver function. There were no apparent trends or clinically significant findings observed upon review of vital signs and electrocardiogram (ECG) data. There were no clinically significant abnormal physical examination findings.

Overall, in LX1606.1-102-NRM, treatment with telotristat etiprate was associated with mild elevations, generally ≤2x the upper limit of normal (ULN), in alanine transaminase (ALT) and aspartate transaminase (AST), with elevations in values observed earlier in the higher dose cohorts. Results were assessed as clinically significant for only 1 patient, in Cohort 4, who was withdrawn on Day 10. The trend was most pronounced in Cohort 5, in which 5 out of 6 patients who received telotristat etiprate had increases in ALT values which were above normal range and 4 patients had increases in AST values which were above normal range at Day 14. Mean increases in ALT and AST appeared earlier in the study for Cohorts 4 and 5 than in the other cohorts, and were noted for all cohorts by Day 12. All patients had normal ALT and AST values at Baseline and most elevated transaminases returned to normal range within 48 hours after the last dose of study drug. No changes in alkaline phosphatase (ALP) or total bilirubin were observed in any patient.

LX1606.1-103-NRM evaluated 2 oral formulations of telotristat etiprate in an open-label crossover study. Each formulation was given as a single oral dose followed by a 5-day washout and then patients were given a single oral dose of the second formulation. During this study, there were no deaths or SAEs reported and no AEs lead to discontinuation. The most commonly reported AE was diarrhea. No clinically significant observations or changes in other safety parameters (eg, clinical laboratory evaluations, vital signs, physical examinations, ECGs, and AEs) were identified in the patient population during the study conduct.

LX1606.1-104-NRM was designed to evaluate the pharmacokinetics, metabolism, and routes and extent of elimination of telotristat ethyl and its primary metabolite (LP-778902) in 8 healthy male subjects after a single oral dose of 500 mg radio-labeled telotristat etiprate (14C-LX1606). This study has been completed and the results will be discussed in the annual update of the Investigator Brochure.

3.2.2 Phase 2 Studies

LX1606.1-202-CS was a randomized, double-blind, placebo-controlled, multiple ascending dose study conducted in 2 parts in order to evaluate a total of 23 patients at a dose range of 450 to 1500 mg given as 150, 250, 350, or 500 mg tid (telotristat etiprate or matching placebo) on a background therapy of octreotide. In Part 1, 16 patients were randomly assigned 3:1 into 4 sequential cohorts. Each cohort evaluated 1 of the following daily doses given as 150, 250, 350, or 500 mg tid over a course of 4 weeks. During the study, all patients continued on a stable-dose background therapy of octreotide. In Part 2, an additional 7 patients were randomly assigned 3:1 in order to evaluate 500 mg tid, the highest tolerated dose as determined in Part 1. Upon completion of the initial 4-week portion, eligible patients had the option to continue into an open-label Extension Period.

There was 1 treatment emergent SAE assessed as possibly related to study drug which occurred in the 350 mg tid dose group. The patient had a history of nausea and vomiting and was hospitalized for exacerbation of these conditions.

Telotristat etiprate was generally well tolerated with no evidence of dose-limiting tolerability. Adverse events were mostly mild to moderate and with similar frequencies between treatment groups and placebo. No significant changes in vital signs, ECG, or physical exam findings were noted after administration of telotristat etiprate at any dose level. The most common AEs were GI-related and reported as diarrhea, nausea, and abdominal pain, respectively. The modest elevations in transaminases seen in the Phase 1 multiple ascending dose study (LX1606.1-102-NRM) were not apparent in this 4-week study in patients with CS.

Patients that received telotristat etiprate achieved a clinical response (28%) defined as at least a 30% reduction in bowel movements (BMs) for at least 2 weeks; a biochemical response (56%) defined as at least a 50% reduction or normalization of urinary 5-hydroxyindoleacetic acid (5-HIAA); and reported adequate relief at Week 4 (46%) while no placebo patients experienced clinical response, biochemical response, or adequate relief.

LX1606.1-203 was an open-label, serial ascending, multiple dose, individual titration study that evaluated the same dose ranges as the LX1606.1-202-CS study in a total of 15 patients. Patients were serially escalated to the next dose level every 2 weeks until a maximally tolerated dose or 500 mg tid was reached. Once a dose had been determined, the patient

would remain on the dose for an additional 4 weeks. Patients then had the option to continue into an Extension Period.

Telotristat etiprate was generally safe and well-tolerated in subjects with CS in the LX1606.1-203 study. Most AEs were mild to moderate in severity and assessed as unrelated to study drug. Events in the Gastrointestinal Disorders system organ class were common, as is anticipated with the underlying illness.

Statistically significant reductions from Baseline in the mean number of BMs/day were observed in this study throughout the entire dose-escalation and stable-dose phases, as were improvements in stool form. Telotristat etiprate produced an improvement in global assessment of GI symptoms associated with CS in the majority of subjects (12 of 15 subjects, 80%) across the 12-week period. The global assessment of GI symptoms was based on 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 BM, abdominal pain or discomfort?” In addition, subjects experienced statistically significant decreases in the mean daily number of cutaneous flushing episodes.

Thirteen subjects (86.7%) experienced a complete biochemical response (defined as a ≥50% reduction from Baseline in u5-HIAA levels at 1 or more time points). Consistent with the proposed mechanism of action for telotristat etiprate, a complete biochemical response correlated closely with measures of clinical response, such as number of bowel movements per day.

LX1606.1-204-UC evaluated patients with active flares of ulcerative colitis. Doses under evaluation are 500 mg once daily (qd) and 500 mg tid vs. placebo; 59 patients were enrolled for an 8-week treatment period. This study has been completed and the results will be discussed in the annual update of the Investigator Brochure.

Detailed information regarding the completed clinical studies can be found in the Investigator Brochure.[8]

3.2.3 Ongoing Studies

The open-label extension portions in LX1606.1-202-CS and LX1606.1-203-CS remain ongoing.

LX1606.1-301-CS is intended to evaluate patients who are currently on a background of SSA therapy and still experiencing breakthrough symptoms such as an increased frequency of BMs ≥4 per day on average: (1) the efficacy of telotristat etiprate on reducing the number of BMs; (2) the efficacy of telotristat etiprate on a number of clinically relevant secondary endpoints; and, (3) the safety of telotristat etiprate over the 12-week double-blind portion

(Treatment Period) of the study. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period (Extension Period).

LX1606.1-303-CS is intended to evaluate patients with carcinoid syndrome whose primary symptoms are not GI related and may be naïve to SSA therapy: (1) the safety of telotristat etiprate over the 12-week double-blind portion (Treatment Period) of the study; (2) percent (%) change from Baseline in 24-hour u5-HIAA levels at Week 12; (3) the effects of telotristat etiprate on a number of clinically relevant secondary endpoints. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period.

3.3 Rationale for Current Study

3.3.1 Rationale for Selection of Dose

The dose levels of telotristat etiprate selected for this study are consistent with prior clinical study experience and based upon clinical safety and pharmacodynamic (PD) data from 2 Phase 2 multiple ascending-dose studies in patients with symptomatic CS (LX1606.1-202-CS and LX1606.1-203-CS).

Based upon observations noted in Section 3.2, it is anticipated that the doses to be utilized in this protocol will be safe and well tolerated and may provide clinical benefit to patients with CS.

3.3.2 Benefit/Risk Assessment

Clinical experience with telotristat etiprate (treated subjects) consists of completed single and multiple ascending dose studies in 96 normal subjects (44 in single dose studies and 52 in the multiple dose study), 2 Phase 2 studies (37 patients with symptomatic CS) and 2 ongoing Phase 3 studies in patients with symptomatic CS.

In healthy volunteer studies, single doses up to 1000 mg were found to be generally well tolerated, while at the 1500 mg dose level GI-related adverse events increased. A similar adverse event profile was observed after multiple dose administration over 14 days with GI events predominating. Mild, dose-dependent increases in hepatic transaminase levels (≤2 x ULN) were observed with increased frequency in relation to dose, with 1 subject requiring withdrawal from therapy at the 500 mg bid dose level. Most subjects that were observed to have increased transaminase levels did not exceed >2 x ULN. No abnormalities in total bilirubin were observed at any dose level. GI events have been the most commonly observed events to date. The adverse event profile in normal subjects may differ significantly from what is observed in patients with hyperserotonemia. All adverse events resolved without sequelae. In addition, there were no significant changes in vital signs or ECG. No physical

examination abnormalities were noted in studies to date. There were no serious adverse events reported in healthy volunteers.

In patients with CS, dose escalations have proceeded up to and including 500 mg tid. To date, there has been no evidence of dose-limiting intolerability. Dose levels have been generally well tolerated with no evidence to suggest elevations in hepatic transaminase levels. Based upon observations from preclinical and clinical studies conducted to date, it is anticipated that orally administered telotristat etiprate will be well tolerated at dose levels required to influence peripheral 5-HT production in patients with symptomatic CS. Potential adverse events primarily involve the GI tract, and could include alterations in gut motility, nausea, vomiting, diarrhea, constipation, abdominal bloating, and/or pain. Regular and ongoing clinical and laboratory assessments should detect any of these events, and depending on the type of event, further dose adjustment or discontinuation from the trial would occur. Although CNS effects are not anticipated at dose levels planned for evaluation, standard adverse event questioning and/or physical examination should reveal any subtle CNS findings. As elevations in hepatic transaminase levels were observed with multiple dosing in normal subjects, monitoring clinical laboratory tests of hepatic function will be incorporated into clinical trials conducted in CS patients.

Treatment has the potential to improve several signs and symptoms of CS. The Phase 2 clinical trial results indicated that treatment may lead to improvements in BM frequency, stool consistency, urgency, abdominal pain, diarrhea, flushing, and reductions in 5-HIAA. These potential benefits relate to a unique mechanism of action. Symptomatic improvement may lead to a better quality of life (QOL) for patients with few treatment options available, and a reduction in serotonin may help reduce the risk of carcinoid heart disease. Overall the benefit/risk profile of telotristat etiprate is expected to be favorable for participation in this clinical study.

3.4 Rationale for Study Design and Control Groups

Currently, no approved therapy exists for the treatment of symptoms driven by underlying serotonin pathophysiology of CS in patients whose disease is refractory to SSA therapy or for those patients who are unable to tolerate SSA therapy or who are unwilling to take SSA therapy.

This study will allow for continued access to telotristat etiprate after patients have completed the required study visits in ongoing Phase 2 and Phase 3 studies. Continuation of CS patients into this study will allow for the collection of additional long-term safety and efficacy data, while providing access to patients who may be receiving benefit. The treatment duration is

supported by results of chronic toxicology studies (6-month rat and 9-month dog) and the current safety profile from completed and ongoing clinical trials.

4. Study Objectives

4.1 Efficacy Objectives

4.1.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

4.1.2 Secondary Objective(s)

The secondary objective of this study is to evaluate changes in patients' QOL.

4.2 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

5. Investigational Plan

5.1 Overall Study Design

The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate.

Patients currently participating in any LX1606 Phase 2 CS study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original protocol to LX1060.1-302-CS.

Following confirmation of eligibility, patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label LX1606 at the same dose level identified in the original study.

Downward dose adjustment will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be

discontinued from the study. Patients may return to the previous dosing at the discretion of the Investigator and in consultation with the Medical Monitor.

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

A Data Safety Monitoring Board (DSMB) will review safety data quarterly throughout the study.

6. Study Population

Adult patients who are currently participating in ongoing Phase 2 or Phase 3 telotristat etiprate CS clinical protocols will be enrolled into the study. Up to 100 patients are expected to enroll in this study. Approximately 70 sites worldwide will participate in the study. Patients may continue allowed medications as background therapy provided they remain on stable-doses throughout the Treatment Period.

6.1 Inclusion Criteria

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

1. Ongoing participation in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study
2. 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 Baseline Day 1 are confirmatory in the absence of a clear postmenopausal history.
3. Ability and willingness to provide written informed consent prior to participation in any study-related procedure.

6.2 Exclusion Criteria

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

1. Major protocol violations or telotristat etiprate tolerability concerns in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study
2. Positive pregnancy test
3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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
4. Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities

6.3 Criteria for Stopping Treatment/Study Withdrawal

A patient may also be discontinued from the study for the following medical or administrative reasons:

- Withdrawal of consent by the patient or legal guardian
- Noncompliance, including refusal of the study medication and/or failure to adhere to the study requirements as in the study protocol
- Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study
- The Sponsor terminates the study (Section 6.4)
- Pregnancy (Section 9.4.1)

Note: If a patients voluntarily withdraws or is discontinued from study treatment before completing the entire duration of the Treatment Period, 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 Appendix A – Schedule of Events and agree to report any SAEs (Section 9.2) that occur within 30 days following the last dose of telotristat etiprate.

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 Case Report Form (CRF).

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.

6.4 Criteria for Termination of the Study

If the 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 carcinoid syndrome or any other indication 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; and,
- Insufficient adherence to protocol requirements.

Study termination and Follow-up would be performed in compliance with applicable governing body regulations.

6.5 Clinical Stopping Rules

Criteria for individual patient withdrawal or study termination are summarized in Sections 6.3 and 6.4, respectively.

6.6 Method of Assigning Patients to Treatment

Patients will enter the study at the same dose level and regimen as identified in the prior Phase 2 or Phase 3 CS study. Randomization will not be used to assign patients to study treatments.

6.7 Blinding and Unblinding of Study Medication

This is an open-label study.

6.8 Replacement of Patients

Patients who do not complete the study will not be replaced.

7. Treatment

7.1.1 Telotristat Etiprate (LX1606)

7.1.1.1 Identity

Telotristat etiprate (LX1606 hippurate) is the salt form of the drug substance. LX1606 hippurate is a crystalline white to off-white to tan solid with a melting point of 147°C. LX1606 is insoluble in water within the pH range of 5 to 9 (≤2 mg/L). It undergoes hydrolysis under strongly basic or strongly acidic conditions. The solubility of LX1606 hippurate in water is about 22 mg/L at 25°C.

Study drug dosage form consists of white coated debossed oval tablets containing 250 mg LX1606.

7.1.1.2 Packaging, Labeling, and Storage

Patients will receive 250-mg telotristat etiprate tablets packaged in 100 cc high density polyethylene bottles with child-resistant polypropylene screw caps and heat-induction seal liners.

Telotristat etiprate should be stored between 15 to 25°C (59 to 77°F).

7.2 Prior and Concomitant Medications

7.2.1 Prior Medications

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

7.2.2 Concomitant Medications

All concomitant medications taken by patients during the study will be recorded on the CRF. Treatment with prescription or over-the-counter (OTC) antidiarrheal therapy, bile acid sequestrants, or pancreatic enzyme is permitted; however, the use of these concomitant

therapies should be associated with a documented history of disease (eg, fat malabsorption, bile acid malabsorption, or steatorrhea).

Medical management of patients and their concomitant medications is allowed at the discretion of the Investigator. However, should the need arise to modify/adjust a patient's therapy due to a concern for patient safety and/or tolerability 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.

7.2.3 Prohibited Medications or Concomitant Therapy

None

7.3 Administration of Study Medication

All patients will be instructed to take the study medication with food. "With food" means taking telotristat etiprate 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.

Study medication and instructions will be dispensed to patients at each visit as described in the schedule of study procedures (Appendix A).

7.3.1 Treatment Compliance

Patients will be asked to bring their unused or unopened study medication to each visit (Appendix A). At each visit and in the presence of the patient, study site personnel will count returned tablets and reconcile the counts against planned number of doses for that interval. Site personnel will clarify any discrepancy and record this information within the CRF.

Patients must maintain at least 75% compliance in dosing to be deemed as compliant. In the event of a missed or vomited dose, patients will take their subsequent dose of study drug at the next scheduled time point, following the tid dosing regimen of approximately every 6 hours. A dose outside of a 3-hour window should be considered missed. Missed or vomited doses will not be made up.

7.4 Dose Adjustment

Downward dose adjustment of telotristat etiprate will be permitted if evidence of intolerability emerges. After a period at the lowered dose level, patients may resume the previous dosing level at the discretion of the Investigator after consultation with the Medical Monitor. Patients who experience intolerability at the 250 mg tid dose level **must** be

discontinued from study treatment. Interruptions or delays in dosing throughout the entire study may be permitted after consultation with the Medical Monitor, at which time the patient will be reassessed for study continuation, dosage reduction, or discontinuation.

8. Study Procedures

A schedule of study assessments is provided in Appendix A.

8.1 Restrictions during Study

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

8.2 Description of Study Assessments

8.2.1 Efficacy Assessments

Efficacy assessments include the patient reported QOL measures; EORTC QLQ-C30 (Appendix D) & GI.NET21 (Appendix E) questionnaires and subjective global assessment of symptoms associated with CS.

A description of the efficacy assessments is provided below.

8.2.1.1 EORTC QLQ-C30 & GI.NET21

Patients will complete the questionnaires during each visit as indicated in Appendix A.

8.2.1.2 Subjective Global Assessment

A subjective global assessment of symptoms associated with CS will be evaluated using 2 methods at each visit.

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."

8.2.2 Clinical Laboratory Assessment

Clinical laboratory assessments will consist of hematology (complete blood count [CBC] with differential and platelet counts), blood chemistry (complete metabolic panel and liver function tests), and urinalysis. 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 9.1 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.

8.2.2.1 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 >3 x 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 >3 x ULN (in patients with previous abnormal liver-test results)

OR

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

For any such event, the Investigator should discuss the Follow-up approach with the 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 function test values 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 continued study participation.

8.2.3 Pharmacodynamic Assessments

8.2.3.1 Plasma 5-HIAA

Fasting blood samples (≥6 hours) 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.

8.2.4 Safety Assessments

In addition to the clinical laboratory assessments described in Section 8.2.2, monitoring of AEs is also considered a safety assessment and is described in detail in Section 9. Clinically significant changes compared with Baseline findings for these variables should be reported as AEs on the CRF. Clinically significant changes compared with Baseline values, which are determined to be AEs, 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.

8.2.4.1 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 with 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. All measurements should be 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 Appendix A.

8.2.4.2 Physical Examinations

Complete physical examinations will be performed as outlined in Appendix A. 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, weight will be captured during each physical examination. Efforts should be made to standardize 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.

8.2.4.3 Electrocardiograms

Electrocardiograms (12-lead ECGs) will be performed as specified in Appendix A.

8.2.4.4 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.

8.2.4.4.1 Central Nervous System Events

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

8.2.4.4.1.1 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.

8.3 Other Assessments

8.3.1 Chromogranin A (CgA)

Blood samples for measurement of chromogranin A (CgA) levels will be collected as indicated in Appendix A.

8.3.2 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 (eg, PET, CAT, MRI scans of tumor), or Investigator assessment of disease status, while the patient is enrolled in the study.

8.3.3 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.

8.4 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.

8.4.1 Blood Collection

An attempt should be made to collect all samples as per the schedule outlined in Appendix A. Any portion of samples remaining after the required tests for this study have been completed will be destroyed.

The estimated amount of blood scheduled for collection per patient, over the course of the study, may be found in Appendix B.

9. Safety Reporting

Medical queries should be addressed to the Medical Monitor responsible for the region.

Sites in North America:

[redacted], MD
[redacted]
INC Research
[redacted]
Phone: [redacted]

Sites outside North America:

[redacted], MD, PhD
[redacted]
INC Research
[redacted]
The Netherlands
Phone: [redacted]
Mobile: [redacted]

[redacted], MD, PhD
Medical Monitor
INC Research, LLC
[redacted]
Czech Republic
Phone: [redacted]
Fax: [redacted]

After-hours 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. **Note**: These calls are not toll-free.

9.1 Adverse Events

It is the responsibility of the Investigator to document all AEs that occur during the study.

Adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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 considered related to the study medication. This definition includes an exacerbation of preexisting 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 9.2) 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 study drug 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

9.2 Serious Adverse Events (SAEs)

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

1. Death
2. A life-threatening adverse event;
3. Inpatient hospitalization or prolonging of an existing hospitalization (see Section 9.2.1 for information on hospitalization as an SAE);

4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
5. A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

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: [redacted]
Belgium: [redacted]
Brazil: [redacted]
France: [redacted]
Germany: [redacted]
Israel: [redacted]
Italy: [redacted]
Netherlands: [redacted]
Spain: [redacted]
Sweden: [redacted]
United Kingdom: [redacted]

Email Address (in case of fax failure): [redacted]

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.

9.2.1 Hospitalization as an SAE

Hospitalization is defined as any in-patient overnight stay in a hospital. A hospitalization in and of itself does not constitute an SAE. The condition which caused the hospitalization must be evaluated and determined to be an AE. Although an AE which results in hospitalization is an SAE, patients are hospitalized for a variety of reasons which may not be associated with or considered an SAE (eg, convenience, logistics, preference, etc). Therefore, each case of hospitalization must be evaluated separately.

For example, the following would not be considered SAEs:

- Hospitalization for a preexisting condition which did not worsen (eg, cataract surgery)
- Hospitalization solely for a procedure or treatment that was not performed to treat an AE
- Hospitalization for a condition that does not normally require treatment, but electively done (eg, cosmetic surgery)
- Hospitalization strictly for convenience reasons or observations (eg, procedures only performed in a hospital because of the distance the subject lives from the hospital)

9.3 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.

9.4 Precautions

9.4.1 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 9.2 for contact information).

10. Statistical Methodology

10.1 Determination of Sample Size

No formal sample size calculation was made. The number of patients expected to participate in this study was calculated from estimated enrollment rates from other carcinoid cancer trials employed in the LX1606 clinical program.

10.2 Analysis Populations

Per protocol: A Per Protocol population will consist of those patients that receive study treatment and have no major protocol violation that would interfere with the collection or interpretation of the efficacy data. The primary analyses of efficacy will be based on the safety population; 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 during this study.

10.3 Study Endpoints

10.3.1 Efficacy Endpoints

The primary efficacy endpoint is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

Secondary efficacy endpoint is to evaluate changes in patients' QOL over multiple years of therapy.

10.3.2 Safety Endpoints

Safety endpoints are as follows:

- Incidence of TEAEs, suspected adverse reaction, AEs leading to discontinuation from the study, SAEs, and deaths
- Actual and change from Baseline in clinical laboratory results
- Actual and change from Baseline in vital signs results
- Actual and change from Baseline in physical examinations
- Actual and change from Baseline in ECG findings

10.4 Statistical Methods

Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study and combined across all treated patients. All data will be listed.

Primary analyses of the data will be based on the Safety population which includes all patients treated with any fraction of study drug during this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. This dataset will include the Safety

population, but limited to those patients that have at least one assessment post Day 1 and do not have any protocol violations that would interfere with collection or interpretation of the data. The Per Protocol analysis will be applied to the QOL measures, subjective global assessment, and plasma 5-HIAA values.

Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.

10.4.1 Efficacy Analyses

All efficacy and PD variables will be summarized descriptively and listed.

Statistical tests and estimates of within patient effects for these measures will be derived from application of a mixed linear model with repeated measures. The model will be generalized to handle missing data and specific to the measurement properties of the dependent variable. There is no plan to impute data for missing observations for any variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model.

Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to how patients were dosed on Day 1 of this study.

10.4.2 Safety Analyses

Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group (corresponding to the LX1606 dose given on Day 1), pooled across all patients, and as needed, by study visit. All safety data will be listed.

Treatment-emergent adverse event 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 serious adverse events.

Vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) 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 and summarized.

10.4.2.1 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.

10.4.2.2 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 using descriptive statistics. Summaries of shifts from Baseline to abnormal clinical laboratory results will also be provided. Actual and change from Baseline in chromogranin A levels will be summarized descriptively as well.

10.4.2.3 Vital Sign Measurements

Actual and changes from Baseline (Day 1) in vital signs results will be summarized by using descriptive statistics.

10.4.2.4 Electrocardiograms

Clinically significant changes in ECGs compared to Baseline, as determined by the Investigator, will be summarized by using descriptive statistics. Actual and change from Baseline (Day 1 predose values) to each time point in corrected QT interval (QTcF) will be summarized as well.

10.4.3 Pharmacodynamic Analyses

Analysis and summarization of the plasma 5-HIAA data are described in Section 10.4.1.

10.4.4 Baseline Characteristics and Other Summaries

Treatment group differences will be summarized descriptively for demographic data, prior and concomitant medications, treatment compliance, and final disposition. Data collected from assessments of tumor status, when available, will be listed.

Protocol deviations will provided as listings.

10.4.5 Interim Analysis

An independent DSMB will be charged with reviewing interim safety data on a quarterly basis 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 may be analyzed and reported in multiple phases. The first report will summarize data obtained from all patients providing information up to a specified data cut-off point. The following reports will update the initial report by including data from the remaining portion of the study. 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.

11. Study Management

The Investigator is responsible for completing and maintaining adequate and accurate CRFs and source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, and discharge summaries.

All data on the CRF must be recorded in accordance with the CRF guidelines. If a correction is necessary, it should be made by the Investigator or a designated qualified individual as specified within the guideline. All CRFs should be completed in their entirety and stored in a secure location. The Investigator must sign the Investigator's statement in each patient's CRF indicating that the data reported are accurate.

At the study site, clinical research associates will verify 100% of CRFs in their entirety against source documentation. Computer programmed edit checks will be run against the database to check for discrepancies and reasonableness of the data, and the safety database will be reconciled with the clinical database. All issues resulting from the computer generated checks and the safety database reconciliation will be resolved according to standard data management practices in conjunction with the Sponsor, clinical study personnel, and the study Investigators.

11.1 Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the

Sponsor's study monitors will contact the study site via visits to the site, telephone calls, and/or letters in order to review study progress, CRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of patients, patient recruitment, patient compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by patients, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

The Investigator must make study data accessible to the clinical monitor, to other authorized representatives of the Sponsor, and to regulatory inspectors

11.2 Audits and Inspections

The Sponsor, regulatory authority, or IRB/ERC may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a Sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

11.3 Amendments

Any amendments to the protocol will be written and approved by the Sponsor. All amendments must be submitted to the IRB/ERC for approval prior to implementing the changes. In some instances, an amendment may require changes to the informed consent form, which also must be submitted for IRB/ERC approval prior to administration to patients. If any changes to the CRF are required, the Sponsor will issue supplemental or revised CRF pages.

11.4 Record Keeping

11.4.1 Drug Accountability

The Investigator must maintain accurate records of receipt of study drug, dispensing information (date, lot, and dose for each patient), and the prompt return or destruction of unused supplies. If the Investigator cannot account for all clinical supplies at the termination of the study, a written explanation must be provided.

11.4.2 Health Insurance Portability Accountability Act of 1996 and Subsequent Updates

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 Code of Federal Regulations (CFR) Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation and any applicable updates). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

11.4.3 Financial Disclosure

The Investigator shall provide to the Sponsor sufficient accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the FDA and/or other applicable regulatory agencies. The Investigator shall promptly update this information if any relevant changes occur in the course of the study or for 1 year following completion of the study.

11.4.4 Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 11) to ensure data integrity. “Original” in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

11.4.5 Retention of Study Documents

According to 21 CFR Part 312.62 and ICH E6, study-related records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor.

The Investigator must not destroy any study-related records without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor must be contacted to arrange alternative record storage options.

12. Administrative Structure of the Study

The study will be monitored by Sponsor personnel or Sponsor representative. The following functions for this study will be performed by organizations designated by the Sponsor: data management and statistical analysis, including PD analysis and reporting.

13. Appendix A – Schedule of Events

Procedure	Extension Period								2-Week Follow-up[4]
	Baseline Day 1[1]	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84 / EOS	
Tolerance (days)	NA	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5
Inclusion/Exclusion criteria	X								
Medical history	X								
Physical examination incl. weight	X	X[3]	X[3]	X[3]	X	X[3]	X[3]	X	X[5]
Urine pregnancy test[2]	X	X	X	X	X	X	X	X	X
~~Serum pregnancy test~~[2]									
Hematology, Blood chemistry	X	X	X	X	X	X	X	X	X[5]
Urinalysis	X				X			X	X[5]
Chromogranin A	X				X			X	
Vital signs	X	X	X	X	X	X	X	X	X
ECG	X				X			X	X[5]
Subjective Global Assessment	X	X	X	X	X	X	X	X	X
EORTC QLQ-C30 & GI.NET21	X		X		X		X	X	
Sleep and Depression Assessment	X	X	X	X	X	X	X	X	X
Plasma 5-HIAA	X	X	X	X	X	X	X	X	X
Dispensation of LX1606	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

[1]Eligibility will be determined at last visit of the original protocol; Day 1 will replace the next scheduled visit in the original protocol schedule. Visits should coincide with LAR injections for those patients receiving SSA therapy. [2]Females of child-bearing potential only. [3]Brief physical examination only (symptom-oriented, including weight). [4]Visit 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. [5]To be performed only if evaluation at Week ~~48~~84/EOS is abnormal.

14. Appendix B – Amount of Blood to be Collected from Each Patient

Assessment		Sample volume (mL)	Number of samples*	Estimated total volume (mL)
Safety	Hematology	2	9	18
	Blood chemistry	6	9	54
Other	CgA	2	3	6
Pharmacodynamic	Plasma 5-HIAA	4	9	36
			Total	114
*Maximum number of samples is indicated				

15. Appendix C – EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Lexicon

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

16. Appendix D – EORTC QLQ - GI.NET21

ENGLISH

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31. Did you have hot flushes?		1	2	3	4
32. Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33. Did you have night sweats?		1	2	3	4
34. Did you have abdominal discomfort?		1	2	3	4
35. Did you have a bloated feeling in your abdomen?		1	2	3	4
36. Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37. Have you had acid indigestion or heartburn?		1	2	3	4
38. Have you had difficulties with eating?		1	2	3	4
39. Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40. Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41. Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42. Were you concerned about disruption of home life?		1	2	3	4
43. Have you worried about your health in the future?		1	2	3	4
44. How distressing has your illness or treatment been to those close to you?		1	2	3	4
45. Has weight loss been a problem for you?		1	2	3	4
46. Has weight gain been a problem for you?		1	2	3	4
47. Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48. Have you had aches or pains in your muscles or bones?		1	2	3	4
49. Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:					
50. Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51. Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

17. Appendix E – Ethical Standards

Ethics and Regulatory Considerations

This study will be conducted according to GCP, 21 CFR Part 50, (Protection of Human Subjects), 21 CFR Part 56 (Institutional Review Boards), International Conference on Harmonisation Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

General Instructions

The FDA regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to GCP regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- Current FDA Guideline for the Monitoring of Clinical Investigations
- Current Guidance for Institutional Review Boards and Clinical Investigators
- ICH E6 – Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

Studies conducted in the European Union are also regulated by Volume 10 of the publications "The rules governing medicinal products in the European Union".

Copies of these materials are available from the Sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- the study is conducted with diligence and in conformance with the protocol in such a way as to insure the integrity of the findings;
- the potential benefits of the research justify the risks.

Lexicon Pharmaceuticals, Inc. is the Sponsor of the IND. The Sponsor is responsible for the following:

- selecting qualified Investigators,
- providing Investigators with the information they need to properly conduct an investigation,
- ensuring proper monitoring of the investigation,
- ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- maintaining the IND, and
- ensuring that regulatory authorities and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied
- ensuring the study is conducted in accordance to FDA and ICH guidelines and all applicable regulations

18. Appendix F – Investigator Obligations

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56 and ICH E6, the study protocol and the final version of the subject informed consent form will be approved by the IRB/ERC before enrollment of any subjects. The opinion of the IRB/ERC will be dated and given in writing. A copy of the letter of approval from the IRB/ERC and a copy of the approved informed consent form will be received by the Sponsor prior to shipment of study medication supplies to the Investigator.

The Investigator will ensure that the IRB/ERC will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to subjects. The Investigator will also ensure that no changes will be made to the protocol without IRB/ERC approval.

As a part of the IRB/ERC requirement for continuing review of approved research, the Investigator will be responsible for submitting periodic progress reports to the IRB/ERC at intervals appropriate to the degree of subject risk involved, but no less than once per year.

Written informed consent must be given freely and obtained from every subject prior to clinical trial participation. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

As described in GCP guidelines, study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (eg, loss of medical licensure, debarment). Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

Principal Investigators must provide Lexicon with a fully executed Form FDA 1572 (statement of Investigator) and all updates on a new fully executed Form FDA 1572.

Principal Investigators must provide Lexicon with his/her own curriculum vitae and current curriculum vitae for each sub-Investigator listed on Form FDA 1572.

Protection of Human Subjects (21 CFR Part 50 and ICH E6)

Informed consent must be obtained from every subject before entry into a clinical study. It must be given freely and not under duress. Consent must be documented by use of an IRB/ERC-approved consent form and signed by the subject or the subject's legally authorized representative. The US Department of Health and Human Services suggests that when minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent, his signature should also be included. Non-English-speaking subjects must be presented with

a consent form written in a language that they understand. A copy of the signed consent form must be given to the subject signing it. Another copy must be kept in the Investigator's files and made available to regulatory authority representatives upon request. If, for any reason, subject risk is increased as the study progresses, a revised, IRB/ERC-approved consent form must be signed by the subject. Before the study begins, a sample of the consent form must be provided to the Sponsor for review. The FDA and/or other applicable regulatory agencies may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all subjects.

Only in the case of a life-threatening incident may an investigational product be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the Investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB/ERC within 5 working days. In this situation, the Investigator may not administer any subsequent product to that subject until informed consent and IRB/ERC approval are obtained.

Informed Consent

Written informed consent must be obtained from each subject prior to entry in the study. One copy of the signed informed consent document will be given to the subject, and another will be retained by the Investigator. Additionally, the subject must be allowed adequate time to consider the potential risks and benefits associated with his/her participation in the study.

In situations where the subject is not legally competent to provide consent (ie, mentally incapacitated), written consent must be obtained from a parent, legal guardian, or legal representative. In these situations, the consent must be signed and dated by a witness.

The informed consent document must have been reviewed and approved by the Sponsor and by the Investigator's IRB/ERC prior to the initiation of the study. The document must contain the 8 basic elements of informed consent and may contain the 6 additional elements described in 21 CFR Part 50. Every consent form must include the following 8 elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the subject

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility that the FDA and/or other applicable regulatory authority representatives may inspect the records
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available, or a statement describing where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research related injury
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

When appropriate, 1 or more of the following elements of information shall also be included in the consent form:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent
- Any additional costs the subject may incur from participation in the research
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject
- The approximate number of subjects involved in the study

The Declaration of Helsinki includes further details regarding the specific requirements for informed consent.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states, such as California and Oregon, require further action on the Investigator's part concerning subject consent.

Study Documentation

IRB/ERC Review/Approval

The protocol and informed consent for this study, including advertisements used to recruit subjects, must be reviewed and approved by an appropriate IRB/ERC prior to enrollment of subjects in the study. It is the responsibility of the Investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, ICH, GCP, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB/ERC approval which specifically identifies the study/protocol and a list of the committee members must be received by the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

A progress report with a request for re-evaluation and re-approval will be submitted by the Investigator to the IRB/ERC at intervals required by the IRB/ERC, and not less than annually. A copy of the report will be sent to the Sponsor.

When the Sponsor provides the Investigator with a Safety Report, the Investigator must promptly forward a copy to the IRB/ERC.

After completion or termination of the study, the Investigator will submit a final report to the IRB/ERC and to the Sponsor, if required. This report should include: deviations from the protocol, the number and types of subjects evaluated, the number of subjects who discontinued (with reasons), results of the study, if known, and significant AEs, including deaths.

Study Files

The Investigator is required to maintain complete and accurate study documentation in compliance with current Good Clinical Practice standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study. Study documents include, but are not limited to, the Investigator's Brochure, drug accountability records, Sponsor/Investigator correspondence, IRB/ERC correspondence, protocol and amendments, information regarding monitoring activities, subject exclusion records, CRFs, and data queries.

Confidentiality

The anonymity of subjects must be maintained. Patients will be identified by their initials and an assigned subject number on CRFs and other documents submitted to the clinical monitor. Documents that will be submitted to the clinical monitor and that identify the subject (eg, the signed informed consent document) must be maintained in strict confidence by the Principal Investigator, except to the extent necessary to allow auditing by regulatory authorities, the clinical monitor, or Sponsor personnel.

All information regarding the nature of the proposed investigation provided by the Sponsor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB/ERC, the subject, or the regulatory authority) must be kept in confidence by the Investigator.

Drug Accountability

The Investigator or designee is responsible for accountability of the investigational product at the site. The Investigator or designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and return to the Sponsor or alternative disposition of any unused product. These records must include dates, quantities, batch/serial/lot numbers, and expiration dates (if applicable).

The Investigator should ensure that the investigational product is used only in accordance with the protocol

19. Appendix G – Guidance on the Selection of Patients

This long-term study in France is intended for patients who experience clinical benefit in their prior experience with telotristat etiprate, either in study LX1606.1-301-CS or LX1606.303.1-303-CS.

Clinical benefit should be present for subjects to meet entry criteria #3 described in section 6.1 of the protocol: ability and willingness to provide written consent prior to participation in any study-related procedure.

In this study population, clinical benefit may be represented by any of the following:

- Reduction in bowel movement frequency, or
- A positive response on the subjective global assessment of adequate relief, or
- A reduction in urinary 5-HIAA either in study LX1606.1-301-CS or LX1606.1-303-CS.

Reduction in bowel movement frequency: a reduction of at least 30% in bowel movement frequency from baseline to the end of study LX1606.1-301-CS or LX1606.303.1-303-CS may represent clinical benefit. In patients with carcinoid syndrome, benefits of this magnitude have been associated with improvements in patient-reported outcomes.

A positive response on the subjective global assessment of adequate relief: An answer of "yes" to the 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?" at the time of completing participation in LX1606.1-301-CS or LX1606.303.1-303-CS is a clinical benefit.

A reduction in urinary 5-HIAA either in study LX1606.1-301-CS or LX1606.1-303-CS: Normalization of urinary 5-HIAA or a reduction of at least 50% in urinary 5-HIAA is a clinical benefit for patients at risk of the development of new or progressive carcinoid heart disease.

In addition to the absence of the above signs of benefit, a lack of clinical benefit may reflect itself in one of the criteria for stopping treatment or study withdrawal (section 6.3 of the protocol): withdrawal of consent, refusal of the study medication, or an investigator decision that it is not medically acceptable to continue participation in the study.

20. Appendix H - Guidance on the Use of Pro-serotonergic Drugs as Concomitant Medications

Serotonin-synthesis reuptake inhibitors (SSRis) are associated with serotonin syndrome, and patients with carcinoid syndrome may be at higher risk of this complication.

There is some experience with the use of SSRis with telotristat etiprate. In study LX1606.1-202-CS there were 8 patients on SSRis at baseline, and one patient had an SSRi added during the study. There were no reports of serotonin syndrome. However, since the experience was relatively limited, caution should be given to the use of SSRis as a concomitant medication in study LX1606.1-302-CS.

21. References

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CLINICAL PROTOCOL AMENDMENT 2
STUDY LX1606.302

A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)

PROTOCOL NO.:	**LX1606.1-302-CS** **LX1606.302** (Abbreviated number)
EudraCT Number:	2013-002596-18
INVESTIGATIONAL PHASE:	3
SPONSOR:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: 001 (281) 863-3000 Safety Hotline: 001 (877) 372-3597 Safety Data Facsimile: 001 (832) 442-5917
PROTOCOL AMENDMENT 2 DATE:	08 October 2014
PROTOCOL AMENDMENT 1 DATE:	31 January 2014
ORIGINAL VERSION DATE:	14 June 2013

Amendment Changes

Rationale

A protocol amendment is proposed to provide additional continued access to telotristat etiprate for patients who are enrolled in the LX1606.1-302-CS protocol. This amendment will allow treatment with telotristat etiprate for an additional 36 weeks following the completion of the original protocol. The total duration of participation is now defined as up to 86 weeks including the Treatment and Follow-up phases.

Modifications have also been made to: (1) revise the number of healthy volunteers that have participated in a Phase 1 study; (2) denote that recently completed studies; (3) clarify that Screening should denote Baseline (Day 1) as there is no Screening period in this study; (4) clarify the criteria for the termination of the study; (5) clarify how change in concomitant medications should be approached; (6) clarify how blood pressure measurement should be collected; (7) further define reporting requirements for hospitalization; (8) denote that the study may be reported in multiple phases; (9) update Schedule of Events to reflect new assessments; (10) update amount of blood to be collected.

The following administrative changes have also been made:

- LX1606 is identified as telotristat etiprate throughout the document for consistency
- Minor formatting, capitalization, and punctuation have been corrected
- Definition of Terms has been updated to accurately identify LX1606
- Due to the insertion of new sections, renumbering has occurred as appropriate
- Table of contents has been updated as appropriate

In response to these changes, the following sections have been revised as follows (changes are indicated in *italics*):

1. **SYNOPSIS – Duration of Participation, page 4 – This section was modified to reflect study duration of 86 weeks. The revised section now reads:**

"Up to *86* weeks including Treatment and Follow-up"

2. **SYNOPSIS – Exclusion Criteria, page 5 and STUDY POPULATION – Exclusion Criterion, Section 6.2, pages 20-21, Criterion #1 – This criterion has been modified to clarify that patients with telotristat etiprate tolerability concerns will be excluded from the study. The revised criterion now reads:**

"Major protocol violations or *telotristat etiprate* tolerability concerns in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study"

3. **INTRODUCTION – Clinical Trials of Telotristat Etiprate (LX1606) in Humans, Section 3.2, page 13 – This section was revised to reflect number of healthy volunteers that have participated in Phase 1 trials. The revised section now reads:**

"Telotristat etiprate has been studied in single/multiple doses in Phase 1 studies, approximately *117* healthy volunteers participated in Phase 1 trials with *96* subjects receiving telotristat etiprate and 21 subjects receiving placebo. In addition, 37 patients with CS have received telotristat etiprate during the clinical development program in Phase 2. An additional 59 patients with ulcerative colitis have been enrolled into an ongoing Phase 2 study to evaluate telotristat etiprate versus placebo in patients with ulcerative colitis experiencing active flares."

4. **INTRODUCTION – Phase 1 Studies, Section 3.2.1, pages 13-14 – This section was revised to reflect a recently completed Phase 1 study. The following paragraph has been inserted:**

"LX1606.1-104-NRM was designed to evaluate the pharmacokinetics, metabolism, and routes and extent of elimination of telotristat ethyl and its primary metabolite (LP-778902) in 8 healthy male subjects after a single oral dose of 500 mg radio-labeled telotristat etiprate (14C-LX1606). This study has been completed and the results will be discussed in the annual update of the Investigator Brochure."

5. **INTRODUCTION – Phase 2 Studies, Section 3.2.2, pages 15-16 – This section was revised to reflect a recently completed Phase 2 study. The following paragraph has been inserted:**

"LX1606.1-204-UC evaluated patients with active flares of ulcerative colitis. Doses under evaluation are 500 mg once daily (qd) and 500 mg tid vs. placebo; 59 patients were enrolled for an 8-week treatment period. This study has been completed and the results will be discussed in the annual update of the Investigator Brochure."

6. **INTRODUCTION – Ongoing Studies, Section 3.2.3, pages 16-17 – This section was revised to reflect a recently completed Phase 2 study. The following paragraph has been removed:**

"LX1606.1-204-UC is currently evaluating patients with active flares of ulcerative colitis. Doses under evaluation are 500 mg once daily (qd) and 500 mg tid vs. placebo; 59 patients have been enrolled for an 8-week treatment period."

7. **INTRODUCTION – Benefit/Risk Assessment, Section 3.3.2, pages 17-18, 1st paragraph – This paragraph was revised to reflect number of healthy volunteers that have participated in Phase 1 trials. The following paragraph now reads:**

"Clinical experience with telotristat etiprate (treated subjects) consists of completed single and multiple ascending dose studies in *96* normal subjects (*44* in single dose studies and 52 in the multiple dose study), *2* Phase 2 studies (37 patients with symptomatic CS) and 2 ongoing Phase 3 studies in patients with symptomatic CS."

8. **STUDY POPULATION – Inclusion Criteria, Section 6.1, page 20, Criterion #2.a. – This criterion has been modified to clarify Baseline Day 1. The revised criterion now reads:**

"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 *Baseline Day 1* are confirmatory in the absence of a clear postmenopausal history."

9. **STUDY POPULATION – Criteria for Termination of the Study, Section 6.4, page 22, bullet #2 – This bullet was modified to clarify that termination of the study may result in a Sponsor decision to suspend or discontinue development for carcinoid syndrome or any other indication. The revised bullet now reads:**

"A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product for *carcinoid syndrome or any other indication for* any reason;"

10. **TREATMENT –Concomitant Medications, Section 7.2.2, pages 23-24, 2nd paragraph – This paragraph was revised to clarify how changes to concomitant medications should be addressed. The revised paragraph now reads:**

"*Medical management of patients and their concomitant medications is allowed at the discretion of the Investigator. However, should the need arise to modify/adjust a patient's therapy due to a concern for patient safety and/or tolerability* 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."

11. **STUDY PROCEDURES – Vital Sign Measurements, Section 8.2.4.1, pages 27-28, 2nd paragraph – This paragraph was revised to remove the requirement to capture the measurement by using Sponsor provided equipment. The paragraph now reads:**

"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. All measurements should be assessed on the same arm, and by the same technician where possible."

12. **SAFETY REPORTING – Serious Adverse Events (SAEs), Section 9.2, pages 33-34, bullet #3 – This bullet was modified to include reference to a new section defining hospitalization as an SAE. The revised bullet now reads:**

"Inpatient hospitalization or prolonging of an existing hospitalization *(see Section 9.2.1 for information on hospitalization as an SAE);*"

13. **SAFETY REPORTING – Hospitalization as an SAE, Section 9.2.1, pages 34 – This section was inserted to further define hospitalization and subsequent reporting expectations. The new section now reads:**

"Hospitalization is defined as any in-patient overnight stay in a hospital. A hospitalization in and of itself does not constitute an SAE. The condition which caused the hospitalization must be evaluated and determined to be an AE. Although an AE which results in hospitalization is an SAE, patients are hospitalized for a variety of reasons which may not be associated with or considered an SAE (eg, convenience, logistics, preference, etc). Therefore, each case of hospitalization must be evaluated separately.

For example, the following would not be considered SAEs:

- Hospitalization for a preexisting condition which did not worsen (eg, cataract surgery)
- Hospitalization solely for a procedure or treatment that was not performed to treat an AE
- Hospitalization for a condition that does not normally require treatment, but electively done (eg, cosmetic surgery)
- Hospitalization strictly for convenience reasons or observations (eg, procedures only performed in a hospital because of the distance the subject lives from the hospital)"

14. **STATISTICAL METHODOLOGY – Interim Analysis, Section 10.4.5, page 39, 2nd paragraph – This paragraph was modified to provide information regarding how the study will be reported. The revised paragraph now reads:**

"The study *may* be analyzed and reported in *multiple* phases. The first report will summarize data obtained from all patients providing information up to a specified data cut-off point. The *following reports* will update the initial report by including data from the remaining portion of the study. 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."

15. APPENDIX A – Schedule of Events, Section 13, page 43 – The Schedule of Events has been updated to reflect the following changes:

- Dispensation of LX1606 at Week 48
- Remove EOS from Week 48
- Remove serum pregnancy testing from the study
- Add urine pregnancy tests to be conducted for females of child-bearing potential at all study weeks
- Addition of Week 60, Week 72, and Week 84/EOS visits
- Update footnote to reflect new EOS visit

Changes are indicated by highlighted cells in 'Revised Appendix A – Schedule of Events' table below.

Revised Appendix A – Schedule of Events

Procedure	Extension Period								2-Week Follow-up[4]
	Baseline Day 1[1]	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84 / EOS	
Tolerance (days)	NA	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5
Inclusion/Exclusion criteria	X								
Medical history	X								
Physical examination incl. weight	X	X[3]	X[3]	X[3]	X	X[3]	X[3]	X	X[5]
Urine pregnancy test[2]	X	X	X	X	X	X	X	X	X
~~Serum pregnancy test~~[2]						-	-	-	-
Hematology, Blood chemistry	X	X	X	X	X	X	X	X	X[5]
Urinalysis	X				X			X	X[5]
Chromogranin A	X				X			X	
Vital signs	X	X	X	X	X	X	X	X	X
ECG	X				X			X	X[5]
Subjective Global Assessment	X	X	X	X	X	X	X	X	X
EORTC QLQ-C30 & GI.NET21	X		X		X		X	X	
Sleep and Depression Assessment	X	X	X	X	X	X	X	X	X
Plasma 5-HIAA	X	X	X	X	X	X	X	X	X
Dispensation of LX1606	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

[1]Eligibility will be determined at last visit of the original protocol; Day 1 will replace the next scheduled visit in the original protocol schedule. Visits should coincide with LAR injections for those patients receiving SSA therapy. [2]Females of child-bearing potential only. [3]Brief physical examination only (symptom-oriented, including weight). [4]Visit 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. [5]To be performed only if evaluation at Week ~~48~~84/EOS is abnormal.

16. Appendix B – Amount of Blood to be Collected from Each Patient, Section 14, page 44 – This section has been modified to reflect estimated volume of blood collected based upon changes reflected in Appendix A. Changes are indicated by highlighted cells. The revised table now reads:

Assessment		Sample volume (mL)	Number of samples*	Estimated total volume (mL)
Safety	Hematology	2	9	18
	Blood chemistry	6	9	54
Other	CgA	2	3	6
	~~Serum Pregnancy~~	~~2~~	~~0~~	~~0~~
Pharmacodynamic	Plasma 5-HIAA	4	9	36
			Total	114
*Maximum number of samples is indicated				

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CLINICAL STUDY PROTOCOL

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
EudraCT Number	2013-002596-18
Investigational Phase:	3
Protocol Title:	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Study Name:	TELEPATH (**Tel**otristat **E**tiprate – Expanded Treatment for **Pat**ients wit**h** Carcinoid Syndrome)
Amendment 1 Date:	31 January 2014
Original Version Date:	14 June 2013
Sponsor:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: 001 (281) 863-3000 Safety Hotline: 001 (877) 372-3597 Safety Data Facsimile: 001 (832) 442-5917

Lexicon Pharmaceuticals, Inc.
8800 Technology Forest Pl.
The Woodlands, TX 77381-1160

Investigator Signature Page

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
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By my signature below, I hereby attest that I have read and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol and will conduct the study in accordance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance.

Additionally, I will not initiate this study without written and dated approval from the appropriate Institutional Review Board (IRB)/ Ethic Review Committee (ERC), and I understand that any changes in the protocol must be approved in writing by the Sponsor, the IRB/ERC, and, in certain cases the Food and Drug Administration (FDA) or other applicable regulatory agencies, before they can be implemented, except where necessary to eliminate hazards to patients.

Principal Investigator's Signature — Date

Principal Investigator's Name (Print) [redacted]

Lexicon [redacted] (Signature) — Date

[redacted] M.D

Lexicon [redacted] (Printed Name)

1. Synopsis

Name of Study Drug	Telotristat etiprate
Protocol Number	LX1606.1-302-CS LX1606.302 (Abbreviated number)
Protocol Title	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Primary Objective	The primary objective of this study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate
Secondary Objective	To evaluate long-term changes in patients' quality of life (QOL)
Phase of Development	3
Methodology	The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate. Patients currently participating in any LX1606 Phase 2 carcinoid syndrome (CS) study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original study to LX1060.1-302-CS. Following confirmation of eligibility, patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label study drug at the same dose level and regimen as identified in their original study. Downward dose adjustment will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. Patients may return to the previous dosing at the discretion of the Investigator and in consultation with the Medical Monitor. Upon completion or early withdrawal from treatment, all patients will be required to complete a 14-day Follow-up Period, during which no study drug will be administered.

	A Data Safety Monitoring Board (DSMB) will review safety data quarterly throughout the study.
Number of Patients	Up to 100 patients are expected to participate in this study.
Patients	Eligible patients are defined as those that are currently participating in a Phase 2 or Phase 3 telotristat etiprate carcinoid syndrome study.
Number of Study Sites	Approximately 70 sites
Treatments	Telotristat etiprate, 250 mg tablet, administered at the same dose level and regimen identified in the patient's original study
Route of Administration	Oral
Duration of Participation	Up to 50 weeks including Treatment and Follow-up
Inclusion Criteria	Patients must meet all of the following criteria to be considered eligible to participate in the study: 1. Ongoing participation in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study 2. 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 entry are confirmatory in the absence of a clear postmenopausal history. 3. Ability and willingness to provide written informed consent prior to participation in any study-related procedure

Exclusion Criteria	Patients who meet any of the following criteria will be excluded from participating in the study: 1. Major protocol violations or tolerability concerns in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study 2. Positive pregnancy test 3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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 4. Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities
Statistical Methods	Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study and combined across all treated patients. Primary analyses of the data will be based on the Safety population which includes all patients treated on Day 1 of this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.
Study Assessments	<u>Safety</u> Safety assessments include monitoring of adverse events, clinical laboratory tests, vital signs measurements, 12-lead ECG, and physical examinations <u>Efficacy</u> Efficacy assessments will include patient reported quality of life measures as captured in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and the module specific for gastrointestinal symptoms of carcinoid neuroendocrine tumors (GI.NET21) and subjective global

	assessment of symptoms associated with CS Pharmacodynamics Pharmacodynamic (PD) assessments include determination of 5-HIAA levels in plasma
Efficacy Data Analysis	All efficacy and PD variables will be summarized descriptively and listed. Statistical tests and estimates of within patient effects for the efficacy and PD measures will be derived from application of a mixed linear model with repeated measures. The form of the model will be specific to measurement properties of the dependent variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model. Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to patients' LX1606 dose level on Day 1 of this study.
Safety Data Analysis	Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group, and as needed, by study visit. Treatment-emergent adverse event 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 serious adverse events. Vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) 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.

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2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ALP	alkaline phosphatase
AST	aspartate transaminase
bid	twice daily
BM	bowel movements
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CgA	chromogranin A
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CS	carcinoid syndrome
CT	computed tomography
DSMB	Data Safety Monitoring Board
EC	enterochromaffin
ECG	electrocardiogram
ERC	Ethic Review Committee
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HEENT	head, eyes, ears, nose, and throat
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
IND	Investigational New Drug

Continued on the next page

Abbreviation	Definition
IRB	Institutional Review Board
ITT	intent-to-treat
IMP	Investigational Medicinal Product
IWRS	interactive web response system
LAR	long-acting release
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MCP	multiple comparison procedure
MRI	magnetic resonance imaging
NET	neuroendocrine tumor
NRS	numeric rating scale
OOR	out-of-range
OTC	over-the-counter
PD	pharmacodynamic
PK	pharmacokinetic
qd	once daily
SAE	serious adverse event
SBS	short bowel syndrome
SOP	standard operating procedure
SSA	somatostatin analog
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse events
tid	3 times daily
TPH	tryptophan hydroxylase
ULN	upper limit of the normal reference range
WRS	Wilcoxon rank sum

Definitions of Terms

Term	Definition
LP-778902	active moiety of LX1606
LX1606	ethyl-ester prodrug of the active moiety LP-778902; a serotonin synthesis inhibitor being developed by Lexicon Pharmaceuticals, Inc.
QTcF	corrected QT interval using Fredericia's formula

3. Introduction

3.1 Background on Telotristat Etiprate (LX1606) and Disease

Serotonin (5-HT) plays a critical role in regulating several major physiological processes of the gastrointestinal tract, including aspects of secretion, motility, inflammation and sensation. Enterochromaffin (EC) cells release 5-HT when the intestinal wall is stimulated by intraluminal pressure or chemicals. Through multiple classes of receptors, 5-HT is believed to initiate directly, or facilitate, peristaltic and secretory reflexes. 5-HT is also reportedly involved in the pathophysiology of various types of functional gastrointestinal (GI) disorders, valvular heart disease, and may play a role in the pathophysiology of inflammatory bowel disease (IBD).

Carcinoid tumors are mostly derived from EC cells of the midgut, and often produce and release large amounts of 5-HT. Such excess of 5-HT is believed to be responsible for the severe diarrhea and eventual valvular heart damage and mesenteric fibrosis in patients with carcinoid syndrome (CS).[1-3] Inhibition of tryptophan hydroxylase (TPH) activity in carcinoid tumors should lead to a reduction of peripheral 5-HT in afflicted patients and thus an amelioration of the pathophysiology and symptomology of CS. A peripheral TPH inhibitor, such as telotristat etiprate, should alleviate the symptoms due to excess 5-HT in carcinoid patients without central nervous system (CNS)-related adverse events (AEs).

Approximately 90% of the body's 5-HT is found in the EC cells of the GI tract, with the remainder distributed between the platelets and CNS.[4] TPH catalyzes the biopterin-dependent monooxygenation of tryptophan to 5-hydroxytryptophan, which is subsequently decarboxylated to form 5-HT. Expression of TPH is limited to a few specialized tissues: raphe neurons, pinealocytes, mast cells, mononuclear leukocytes, beta cells of the islets of Langerhans, and intestinal and pancreatic EC cells.[5] Two isoforms of the enzyme exist, TPH1 and TPH2. TPH1 is exclusively located in the EC cells of the GI tract and pineal gland and is the rate limiting enzyme responsible for the majority of systemic 5-HT production and is also responsible for 5-HT synthesis in carcinoid tumors. TPH2 is located in the central and enteric nervous systems and is the rate-limiting enzyme in the production of neuronal 5-HT.

The oral TPH inhibitor, telotristat etiprate, represents a novel approach to potentially lessen the pathophysiology of CS by reducing 5-HT levels via inhibition of TPH. Telotristat etiprate was designed specifically as a prodrug in order to gain greater systemic exposure, opening the potential application for indications in which hyperserotonemia is thought to contribute to the disorder, such as CS. Preclinical pharmacology studies of telotristat etiprate were designed to evaluate the compound’s mechanism of action and effects in vivo. Telotristat etiprate is the ethyl-ester prodrug of the active moiety LP-778902. Telotristat etiprate was

designed as a prodrug in order to enhance peripheral exposure without crossing the blood-brain barrier. In vivo, telotristat etiprate is readily converted through esterase activity to its corresponding acid, LP-778902. LP-778902 has an in vitro potency of 0.028 μM on purified human TPH1 enzyme and 0.032 μM on purified human TPH2 enzyme. Therefore, telotristat etiprate is a robust inhibitor of TPH both in vitro and in vivo and has been shown in Phase 2 studies to provide clinical benefit to patients with carcinoid tumors and associated CS.

Telotristat etiprate is being developed to manage GI symptoms and possibly other symptoms associated with CS. Currently, the standard of care for patients with CS is symptom management using somatostatin analogs (SSA), which are available in both short- and long-acting release (LAR) formulations. Somatostatin analogs such as octreotide are indicated for the control of flushing, diarrhea, and other symptoms associated with CS. Common side effects of the long-acting depot form of the drug are pain at the site of the injection, reported in as many as 30 to 50% of carcinoid patients at the 20 and 30 mg dose levels, and less commonly, stomach cramps, nausea, vomiting, headaches, dizziness, and fatigue.[6] Other side effects identified in the product labeling include biliary tract abnormalities (gallstones, sludge, and dilatation), hypothyroidism, dietary fat malabsorption, and hyper or hypoglycemia.[7] In addition to the morbidity associated with parenterally administered agents, tachyphylaxis will occur in the majority of patients, resulting in recurrent symptoms.

There are currently no specific oral treatments indicated for the management of symptoms associated with CS. As a result of the morbidity associated with SSAs and the associated tachyphylaxis, there is an unmet medical need to provide symptom management and modify the pathophysiology of patients with metastatic CS. Inhibition of the excessive 5-HT produced by these tumors with an orally delivered agent such as telotristat etiprate could provide significant benefit as an additional treatment option for patients and clinicians.

3.2 Clinical Trials of Telotristat Etiprate (LX1606) in Humans

Telotristat etiprate has been studied in single/multiple doses in Phase 1 studies, approximately 109 healthy volunteers participated in Phase 1 trials with 88 subjects receiving telotristat etiprate and 21 subjects receiving placebo. In addition, 37 patients with CS have received telotristat etiprate during the clinical development program in Phase 2. An additional 59 patients with ulcerative colitis have been enrolled into an ongoing Phase 2 study to evaluate telotristat etiprate versus placebo in patients with ulcerative colitis experiencing active flares.

3.2.1 Phase 1 Studies

LX1606.1-101-NRM utilized telotristat etiprate as a single oral dose and was noted to be safe and well tolerated up to doses of 1,000 mg. At doses of ≥1,000 mg, an increase in GI AEs was observed, which were assessed as at least possibly related to study drug. These AEs led

to a decision not to escalate the dose beyond 1,500 mg. No serious adverse events (SAEs) or deaths were reported and no patient discontinued due to an AE. Twenty-three patients experienced at least 1 AE. The majority of the AEs were assessed as mild. The most common AEs were diarrhea and nausea. Random out-of-range laboratory values at various time points in several patients occurred without any apparent trend. There were no other clinically significant vital signs, laboratory or physical examination findings.

LX1606.1-102-NRM utilized telotristat etiprate as multiple oral doses over 14 days and was tolerated up to the maximum dose assessed, 500 mg tid; 1,500 mg total dose daily. Most AEs were mild, the most common being nausea and headache; all resolved. Most AEs were at least possibly related to study treatment. Four AEs required treatment with concomitant medication, 3 AEs of constipation and 1 of headache. No deaths or SAEs were reported. One patient was discontinued due to an AE of abnormal liver function. There were no apparent trends or clinically significant findings observed upon review of vital signs and electrocardiogram (ECG) data. There were no clinically significant abnormal physical examination findings.

Overall, in LX1606.1-102-NRM, treatment with telotristat etiprate was associated with mild elevations, generally ≤2x the upper limit of normal (ULN), in alanine transaminase (ALT) and aspartate transaminase (AST), with elevations in values observed earlier in the higher dose cohorts. Results were assessed as clinically significant for only 1 patient, in Cohort 4, who was withdrawn on Day 10. The trend was most pronounced in Cohort 5, in which 5 out of 6 patients who received telotristat etiprate had increases in ALT values which were above normal range and 4 patients had increases in AST values which were above normal range at Day 14. Mean increases in ALT and AST appeared earlier in the study for Cohorts 4 and 5 than in the other cohorts, and were noted for all cohorts by Day 12. All patients had normal ALT and AST values at Baseline and most elevated transaminases returned to normal range within 48 hours after the last dose of study drug. No changes in alkaline phosphatase (ALP) or total bilirubin were observed in any patient.

LX1606.1-103-NRM evaluated 2 oral formulations of telotristat etiprate in an open-label crossover study. Each formulation was given as a single oral dose followed by a 5-day washout and then patients were given a single oral dose of the second formulation. During this study, there were no deaths or SAEs reported and no AEs lead to discontinuation. The most commonly reported AE was diarrhea. No clinically significant observations or changes in other safety parameters (eg, clinical laboratory evaluations, vital signs, physical examinations, ECGs, and AEs) were identified in the patient population during the study conduct.

3.2.2 Phase 2 Studies

LX1606.1-202-CS was a randomized, double-blind, placebo-controlled, multiple ascending dose study conducted in 2 parts in order to evaluate a total of 23 patients at a dose range of 450 to 1500 mg given as 150, 250, 350, or 500 mg tid (telotristat etiprate or matching placebo) on a background therapy of octreotide. In Part 1, 16 patients were randomly assigned 3:1 into 4 sequential cohorts. Each cohort evaluated 1 of the following daily doses given as 150, 250, 350, or 500 mg tid over a course of 4 weeks. During the study, all patients continued on a stable-dose background therapy of octreotide. In Part 2, an additional 7 patients were randomly assigned 3:1 in order to evaluate 500 mg tid, the highest tolerated dose as determined in Part 1. Upon completion of the initial 4-week portion, eligible patients had the option to continue into an open-label Extension Period.

There was 1 treatment emergent SAE assessed as possibly related to study drug which occurred in the 350 mg tid dose group. The patient had a history of nausea and vomiting and was hospitalized for exacerbation of these conditions.

Telotristat etiprate was generally well tolerated with no evidence of dose-limiting tolerability. Adverse events were mostly mild to moderate and with similar frequencies between treatment groups and placebo. No significant changes in vital signs, ECG, or physical exam findings were noted after administration of telotristat etiprate at any dose level. The most common AEs were GI-related and reported as diarrhea, nausea, and abdominal pain, respectively. The modest elevations in transaminases seen in the Phase 1 multiple ascending dose study (LX1606.1-102-NRM) were not apparent in this 4-week study in patients with CS.

Patients that received telotristat etiprate achieved a clinical response (28%) defined as at least a 30% reduction in bowel movements (BMs) for at least 2 weeks; a biochemical response (56%) defined as at least a 50% reduction or normalization of urinary 5-hydroxyindoleacetic acid (5-HIAA); and reported adequate relief at Week 4 (46%) while no placebo patients experienced clinical response, biochemical response, or adequate relief.

LX1606.1-203 was an open-label, serial ascending, multiple dose, individual titration study that evaluated the same dose ranges as the LX1606.1-202-CS study in a total of 15 patients. Patients were serially escalated to the next dose level every 2 weeks until a maximally tolerated dose or 500 mg tid was reached. Once a dose had been determined, the patient would remain on the dose for an additional 4 weeks. Patients then had the option to continue into an Extension Period.

Telotristat etiprate was generally safe and well-tolerated in subjects with CS in the LX1606.1-203 study. Most AEs were mild to moderate in severity and assessed as unrelated

to study drug. Events in the Gastrointestinal Disorders SOC were common, as is anticipated with the underlying illness.

Statistically significant reductions from Baseline in the mean number of BMs/day were observed in this study throughout the entire dose-escalation and stable-dose phases, as were improvements in stool form. Telotristat etiprate produced an improvement in global assessment of GI symptoms associated with CS in the majority of subjects (12 of 15 subjects, 80%) across the 12-week period. The global assessment of GI symptoms was based on 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 BM, abdominal pain or discomfort?" In addition, subjects experienced statistically significant decreases in the mean daily number of cutaneous flushing episodes.

Thirteen subjects (86.7%) experienced a complete biochemical response (defined as a ≥50% reduction from Baseline in u5-HIAA levels at 1 or more time points). Consistent with the proposed mechanism of action for telotristat etiprate, a complete biochemical response correlated closely with measures of clinical response, such as number of bowel movements per day.

Detailed information regarding the completed clinical studies can be found in the Investigator Brochure.[8]

3.2.3 Ongoing Studies

The open-label extension portions in LX1606.1-202-CS and LX1606.1-203-CS remain ongoing.

LX1606.1-204-UC is currently evaluating patients with active flares of ulcerative colitis. Doses under evaluation are 500 mg once daily (qd) and 500 mg tid vs. placebo; 59 patients have been enrolled for an 8-week treatment period.

LX1606.1-301-CS is intended to evaluate patients who are currently on a background of SSA therapy and still experiencing breakthrough symptoms such as an increased frequency of BMs ≥ 4 per day on average: (1) the efficacy of telotristat etiprate on reducing the number of BMs; (2) the efficacy of telotristat etiprate on a number of clinically relevant secondary endpoints; and, (3) the safety of telotristat etiprate over the 12-week double-blind portion (Treatment Period) of the study. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period (Extension Period).

LX1606.1-303-CS is intended to evaluate patients with carcinoid syndrome whose primary symptoms are not GI related and may be naïve to SSA therapy: (1) the safety of telotristat etiprate over the 12-week double-blind portion (Treatment Period) of the study; (2) percent

(%) change from Baseline in 24-hour u5-HIAA levels at Week 12; (3) the effects of telotristat etiprate on a number of clinically relevant secondary endpoints. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period.

3.3 Rationale for Current Study

3.3.1 Rationale for Selection of Dose

The dose levels of telotristat etiprate selected for this study are consistent with prior clinical study experience and based upon clinical safety and pharmacodynamic (PD) data from 2 Phase 2 multiple ascending-dose studies in patients with symptomatic CS (LX1606.1-202-CS and LX1606.1-203-CS).

Based upon observations noted in Section 3.2, it is anticipated that the doses to be utilized in this protocol will be safe and well tolerated and may provide clinical benefit to patients with CS.

3.3.2 Benefit/Risk Assessment

Clinical experience with telotristat etiprate (treated subjects) consists of completed single and multiple ascending dose studies in 88 normal subjects (36 in single dose studies and 52 in the multiple dose study), two Phase 2 studies (37 patients with symptomatic CS) and 2 ongoing Phase 3 studies in patients with symptomatic CS.

In healthy volunteer studies, single doses up to 1000 mg were found to be generally well tolerated, while at the 1500 mg dose level GI-related adverse events increased. A similar adverse event profile was observed after multiple dose administration over 14 days with GI events predominating. Mild, dose-dependent increases in hepatic transaminase levels (≤2 x ULN) were observed with increased frequency in relation to dose, with 1 subject requiring withdrawal from therapy at the 500 mg bid dose level. Most subjects that were observed to have increased transaminase levels did not exceed >2 x ULN. No abnormalities in total bilirubin were observed at any dose level. GI events have been the most commonly observed events to date. The adverse event profile in normal subjects may differ significantly from what is observed in patients with hyperserotonemia. All adverse events resolved without sequelae. In addition, there were no significant changes in vital signs or ECG. No physical examination abnormalities were noted in studies to date. There were no serious adverse events reported in healthy volunteers.

In patients with CS, dose escalations have proceeded up to and including 500 mg tid. To date, there has been no evidence of dose-limiting intolerability. Dose levels have been generally well tolerated with no evidence to suggest elevations in hepatic transaminase levels. Based upon observations from preclinical and clinical studies conducted to date, it is anticipated that

orally administered telotristat etiprate will be well tolerated at dose levels required to influence peripheral 5-HT production in patients with symptomatic CS. Potential adverse events primarily involve the GI tract, and could include alterations in gut motility, nausea, vomiting, diarrhea, constipation, abdominal bloating, and/or pain. Regular and ongoing clinical and laboratory assessments should detect any of these events, and depending on the type of event, further dose adjustment or discontinuation from the trial would occur. Although CNS effects are not anticipated at dose levels planned for evaluation, standard adverse event questioning and/or physical examination should reveal any subtle CNS findings. As elevations in hepatic transaminase levels were observed with multiple dosing in normal subjects, monitoring clinical laboratory tests of hepatic function will be incorporated into clinical trials conducted in CS patients.

Treatment has the potential to improve several signs and symptoms of CS. The Phase 2 clinical trial results indicated that treatment may lead to improvements in BM frequency, stool consistency, urgency, abdominal pain, diarrhea, flushing, and reductions in 5-HIAA. These potential benefits relate to a unique mechanism of action. Symptomatic improvement may lead to a better quality of life (QOL) for patients with few treatment options available, and a reduction in serotonin may help reduce the risk of carcinoid heart disease. Overall the benefit/risk profile of telotristat etiprate is expected to be favorable for participation in this clinical study.

3.4 Rationale for Study Design and Control Groups

Currently, no approved therapy exists for the treatment of symptoms driven by underlying serotonin pathophysiology of CS in patients whose disease is refractory to SSA therapy or for those patients who are unable to tolerate SSA therapy or who are unwilling to take SSA therapy.

This study will allow for continued access to telotristat etiprate after patients have completed the required study visits in ongoing Phase 2 and Phase 3 studies. Continuation of CS patients into this study will allow for the collection of additional long-term safety and efficacy data, while providing access to patients who may be receiving benefit. The treatment duration is supported by results of chronic toxicology studies (6-month rat and 9-month dog) and the current safety profile from completed and ongoing clinical trials.

4. Study Objectives

4.1 Efficacy Objectives

4.1.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

4.1.2 Secondary Objective(s)

The secondary objective of this study is to evaluate changes in patients' QOL.

4.2 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

5. Investigational Plan

5.1 Overall Study Design

The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate.

Patients currently participating in any LX1606 Phase 2 CS study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original protocol to LX1060.1-302-CS.

Following confirmation of eligibility, patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label LX1606 at the same dose level identified in the original study.

Downward dose adjustment will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. Patients may return to the previous dosing at the discretion of the Investigator and in consultation with the Medical Monitor.

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

A Data Safety Monitoring Board (DSMB) will review safety data quarterly throughout the study.

6. Study Population

Adult patients who are currently participating in ongoing Phase 2 or Phase 3 telotristat etiprate CS clinical protocols will be enrolled into the study. Up to 100 patients are expected to enroll in this study. Approximately 70 sites worldwide will participate in the study. Patients may continue allowed medications as background therapy provided they remain on stable-doses throughout the Treatment Period.

6.1 Inclusion Criteria

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

1. Ongoing participation in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study
2. 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.
3. Ability and willingness to provide written informed consent prior to participation in any study-related procedure.

6.2 Exclusion Criteria

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

1. Major protocol violations or tolerability concerns in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study
2. Positive pregnancy test
3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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
4. Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities

6.3 Criteria for Stopping Treatment/Study Withdrawal

A patient may also be discontinued from the study for the following medical or administrative reasons:

- Withdrawal of consent by the patient or legal guardian
- Noncompliance, including refusal of the study medication and/or failure to adhere to the study requirements as in the study protocol
- Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study
- The Sponsor terminates the study (Section 6.4)
- Pregnancy (Section 9.4.1)

Note: If a patients voluntarily withdraws or is discontinued from study treatment before completing the entire duration of the Treatment Period, 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 Appendix A – Schedule of Events and agree to report any SAEs (Section 9.2) that occur within 30 days following the last dose of telotristat etiprate.

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 Case Report Form (CRF).

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.

6.4 Criteria for Termination of the Study

If the 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; and,
- Insufficient adherence to protocol requirements.

Study termination and Follow-up would be performed in compliance with applicable governing body regulations.

6.5 Clinical Stopping Rules

Criteria for individual patient withdrawal or study termination are summarized in Sections 6.3 and 6.4, respectively.

6.6 Method of Assigning Patients to Treatment

Patients will enter the study at the same dose level and regimen as identified in the prior Phase 2 or Phase 3 CS study. Randomization will not be used to assign patients to study treatments.

6.7 Blinding and Unblinding of Study Medication

This is an open-label study.

6.8 Replacement of Patients

Patients who do not complete the study will not be replaced.

7. Treatment

7.1.1 Telotristat Etiprate (LX1606)

7.1.1.1 Identity

LX1606 hippurate is the salt form of the drug substance. LX1606 hippurate is a crystalline white to off-white to tan solid with a melting point of 147°C. LX1606 is insoluble in water within the pH range of 5 to 9 (≤2 mg/L). It undergoes hydrolysis under strongly basic or strongly acidic conditions. The solubility of LX1606 hippurate in water is about 22 mg/L at 25°C.

Study drug dosage form consists of white coated debossed oval tablets containing 250 mg LX1606.

7.1.1.2 Packaging, Labeling, and Storage

Patients will receive 250 mg telotristat etiprate tablets packaged in 100 cc high density polyethylene bottles with child-resistant polypropylene screw caps and heat-induction seal liners.

Telotristat etiprate should be stored between 15 to 25°C (59 to 77°F).

7.2 Prior and Concomitant Medications

7.2.1 Prior Medications

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

7.2.2 Concomitant Medications

All concomitant medications taken by patients during the study will be recorded on the CRF. Treatment with prescription or over-the-counter (OTC) antidiarrheal therapy, bile acid sequestrants, or pancreatic enzyme is permitted; 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 dosage(s) of all concomitant medication should remain stable. Should the need arise to modify/adjust a patient's therapy 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.

7.2.3 Prohibited Medications or Concomitant Therapy

None

7.3 Administration of Study Medication

All patients will be instructed to take the study medication with food. “With food” means taking telotristat etiprate 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.

Study medication and instructions will be dispensed to patients at each visit as described in the schedule of study procedures (Appendix A).

7.3.1 Treatment Compliance

Patients will be asked to bring their unused or unopened study medication to each visit (Appendix A). At each visit and in the presence of the patient, study site personnel will count returned tablets and reconcile the counts against planned number of doses for that interval. Site personnel will clarify any discrepancy and record this information within the CRF.

Patients must maintain at least 75% compliance in dosing to be deemed as compliant. In the event of a missed or vomited dose, patients will take their subsequent dose of study drug at the next scheduled time point, following the tid dosing regimen of approximately every 6 hours. A dose outside of a 3 hour window should be considered missed. Missed or vomited doses will not be made up.

7.4 Dose Adjustment

Downward dose adjustment of telotristat etiprate will be permitted if evidence of intolerability emerges. After a period at the lowered dose level, patients may resume the previous dosing level at the discretion of the Investigator after consultation with the Medical Monitor. Patients who experience intolerability at the 250 mg tid dose level **must** be discontinued from study treatment. Interruptions or delays in dosing throughout the entire study may be permitted after consultation with the Medical Monitor, at which time the patient will be reassessed for study continuation, dosage reduction, or discontinuation.

8. Study Procedures

A schedule of study assessments is provided in Appendix A.

8.1 Restrictions during Study

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

8.2 Description of Study Assessments

8.2.1 Efficacy Assessments

Efficacy assessments include the patient reported QOL measures; EORTC QLQ-C30 (Appendix D) & GI.NET21 (Appendix E) questionnaires and subjective global assessment of symptoms associated with CS.

A description of the efficacy assessments is provided below.

8.2.1.1 EORTC QLQ-C30 & GI.NET21

Patients will complete the questionnaires during each visit as indicated in Appendix A.

8.2.1.2 Subjective Global Assessment

A subjective global assessment of symptoms associated with CS will be evaluated using 2 methods at each visit.

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."

8.2.2 Clinical Laboratory Assessment

Clinical laboratory assessments will consist of hematology (complete blood count [CBC] with differential and platelet counts), blood chemistry (complete metabolic panel and liver function tests), and urinalysis. 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 9.1 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.

8.2.2.1 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 >3 x 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 >3 x ULN (in patients with previous abnormal liver-test results)

OR

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

For any such event, the Investigator should discuss the Follow-up approach with the 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 function test values 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 continued study participation.

8.2.3 Pharmacodynamic Assessments

8.2.3.1 Plasma 5-HIAA

Fasting blood samples (≥6 hours) 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.

8.2.4 Safety Assessments

In addition to the clinical laboratory assessments described in Section 8.2.2, monitoring of AEs is also considered a safety assessment and is described in detail in Section 9. Clinically significant changes compared with Baseline findings for these variables should be reported as AEs on the CRF. Clinically significant changes compared with Baseline values, which are determined to be AEs, 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.

8.2.4.1 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 with 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. 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 Appendix A.

8.2.4.2 Physical Examinations

Complete physical examinations will be performed as outlined in Appendix A. 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, weight will be captured during each physical examination. Efforts should be made to standardize 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.

8.2.4.3 Electrocardiograms

Electrocardiograms (12-lead ECGs) will be performed as specified in Appendix A.

8.2.4.4 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.

8.2.4.4.1 Central Nervous System Events

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

8.2.4.4.1.1 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.

8.3 Other Assessments

8.3.1 Chromogranin A (CgA)

Blood samples for measurement of chromogranin A (CgA) levels will be collected as indicated in Appendix A.

8.3.2 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 [eg, PET, CAT, MRI scans of tumor], Investigator assessment of disease status) while the patient is enrolled in the study.

8.3.3 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.

8.4 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.

8.4.1 Blood Collection

An attempt should be made to collect all samples as per the schedule outlined in Appendix A. Any portion of samples remaining after the required tests for this study have been completed will be destroyed.

The estimated amount of blood scheduled for collection per patient, over the course of the study, may be found in Appendix B.

9. Safety Reporting

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

Sites in North America:

[redacted], MD
[redacted]
INC Research
[redacted]
Phone: [redacted]

Sites outside North America:

[redacted], MD, PhD
[redacted]
INC Research
[redacted]
The Netherlands
Phone: [redacted]
Mobile: [redacted]

[redacted], MD, PhD
Medical Monitor
INC Research, LLC
[redacted]
Czech Republic
Phone: [redacted]
Fax: [redacted]

After-hours 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. **Note**: These calls are not toll-free.

9.1 Adverse Events

It is the responsibility of the Investigator to document all AEs that occur during the study.

Adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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 considered related to the study medication. This definition includes an exacerbation of preexisting 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 9.2) 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

9.2 Serious Adverse Events (SAEs)

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

1. Death
2. A life-threatening adverse event;
3. Inpatient hospitalization or prolonging of an existing hospitalization;
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
5. A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

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: [redacted]
Belgium: [redacted]
Brazil: [redacted]
France: [redacted]
Germany: [redacted]
Israel: [redacted]
Italy: [redacted]
Netherlands: [redacted]
Spain: [redacted]
Sweden: [redacted]
United Kingdom: [redacted]

Email Address (in case of fax failure): [redacted]

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.

9.3 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.

9.4 Precautions

9.4.1 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 9.2 for contact information).

10. Statistical Methodology

10.1 Determination of Sample Size

No formal sample size calculation was made. The number of patients expected to participate in this study was calculated from estimated enrollment rates from other carcinoid cancer trials employed in the LX1606 clinical program.

10.2 Analysis Populations

Per protocol: A Per Protocol population will consist of those patients that receive study treatment and have no major protocol violation that would interfere with the collection or interpretation of the efficacy data. The primary analyses of efficacy will be based on the safety population; 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 during this study.

10.3 Study Endpoints

10.3.1 Efficacy Endpoints

The primary efficacy endpoint is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

Secondary efficacy endpoint is to evaluate changes in patients' QOL over multiple years of therapy.

10.3.2 Safety Endpoints

Safety endpoints are as follows:

- Incidence of TEAEs, suspected adverse reaction, AEs leading to discontinuation from the study, SAEs, and deaths
- Actual and change from Baseline in clinical laboratory results
- Actual and change from Baseline in vital signs results
- Actual and change from Baseline in physical examinations
- Actual and change from Baseline in ECG findings

10.4 Statistical Methods

Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values.

Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study and combined across all treated patients. All data will be listed.

Primary analyses of the data will be based on the Safety population which includes all patients treated with any fraction of study drug during this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. This dataset will include the Safety population, but limited to those patients that have at least one assessment post Day 1 and do not have any protocol violations that would interfere with collection or interpretation of the data. The Per Protocol analysis will be applied to the QOL measures, subjective global assessment, and plasma 5-HIAA values.

Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.

10.4.1 Efficacy Analyses

All efficacy and PD variables will be summarized descriptively and listed.

Statistical tests and estimates of within patient effects for these measures will be derived from application of a mixed linear model with repeated measures. The model will be generalized to handle missing data and specific to the measurement properties of the dependent variable. There is no plan to impute data for missing observations for any variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model.

Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to how patients were dosed on Day 1 of this study.

10.4.2 Safety Analyses

Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group (corresponding to the LX1606 dose given on Day 1), pooled across all patients, and as needed, by study visit. All safety data will be listed.

Treatment-emergent adverse event 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 serious adverse events.

Vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) 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 and summarized.

10.4.2.1 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.

10.4.2.2 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 using descriptive statistics. Summaries of shifts from Baseline to abnormal clinical laboratory results will also be provided. Actual and change from Baseline in chromogranin A levels will be summarized descriptively as well.

10.4.2.3 Vital Sign Measurements

Actual and changes from Baseline (Day 1) in vital signs results will be summarized by using descriptive statistics.

10.4.2.4 Electrocardiograms

Clinically significant changes in ECGs compared to Baseline, as determined by the Investigator, will be summarized by using descriptive statistics. Actual and change from Baseline (Day 1 predose values) to each time point in corrected QT interval (QTcF) will be summarized as well.

10.4.3 Pharmacodynamic Analyses

Analysis and summarization of the plasma 5-HIAA data are described in Section 10.4.1.

10.4.4 Baseline Characteristics and Other Summaries

Treatment group differences will be summarized descriptively for demographic data, prior and concomitant medications, treatment compliance, and final disposition. Data collected from assessments of tumor status, when available, will be listed.

Protocol deviations will provided as listings.

10.4.5 Interim Analysis

An independent DSMB will be charged with reviewing interim safety data on a quarterly basis 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 up to a specified data cut-off point. The second report will update the initial report by including data from the remaining portion of the study. 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.

11. Study Management

The Investigator is responsible for completing and maintaining adequate and accurate CRFs and source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, and discharge summaries.

All data on the CRF must be recorded in accordance with the CRF guidelines. If a correction is necessary, it should be made by the Investigator or a designated qualified individual as specified within the guideline. All CRFs should be completed in their entirety and stored in a secure location. The Investigator must sign the Investigator's statement in each patient's CRF indicating that the data reported are accurate.

At the study site, clinical research associates will verify 100% of CRFs in their entirety against source documentation. Computer programmed edit checks will be run against the database to check for discrepancies and reasonableness of the data, and the safety database will be reconciled with the clinical database. All issues resulting from the computer generated

checks and the safety database reconciliation will be resolved according to standard data management practices in conjunction with the Sponsor, clinical study personnel, and the study Investigators.

11.1 Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the Sponsor's study monitors will contact the study site via visits to the site, telephone calls, and/or letters in order to review study progress, CRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of patients, patient recruitment, patient compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by patients, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

The Investigator must make study data accessible to the clinical monitor, to other authorized representatives of the Sponsor, and to regulatory inspectors

11.2 Audits and Inspections

The Sponsor, regulatory authority, or IRB/ERC may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a Sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

11.3 Amendments

Any amendments to the protocol will be written and approved by the Sponsor. All amendments must be submitted to the IRB/ERC for approval prior to implementing the changes. In some instances, an amendment may require changes to the informed consent form, which also must be submitted for IRB/ERC approval prior to administration to patients. If any changes to the CRF are required, the Sponsor will issue supplemental or revised CRF pages.

11.4 Record Keeping

11.4.1 Drug Accountability

The Investigator must maintain accurate records of receipt of study drug, dispensing information (date, lot, and dose for each patient), and the prompt return or destruction of unused supplies. If the Investigator cannot account for all clinical supplies at the termination of the study, a written explanation must be provided.

11.4.2 Health Insurance Portability Accountability Act of 1996 and Subsequent Updates

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 Code of Federal Regulations (CFR) Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation and any applicable updates). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

11.4.3 Financial Disclosure

The Investigator shall provide to the Sponsor sufficient accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the FDA and/or other applicable regulatory agencies. The Investigator shall promptly update this information if any relevant changes occur in the course of the study or for 1 year following completion of the study.

11.4.4 Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 11) to ensure data integrity. “Original” in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

11.4.5 Retention of Study Documents

According to 21 CFR Part 312.62 and ICH E6, study-related records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the

investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor.

The Investigator must not destroy any study-related records without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor must be contacted to arrange alternative record storage options.

12. Administrative Structure of the Study

The study will be monitored by Sponsor personnel or Sponsor representative. The following functions for this study will be performed by organizations designated by the Sponsor: data management and statistical analysis, including PD analysis and reporting.

13. Appendix A – Schedule of Events

Procedure	Extension Period					2 Week Follow-up[4]
	Baseline Day 1[1]	Week 12	Week 24	Week 36	Week 48/ EOS	
Tolerance (days)	NA	± 5	± 5	± 5	± 5	± 5
Inclusion/Exclusion criteria	X					
Medical history	X					
Physical examination incl. weight	X	X[3]	X[3]	X[3]	X	X[5]
Urine pregnancy test[2]	X	X	X	X		X
Serum pregnancy test[2]					X	
Hematology, Blood chemistry	X	X	X	X	X	X[5]
Urinalysis	X				X	X[5]
Chromogranin A	X				X	
Vital signs	X	X	X	X	X	X
ECG	X				X	X[5]
Subjective Global Assessment	X	X	X	X	X	X
EORTC QLQ-C30 and GI.NET21	X		X		X	
Sleep and Depression Assessments	X	X	X	X	X	X
Plasma 5-HIAA	X	X	X	X	X	X
Dispensation of telotristat etiprate (LX1606)	X	X	X	X		
Concomitant medications	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X

[1]Eligibility will be determined at last visit of the original protocol; Day 1 will replace the next scheduled visit in the original protocol schedule. Visits should coincide with LAR injections for those patients receiving SSA therapy. [2]Females of child-bearing potential only. [3]Brief physical examination only (symptom-oriented, including weight). [4]Visit 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. [5]To be performed only if evaluation at Week 48/EOS is abnormal.

14. Appendix B – Amount of Blood to be Collected from Each Patient

Assessment		Sample volume (mL)	Number of samples*	Estimated total volume (mL)
Safety	Hematology	2	6	12
	Blood chemistry	6	6	36
Other	CgA	2	2	4
	Serum Pregnancy	2	1	2
Pharmacodynamic	Plasma 5-HIAA	4	6	24
			Total	78
*Maximum number of samples is indicated				

15. Appendix C – EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Lexicon

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

16. Appendix D – EORTC QLQ - GI.NET21

ENGL201

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31. Did you have hot flushes?		1	2	3	4
32. Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33. Did you have night sweats?		1	2	3	4
34. Did you have abdominal discomfort?		1	2	3	4
35. Did you have a bloated feeling in your abdomen?		1	2	3	4
36. Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37. Have you had acid indigestion or heartburn?		1	2	3	4
38. Have you had difficulties with eating?		1	2	3	4
39. Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40. Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41. Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42. Were you concerned about disruption of home life?		1	2	3	4
43. Have you worried about your health in the future?		1	2	3	4
44. How distressing has your illness or treatment been to those close to you?		1	2	3	4
45. Has weight loss been a problem for you?		1	2	3	4
46. Has weight gain been a problem for you?		1	2	3	4
47. Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48. Have you had aches or pains in your muscles or bones?		1	2	3	4
49. Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:					
50. Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51. Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

17. Appendix E – Ethical Standards

Ethics and Regulatory Considerations

This study will be conducted according to GCP, 21 CFR Part 50, (Protection of Human Subjects), 21 CFR Part 56 (Institutional Review Boards), International Conference on Harmonisation Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

General Instructions

The FDA regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to GCP regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- Current FDA Guideline for the Monitoring of Clinical Investigations
- Current Guidance for Institutional Review Boards and Clinical Investigators
- ICH E6 – Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

Studies conducted in the European Union are also regulated by Volume 10 of the publications "The rules governing medicinal products in the European Union".

Copies of these materials are available from the Sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- the study is conducted with diligence and in conformance with the protocol in such a way as to insure the integrity of the findings;
- the potential benefits of the research justify the risks.

Lexicon Pharmaceuticals, Inc. is the Sponsor of the IND. The Sponsor is responsible for the following:

- selecting qualified Investigators,
- providing Investigators with the information they need to properly conduct an investigation,
- ensuring proper monitoring of the investigation,
- ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- maintaining the IND, and
- ensuring that regulatory authorities and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied
- ensuring the study is conducted in accordance to FDA and ICH guidelines and all applicable regulations

18. Appendix F – Investigator Obligations

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56 and ICH E6, the study protocol and the final version of the subject informed consent form will be approved by the IRB/ERC before enrollment of any subjects. The opinion of the IRB/ERC will be dated and given in writing. A copy of the letter of approval from the IRB/ERC and a copy of the approved informed consent form will be received by the Sponsor prior to shipment of study medication supplies to the Investigator.

The Investigator will ensure that the IRB/ERC will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to subjects. The Investigator will also ensure that no changes will be made to the protocol without IRB/ERC approval.

As a part of the IRB/ERC requirement for continuing review of approved research, the Investigator will be responsible for submitting periodic progress reports to the IRB/ERC at intervals appropriate to the degree of subject risk involved, but no less than once per year.

Written informed consent must be given freely and obtained from every subject prior to clinical trial participation. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

As described in GCP guidelines, study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (eg, loss of medical licensure, debarment). Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

Principal Investigators must provide Lexicon with a fully executed Form FDA 1572 (statement of Investigator) and all updates on a new fully executed Form FDA 1572.

Principal Investigators must provide Lexicon with his/her own curriculum vitae and current curriculum vitae for each sub-Investigator listed on Form FDA 1572.

Protection of Human Subjects (21 CFR Part 50 and ICH E6)

Informed consent must be obtained from every subject before entry into a clinical study. It must be given freely and not under duress. Consent must be documented by use of an IRB/ERC-approved consent form and signed by the subject or the subject's legally authorized representative. The US Department of Health and Human Services suggests that when minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent, his signature should also be included. Non-English-speaking subjects must be presented with

a consent form written in a language that they understand. A copy of the signed consent form must be given to the subject signing it. Another copy must be kept in the Investigator's files and made available to regulatory authority representatives upon request. If, for any reason, subject risk is increased as the study progresses, a revised, IRB/ERC-approved consent form must be signed by the subject. Before the study begins, a sample of the consent form must be provided to the Sponsor for review. The FDA and/or other applicable regulatory agencies may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all subjects.

Only in the case of a life-threatening incident may an investigational product be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the Investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB/ERC within 5 working days. In this situation, the Investigator may not administer any subsequent product to that subject until informed consent and IRB/ERC approval are obtained.

Informed Consent

Written informed consent must be obtained from each subject prior to entry in the study. One copy of the signed informed consent document will be given to the subject, and another will be retained by the Investigator. Additionally, the subject must be allowed adequate time to consider the potential risks and benefits associated with his/her participation in the study.

In situations where the subject is not legally competent to provide consent (ie, mentally incapacitated), written consent must be obtained from a parent, legal guardian, or legal representative. In these situations, the consent must be signed and dated by a witness.

The informed consent document must have been reviewed and approved by the Sponsor and by the Investigator's IRB/ERC prior to the initiation of the study. The document must contain the 8 basic elements of informed consent and may contain the 6 additional elements described in 21 CFR Part 50. Every consent form must include the following 8 elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the subject

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility that the FDA and/or other applicable regulatory authority representatives may inspect the records
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available, or a statement describing where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research related injury
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

When appropriate, 1 or more of the following elements of information shall also be included in the consent form:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent
- Any additional costs the subject may incur from participation in the research
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject
- The approximate number of subjects involved in the study

The Declaration of Helsinki includes further details regarding the specific requirements for informed consent.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states, such as California and Oregon, require further action on the Investigator's part concerning subject consent.

Study Documentation

IRB/ERC Review/Approval

The protocol and informed consent for this study, including advertisements used to recruit subjects, must be reviewed and approved by an appropriate IRB/ERC prior to enrollment of subjects in the study. It is the responsibility of the Investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, ICH, GCP, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB/ERC approval which specifically identifies the study/protocol and a list of the committee members must be received by the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

A progress report with a request for re-evaluation and re-approval will be submitted by the Investigator to the IRB/ERC at intervals required by the IRB/ERC, and not less than annually. A copy of the report will be sent to the Sponsor.

When the Sponsor provides the Investigator with a Safety Report, the Investigator must promptly forward a copy to the IRB/ERC.

After completion or termination of the study, the Investigator will submit a final report to the IRB/ERC and to the Sponsor, if required. This report should include: deviations from the protocol, the number and types of subjects evaluated, the number of subjects who discontinued (with reasons), results of the study, if known, and significant AEs, including deaths.

Study Files

The Investigator is required to maintain complete and accurate study documentation in compliance with current Good Clinical Practice standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study. Study documents include, but are not limited to, the Investigator's Brochure, drug accountability records, Sponsor/Investigator correspondence, IRB/ERC correspondence, protocol and amendments, information regarding monitoring activities, subject exclusion records, CRFs, and data queries.

Confidentiality

The anonymity of subjects must be maintained. Patients will be identified by their initials and an assigned subject number on CRFs and other documents submitted to the clinical monitor. Documents that will be submitted to the clinical monitor and that identify the subject (eg, the signed informed consent document) must be maintained in strict confidence by the Principal Investigator, except to the extent necessary to allow auditing by regulatory authorities, the clinical monitor, or Sponsor personnel.

All information regarding the nature of the proposed investigation provided by the Sponsor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB/ERC, the subject, or the regulatory authority) must be kept in confidence by the Investigator.

Drug Accountability

The Investigator or designee is responsible for accountability of the investigational product at the site. The Investigator or designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and return to the Sponsor or alternative disposition of any unused product. These records must include dates, quantities, batch/serial/lot numbers, and expiration dates (if applicable).

The Investigator should ensure that the investigational product is used only in accordance with the protocol

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CLINICAL STUDY PROTOCOL

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
EudraCT Number	2013-002596-18
Investigational Phase:	3
Protocol Title:	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Study Name:	TELEPATH (**Tel**otristat **E**tiprate – Expanded Treatment for **Pat**ients wit**h** Carcinoid Syndrome)
Amendment 1 Date:	30 December 2014 (France only)
Original Version Date:	14 June 2013
Sponsor:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: 001 (281) 863-3000 Safety Hotline: 001 (877) 372-3597 Safety Data Facsimile: 001 (832) 442-5917

Lexicon Pharmaceuticals, Inc.
8800 Technology Forest Pl.
The Woodlands, TX 77381-1160

Investigator Signature Page

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
Protocol Title:	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
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By my signature below, I hereby attest that I have read and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol and will conduct the study in accordance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance.

Additionally, I will not initiate this study without written and dated approval from the appropriate Institutional Review Board (IRB)/ Ethic Review Committee (ERC), and I understand that any changes in the protocol must be approved in writing by the Sponsor, the IRB/ERC, and, in certain cases the Food and Drug Administration (FDA) or other applicable regulatory agencies, before they can be implemented, except where necessary to eliminate hazards to patients.

Principal Investigator's Signature — Date

Principal Investigator's Name (Print) [redacted]

Lexicon [redacted] and [redacted] (Signature) — Date [redacted]

[redacted], M.D

Lexicon [redacted] and [redacted] (Printed Name)

1. Synopsis

Name of Study Drug	Telotristat etiprate
Protocol Number	LX1606.1-302-CS LX1606.302 (Abbreviated number)
Protocol Title	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Primary Objective	The primary objective of this study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate
Secondary Objective	To evaluate long-term changes in patients' quality of life (QOL)
Phase of Development	3
Methodology	The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate. Patients currently participating in any LX1606 Phase 2 carcinoid syndrome (CS) study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original study to LX1060.1-302-CS. Following confirmation of eligibility, patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label study drug at the same dose level and regimen as identified in their original study. Downward dose adjustment will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. Patients may return to the previous dosing at the discretion of the Investigator and in consultation with the Medical Monitor. Upon completion or early withdrawal from treatment, all patients will be required to complete a 14-day Follow-up Period, during which no study drug will be administered.

	A Data Safety Monitoring Board (DSMB) will review safety data quarterly throughout the study.
Number of Patients	Up to 100 patients are expected to participate in this study.
Patients	Eligible patients are defined as those that are currently participating in a Phase 2 or Phase 3 telotristat etiprate carcinoid syndrome study.
Number of Study Sites	Approximately 70 sites
Treatments	Telotristat etiprate, 250 mg tablet, administered at the same dose level and regimen identified in the patient's original study
Route of Administration	Oral
Duration of Participation	Up to 50 weeks including Treatment and Follow-up
Inclusion Criteria	Patients must meet all of the following criteria to be considered eligible to participate in the study: 1. Ongoing participation in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study 2. 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 entry are confirmatory in the absence of a clear postmenopausal history. 3. Ability and willingness to provide written informed consent prior to participation in any study-related procedure

Exclusion Criteria	Patients who meet any of the following criteria will be excluded from participating in the study: 1. Major protocol violations or tolerability concerns in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study 2. Positive pregnancy test 3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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 4. Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities
Statistical Methods	Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study and combined across all treated patients. Primary analyses of the data will be based on the Safety population which includes all patients treated on Day 1 of this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.
Study Assessments	<u>Safety</u> Safety assessments include monitoring of adverse events, clinical laboratory tests, vital signs measurements, 12-lead ECG, and physical examinations <u>Efficacy</u> Efficacy assessments will include patient reported quality of life measures as captured in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and the module specific for gastrointestinal symptoms of

	carcinoid neuroendocrine tumors (GI.NET21) and subjective global assessment of symptoms associated with CS Pharmacodynamics Pharmacodynamic (PD) assessments include determination of 5-HIAA levels in plasma
Efficacy Data Analysis	All efficacy and PD variables will be summarized descriptively and listed. Statistical tests and estimates of within patient effects for the efficacy and PD measures will be derived from application of a mixed linear model with repeated measures. The form of the model will be specific to measurement properties of the dependent variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model. Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to patients' LX1606 dose level on Day 1 of this study.
Safety Data Analysis	Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group, and as needed, by study visit. Treatment-emergent adverse event 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 serious adverse events. Vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) 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.

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2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ALP	alkaline phosphatase
AST	aspartate transaminase
bid	twice daily
BM	bowel movements
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CgA	chromogranin A
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CS	carcinoid syndrome
CT	computed tomography
DSMB	Data Safety Monitoring Board
EC	enterochromaffin
ECG	electrocardiogram
ERC	Ethic Review Committee
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HEENT	head, eyes, ears, nose, and throat
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
IND	Investigational New Drug

Continued on the next page

Abbreviation	Definition
IRB	Institutional Review Board
ITT	intent-to-treat
IMP	Investigational Medicinal Product
IWRS	interactive web response system
LAR	long-acting release
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MCP	multiple comparison procedure
MRI	magnetic resonance imaging
NET	neuroendocrine tumor
NRS	numeric rating scale
OOR	out-of-range
OTC	over-the-counter
PD	pharmacodynamic
PK	pharmacokinetic
qd	once daily
SAE	serious adverse event
SBS	short bowel syndrome
SOP	standard operating procedure
SSA	somatostatin analog
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse events
tid	3 times daily
TPH	tryptophan hydroxylase
ULN	upper limit of the normal reference range
WRS	Wilcoxon rank sum

Definitions of Terms

Term	Definition
LP-778902	active moiety of LX1606
LX1606	ethyl-ester prodrug of the active moiety LP-778902; a serotonin synthesis inhibitor being developed by Lexicon Pharmaceuticals, Inc.
QTcF	corrected QT interval using Fredericia's formula

3. Introduction

3.1 Background on Telotristat Etiprate (LX1606) and Disease

Serotonin (5-HT) plays a critical role in regulating several major physiological processes of the gastrointestinal tract, including aspects of secretion, motility, inflammation and sensation. Enterochromaffin (EC) cells release 5-HT when the intestinal wall is stimulated by intraluminal pressure or chemicals. Through multiple classes of receptors, 5-HT is believed to initiate directly, or facilitate, peristaltic and secretory reflexes. 5-HT is also reportedly involved in the pathophysiology of various types of functional gastrointestinal (GI) disorders, valvular heart disease, and may play a role in the pathophysiology of inflammatory bowel disease (IBD).

Carcinoid tumors are mostly derived from EC cells of the midgut, and often produce and release large amounts of 5-HT. Such excess of 5-HT is believed to be responsible for the severe diarrhea and eventual valvular heart damage and mesenteric fibrosis in patients with carcinoid syndrome (CS).[1-3] Inhibition of tryptophan hydroxylase (TPH) activity in carcinoid tumors should lead to a reduction of peripheral 5-HT in afflicted patients and thus an amelioration of the pathophysiology and symptomology of CS. A peripheral TPH inhibitor, such as telotristat etiprate, should alleviate the symptoms due to excess 5-HT in carcinoid patients without central nervous system (CNS)-related adverse events (AEs).

Approximately 90% of the body's 5-HT is found in the EC cells of the GI tract, with the remainder distributed between the platelets and CNS.[4] TPH catalyzes the biopterin-dependent monooxygenation of tryptophan to 5-hydroxytryptophan, which is subsequently decarboxylated to form 5-HT. Expression of TPH is limited to a few specialized tissues: raphe neurons, pinealocytes, mast cells, mononuclear leukocytes, beta cells of the islets of Langerhans, and intestinal and pancreatic EC cells.[5] Two isoforms of the enzyme exist, TPH1 and TPH2. TPH1 is exclusively located in the EC cells of the GI tract and pineal gland and is the rate limiting enzyme responsible for the majority of systemic 5-HT production and is also responsible for 5-HT synthesis in carcinoid tumors. TPH2 is located in the central and enteric nervous systems and is the rate-limiting enzyme in the production of neuronal 5-HT.

The oral TPH inhibitor, telotristat etiprate, represents a novel approach to potentially lessen the pathophysiology of CS by reducing 5-HT levels via inhibition of TPH. Telotristat etiprate was designed specifically as a prodrug in order to gain greater systemic exposure, opening the potential application for indications in which hyperserotonemia is thought to contribute to the disorder, such as CS. Preclinical pharmacology studies of telotristat etiprate were designed to evaluate the compound’s mechanism of action and effects in vivo. Telotristat etiprate is the ethyl-ester prodrug of the active moiety LP-778902. Telotristat etiprate was

designed as a prodrug in order to enhance peripheral exposure without crossing the blood-brain barrier. In vivo, telotristat etiprate is readily converted through esterase activity to its corresponding acid, LP-778902. LP-778902 has an in vitro potency of 0.028 μM on purified human TPH1 enzyme and 0.032 μM on purified human TPH2 enzyme. Therefore, telotristat etiprate is a robust inhibitor of TPH both in vitro and in vivo and has been shown in Phase 2 studies to provide clinical benefit to patients with carcinoid tumors and associated CS.

Telotristat etiprate is being developed to manage GI symptoms and possibly other symptoms associated with CS. Currently, the standard of care for patients with CS is symptom management using somatostatin analogs (SSA), which are available in both short- and long-acting release (LAR) formulations. Somatostatin analogs such as octreotide are indicated for the control of flushing, diarrhea, and other symptoms associated with CS. Common side effects of the long-acting depot form of the drug are pain at the site of the injection, reported in as many as 30 to 50% of carcinoid patients at the 20 and 30 mg dose levels, and less commonly, stomach cramps, nausea, vomiting, headaches, dizziness, and fatigue.[6] Other side effects identified in the product labeling include biliary tract abnormalities (gallstones, sludge, and dilatation), hypothyroidism, dietary fat malabsorption, and hyper or hypoglycemia.[7] In addition to the morbidity associated with parenterally administered agents, tachyphylaxis will occur in the majority of patients, resulting in recurrent symptoms.

There are currently no specific oral treatments indicated for the management of symptoms associated with CS. As a result of the morbidity associated with SSAs and the associated tachyphylaxis, there is an unmet medical need to provide symptom management and modify the pathophysiology of patients with metastatic CS. Inhibition of the excessive 5-HT produced by these tumors with an orally delivered agent such as telotristat etiprate could provide significant benefit as an additional treatment option for patients and clinicians.

3.2 Clinical Trials of Telotristat Etiprate (LX1606) in Humans

Telotristat etiprate has been studied in single/multiple doses in Phase 1 studies, approximately 109 healthy volunteers participated in Phase 1 trials with 88 subjects receiving telotristat etiprate and 21 subjects receiving placebo. In addition, 37 patients with CS have received telotristat etiprate during the clinical development program in Phase 2. An additional 59 patients with ulcerative colitis have been enrolled into an ongoing Phase 2 study to evaluate telotristat etiprate versus placebo in patients with ulcerative colitis experiencing active flares.

3.2.1 Phase 1 Studies

LX1606.1-101-NRM utilized telotristat etiprate as a single oral dose and was noted to be safe and well tolerated up to doses of 1,000 mg. At doses of ≥1,000 mg, an increase in GI AEs was observed, which were assessed as at least possibly related to study drug. These AEs led

to a decision not to escalate the dose beyond 1,500 mg. No serious adverse events (SAEs) or deaths were reported and no patient discontinued due to an AE. Twenty-three patients experienced at least 1 AE. The majority of the AEs were assessed as mild. The most common AEs were diarrhea and nausea. Random out-of-range laboratory values at various time points in several patients occurred without any apparent trend. There were no other clinically significant vital signs, laboratory or physical examination findings.

LX1606.1-102-NRM utilized telotristat etiprate as multiple oral doses over 14 days and was tolerated up to the maximum dose assessed, 500 mg tid; 1,500 mg total dose daily. Most AEs were mild, the most common being nausea and headache; all resolved. Most AEs were at least possibly related to study treatment. Four AEs required treatment with concomitant medication, 3 AEs of constipation and 1 of headache. No deaths or SAEs were reported. One patient was discontinued due to an AE of abnormal liver function. There were no apparent trends or clinically significant findings observed upon review of vital signs and electrocardiogram (ECG) data. There were no clinically significant abnormal physical examination findings.

Overall, in LX1606.1-102-NRM, treatment with telotristat etiprate was associated with mild elevations, generally ≤2x the upper limit of normal (ULN), in alanine transaminase (ALT) and aspartate transaminase (AST), with elevations in values observed earlier in the higher dose cohorts. Results were assessed as clinically significant for only 1 patient, in Cohort 4, who was withdrawn on Day 10. The trend was most pronounced in Cohort 5, in which 5 out of 6 patients who received telotristat etiprate had increases in ALT values which were above normal range and 4 patients had increases in AST values which were above normal range at Day 14. Mean increases in ALT and AST appeared earlier in the study for Cohorts 4 and 5 than in the other cohorts, and were noted for all cohorts by Day 12. All patients had normal ALT and AST values at Baseline and most elevated transaminases returned to normal range within 48 hours after the last dose of study drug. No changes in alkaline phosphatase (ALP) or total bilirubin were observed in any patient.

LX1606.1-103-NRM evaluated 2 oral formulations of telotristat etiprate in an open-label crossover study. Each formulation was given as a single oral dose followed by a 5-day washout and then patients were given a single oral dose of the second formulation. During this study, there were no deaths or SAEs reported and no AEs lead to discontinuation. The most commonly reported AE was diarrhea. No clinically significant observations or changes in other safety parameters (eg, clinical laboratory evaluations, vital signs, physical examinations, ECGs, and AEs) were identified in the patient population during the study conduct.

3.2.2 Phase 2 Studies

LX1606.1-202-CS was a randomized, double-blind, placebo-controlled, multiple ascending dose study conducted in 2 parts in order to evaluate a total of 23 patients at a dose range of 450 to 1500 mg given as 150, 250, 350, or 500 mg tid (telotristat etiprate or matching placebo) on a background therapy of octreotide. In Part 1, 16 patients were randomly assigned 3:1 into 4 sequential cohorts. Each cohort evaluated 1 of the following daily doses given as 150, 250, 350, or 500 mg tid over a course of 4 weeks. During the study, all patients continued on a stable-dose background therapy of octreotide. In Part 2, an additional 7 patients were randomly assigned 3:1 in order to evaluate 500 mg tid, the highest tolerated dose as determined in Part 1. Upon completion of the initial 4-week portion, eligible patients had the option to continue into an open-label Extension Period.

There was 1 treatment emergent SAE assessed as possibly related to study drug which occurred in the 350 mg tid dose group. The patient had a history of nausea and vomiting and was hospitalized for exacerbation of these conditions.

Telotristat etiprate was generally well tolerated with no evidence of dose-limiting tolerability. Adverse events were mostly mild to moderate and with similar frequencies between treatment groups and placebo. No significant changes in vital signs, ECG, or physical exam findings were noted after administration of telotristat etiprate at any dose level. The most common AEs were GI-related and reported as diarrhea, nausea, and abdominal pain, respectively. The modest elevations in transaminases seen in the Phase 1 multiple ascending dose study (LX1606.1-102-NRM) were not apparent in this 4-week study in patients with CS.

Patients that received telotristat etiprate achieved a clinical response (28%) defined as at least a 30% reduction in bowel movements (BMs) for at least 2 weeks; a biochemical response (56%) defined as at least a 50% reduction or normalization of urinary 5-hydroxyindoleacetic acid (5-HIAA); and reported adequate relief at Week 4 (46%) while no placebo patients experienced clinical response, biochemical response, or adequate relief.

LX1606.1-203 was an open-label, serial ascending, multiple dose, individual titration study that evaluated the same dose ranges as the LX1606.1-202-CS study in a total of 15 patients. Patients were serially escalated to the next dose level every 2 weeks until a maximally tolerated dose or 500 mg tid was reached. Once a dose had been determined, the patient would remain on the dose for an additional 4 weeks. Patients then had the option to continue into an Extension Period.

Telotristat etiprate was generally safe and well-tolerated in subjects with CS in the LX1606.1-203 study. Most AEs were mild to moderate in severity and assessed as unrelated

to study drug. Events in the Gastrointestinal Disorders SOC were common, as is anticipated with the underlying illness.

Statistically significant reductions from Baseline in the mean number of BMs/day were observed in this study throughout the entire dose-escalation and stable-dose phases, as were improvements in stool form. Telotristat etiprate produced an improvement in global assessment of GI symptoms associated with CS in the majority of subjects (12 of 15 subjects, 80%) across the 12-week period. The global assessment of GI symptoms was based on 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 BM, abdominal pain or discomfort?" In addition, subjects experienced statistically significant decreases in the mean daily number of cutaneous flushing episodes.

Thirteen subjects (86.7%) experienced a complete biochemical response (defined as a ≥50% reduction from Baseline in u5-HIAA levels at 1 or more time points). Consistent with the proposed mechanism of action for telotristat etiprate, a complete biochemical response correlated closely with measures of clinical response, such as number of bowel movements per day.

Detailed information regarding the completed clinical studies can be found in the Investigator Brochure.[8]

3.2.3 Ongoing Studies

The open-label extension portions in LX1606.1-202-CS and LX1606.1-203-CS remain ongoing.

LX1606.1-204-UC is currently evaluating patients with active flares of ulcerative colitis. Doses under evaluation are 500 mg once daily (qd) and 500 mg tid vs. placebo; 59 patients have been enrolled for an 8-week treatment period.

LX1606.1-301-CS is intended to evaluate patients who are currently on a background of SSA therapy and still experiencing breakthrough symptoms such as an increased frequency of BMs ≥ 4 per day on average: (1) the efficacy of telotristat etiprate on reducing the number of BMs; (2) the efficacy of telotristat etiprate on a number of clinically relevant secondary endpoints; and, (3) the safety of telotristat etiprate over the 12-week double-blind portion (Treatment Period) of the study. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period (Extension Period).

LX1606.1-303-CS is intended to evaluate patients with carcinoid syndrome whose primary symptoms are not GI related and may be naïve to SSA therapy: (1) the safety of telotristat etiprate over the 12-week double-blind portion (Treatment Period) of the study; (2) percent

(%) change from Baseline in 24-hour u5-HIAA levels at Week 12; (3) the effects of telotristat etiprate on a number of clinically relevant secondary endpoints. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period.

3.3 Rationale for Current Study

3.3.1 Rationale for Selection of Dose

The dose levels of telotristat etiprate selected for this study are consistent with prior clinical study experience and based upon clinical safety and pharmacodynamic (PD) data from 2 Phase 2 multiple ascending-dose studies in patients with symptomatic CS (LX1606.1-202-CS and LX1606.1-203-CS).

Based upon observations noted in Section 3.2, it is anticipated that the doses to be utilized in this protocol will be safe and well tolerated and may provide clinical benefit to patients with CS.

3.3.2 Benefit/Risk Assessment

Clinical experience with telotristat etiprate (treated subjects) consists of completed single and multiple ascending dose studies in 88 normal subjects (36 in single dose studies and 52 in the multiple dose study), two Phase 2 studies (37 patients with symptomatic CS) and 2 ongoing Phase 3 studies in patients with symptomatic CS.

In healthy volunteer studies, single doses up to 1000 mg were found to be generally well tolerated, while at the 1500 mg dose level GI-related adverse events increased. A similar adverse event profile was observed after multiple dose administration over 14 days with GI events predominating. Mild, dose-dependent increases in hepatic transaminase levels (≤2 x ULN) were observed with increased frequency in relation to dose, with 1 subject requiring withdrawal from therapy at the 500 mg bid dose level. Most subjects that were observed to have increased transaminase levels did not exceed >2 x ULN. No abnormalities in total bilirubin were observed at any dose level. GI events have been the most commonly observed events to date. The adverse event profile in normal subjects may differ significantly from what is observed in patients with hyperserotonemia. All adverse events resolved without sequelae. In addition, there were no significant changes in vital signs or ECG. No physical examination abnormalities were noted in studies to date. There were no serious adverse events reported in healthy volunteers.

In patients with CS, dose escalations have proceeded up to and including 500 mg tid. To date, there has been no evidence of dose-limiting intolerability. Dose levels have been generally well tolerated with no evidence to suggest elevations in hepatic transaminase levels. Based upon observations from preclinical and clinical studies conducted to date, it is anticipated that

orally administered telotristat etiprate will be well tolerated at dose levels required to influence peripheral 5-HT production in patients with symptomatic CS. Potential adverse events primarily involve the GI tract, and could include alterations in gut motility, nausea, vomiting, diarrhea, constipation, abdominal bloating, and/or pain. Regular and ongoing clinical and laboratory assessments should detect any of these events, and depending on the type of event, further dose adjustment or discontinuation from the trial would occur. Although CNS effects are not anticipated at dose levels planned for evaluation, standard adverse event questioning and/or physical examination should reveal any subtle CNS findings. As elevations in hepatic transaminase levels were observed with multiple dosing in normal subjects, monitoring clinical laboratory tests of hepatic function will be incorporated into clinical trials conducted in CS patients.

Treatment has the potential to improve several signs and symptoms of CS. The Phase 2 clinical trial results indicated that treatment may lead to improvements in BM frequency, stool consistency, urgency, abdominal pain, diarrhea, flushing, and reductions in 5-HIAA. These potential benefits relate to a unique mechanism of action. Symptomatic improvement may lead to a better quality of life (QOL) for patients with few treatment options available, and a reduction in serotonin may help reduce the risk of carcinoid heart disease. Overall the benefit/risk profile of telotristat etiprate is expected to be favorable for participation in this clinical study.

3.4 Rationale for Study Design and Control Groups

Currently, no approved therapy exists for the treatment of symptoms driven by underlying serotonin pathophysiology of CS in patients whose disease is refractory to SSA therapy or for those patients who are unable to tolerate SSA therapy or who are unwilling to take SSA therapy.

This study will allow for continued access to telotristat etiprate after patients have completed the required study visits in ongoing Phase 2 and Phase 3 studies. Continuation of CS patients into this study will allow for the collection of additional long-term safety and efficacy data, while providing access to patients who may be receiving benefit. The treatment duration is supported by results of chronic toxicology studies (6-month rat and 9-month dog) and the current safety profile from completed and ongoing clinical trials.

4. Study Objectives

4.1 Efficacy Objectives

4.1.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

4.1.2 Secondary Objective(s)

The secondary objective of this study is to evaluate changes in patients' QOL.

4.2 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

5. Investigational Plan

5.1 Overall Study Design

The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate.

Patients currently participating in any LX1606 Phase 2 CS study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original protocol to LX1060.1-302-CS.

Following confirmation of eligibility, patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label LX1606 at the same dose level identified in the original study.

Downward dose adjustment will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. Patients may return to the previous dosing at the discretion of the Investigator and in consultation with the Medical Monitor.

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

A Data Safety Monitoring Board (DSMB) will review safety data quarterly throughout the study.

6. Study Population

Adult patients who are currently participating in ongoing Phase 2 or Phase 3 telotristat etiprate CS clinical protocols will be enrolled into the study. Up to 100 patients are expected to enroll in this study. Approximately 70 sites worldwide will participate in the study. Patients may continue allowed medications as background therapy provided they remain on stable-doses throughout the Treatment Period.

6.1 Inclusion Criteria

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

1. Ongoing participation in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study
2. 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.
3. Ability and willingness to provide written informed consent prior to participation in any study-related procedure.

6.2 Exclusion Criteria

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

1. Major protocol violations or tolerability concerns in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study
2. Positive pregnancy test
3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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
4. Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities

6.3 Criteria for Stopping Treatment/Study Withdrawal

A patient may also be discontinued from the study for the following medical or administrative reasons:

- Withdrawal of consent by the patient or legal guardian
- Noncompliance, including refusal of the study medication and/or failure to adhere to the study requirements as in the study protocol
- Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study
- The Sponsor terminates the study (Section 6.4)
- Pregnancy (Section 9.4.1)

Note: If a patients voluntarily withdraws or is discontinued from study treatment before completing the entire duration of the Treatment Period, 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 Appendix A – Schedule of Events and agree to report any SAEs (Section 9.2) that occur within 30 days following the last dose of telotristat etiprate.

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 Case Report Form (CRF).

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.

6.4 Criteria for Termination of the Study

If the 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; and,
- Insufficient adherence to protocol requirements.

Study termination and Follow-up would be performed in compliance with applicable governing body regulations.

6.5 Clinical Stopping Rules

Criteria for individual patient withdrawal or study termination are summarized in Sections 6.3 and 6.4, respectively.

6.6 Method of Assigning Patients to Treatment

Patients will enter the study at the same dose level and regimen as identified in the prior Phase 2 or Phase 3 CS study. Randomization will not be used to assign patients to study treatments.

6.7 Blinding and Unblinding of Study Medication

This is an open-label study.

6.8 Replacement of Patients

Patients who do not complete the study will not be replaced.

7. Treatment

7.1.1 Telotristat Etiprate (LX1606)

7.1.1.1 Identity

LX1606 hippurate is the salt form of the drug substance. LX1606 hippurate is a crystalline white to off-white to tan solid with a melting point of 147°C. LX1606 is insoluble in water within the pH range of 5 to 9 (≤2 mg/L). It undergoes hydrolysis under strongly basic or strongly acidic conditions. The solubility of LX1606 hippurate in water is about 22 mg/L at 25°C.

Study drug dosage form consists of white coated debossed oval tablets containing 250 mg LX1606.

7.1.1.2 Packaging, Labeling, and Storage

Patients will receive 250 mg telotristat etiprate tablets packaged in 100 cc high density polyethylene bottles with child-resistant polypropylene screw caps and heat-induction seal liners.

Telotristat etiprate should be stored between 15 to 25°C (59 to 77°F).

7.2 Prior and Concomitant Medications

7.2.1 Prior Medications

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

7.2.2 Concomitant Medications

All concomitant medications taken by patients during the study will be recorded on the CRF. Treatment with prescription or over-the-counter (OTC) antidiarrheal therapy, bile acid sequestrants, or pancreatic enzyme is permitted; 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 dosage(s) of all concomitant medication should remain stable. Should the need arise to modify/adjust a patient's therapy 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.

7.2.3 Prohibited Medications or Concomitant Therapy

None

7.3 Administration of Study Medication

All patients will be instructed to take the study medication with food. "With food" means taking telotristat etiprate 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.

Study medication and instructions will be dispensed to patients at each visit as described in the schedule of study procedures (Appendix A).

7.3.1 Treatment Compliance

Patients will be asked to bring their unused or unopened study medication to each visit (Appendix A). At each visit and in the presence of the patient, study site personnel will count returned tablets and reconcile the counts against planned number of doses for that interval. Site personnel will clarify any discrepancy and record this information within the CRF.

Patients must maintain at least 75% compliance in dosing to be deemed as compliant. In the event of a missed or vomited dose, patients will take their subsequent dose of study drug at the next scheduled time point, following the tid dosing regimen of approximately every 6 hours. A dose outside of a 3 hour window should be considered missed. Missed or vomited doses will not be made up.

7.4 Dose Adjustment

Downward dose adjustment of telotristat etiprate will be permitted if evidence of intolerability emerges. After a period at the lowered dose level, patients may resume the previous dosing level at the discretion of the Investigator after consultation with the Medical Monitor. Patients who experience intolerability at the 250 mg tid dose level **must** be discontinued from study treatment. Interruptions or delays in dosing throughout the entire study may be permitted after consultation with the Medical Monitor, at which time the patient will be reassessed for study continuation, dosage reduction, or discontinuation.

8. Study Procedures

A schedule of study assessments is provided in Appendix A.

8.1 Restrictions during Study

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

8.2 Description of Study Assessments

8.2.1 Efficacy Assessments

Efficacy assessments include the patient reported QOL measures; EORTC QLQ-C30 (Appendix D) & GI.NET21 (Appendix E) questionnaires and subjective global assessment of symptoms associated with CS.

A description of the efficacy assessments is provided below.

8.2.1.1 EORTC QLQ-C30 & GI.NET21

Patients will complete the questionnaires during each visit as indicated in Appendix A.

8.2.1.2 Subjective Global Assessment

A subjective global assessment of symptoms associated with CS will be evaluated using 2 methods at each visit.

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."

8.2.2 Clinical Laboratory Assessment

Clinical laboratory assessments will consist of hematology (complete blood count [CBC] with differential and platelet counts), blood chemistry (complete metabolic panel and liver function tests), and urinalysis. 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 9.1 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.

8.2.2.1 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 >3 x 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 >3 x ULN (in patients with previous abnormal liver-test results)

OR

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

For any such event, the Investigator should discuss the Follow-up approach with the 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 function test values 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 continued study participation.

8.2.3 Pharmacodynamic Assessments

8.2.3.1 Plasma 5-HIAA

Fasting blood samples (≥6 hours) 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.

8.2.4 Safety Assessments

In addition to the clinical laboratory assessments described in Section 8.2.2, monitoring of AEs is also considered a safety assessment and is described in detail in Section 9. Clinically significant changes compared with Baseline findings for these variables should be reported as AEs on the CRF. Clinically significant changes compared with Baseline values, which are determined to be AEs, 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.

8.2.4.1 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 with 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. 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 Appendix A.

8.2.4.2 Physical Examinations

Complete physical examinations will be performed as outlined in Appendix A. 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, weight will be captured during each physical examination. Efforts should be made to standardize 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.

8.2.4.3 Electrocardiograms

Electrocardiograms (12-lead ECGs) will be performed as specified in Appendix A.

8.2.4.4 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.

8.2.4.4.1 Central Nervous System Events

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

8.2.4.4.1.1 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.

8.3 Other Assessments

8.3.1 Chromogranin A (CgA)

Blood samples for measurement of chromogranin A (CgA) levels will be collected as indicated in Appendix A.

8.3.2 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 [eg, PET, CAT, MRI scans of tumor], Investigator assessment of disease status) while the patient is enrolled in the study.

8.3.3 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.

8.4 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.

8.4.1 Blood Collection

An attempt should be made to collect all samples as per the schedule outlined in Appendix A. Any portion of samples remaining after the required tests for this study have been completed will be destroyed.

The estimated amount of blood scheduled for collection per patient, over the course of the study, may be found in Appendix B.

9. Safety Reporting

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

Sites in North America:

[redacted], MD
[redacted]
INC Research
[redacted]
Phone: [redacted]

Sites outside North America:

[redacted] MD, PhD
[redacted]
INC Research
[redacted]
The Netherlands
Phone: [redacted]
Mobile: [redacted]

[redacted], MD, PhD
Medical Monitor
INC Research, LLC
[redacted]
Czech Republic
Phone: [redacted]
Fax: [redacted]

After-hours 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. **Note**: These calls are not toll-free.

9.1 Adverse Events

It is the responsibility of the Investigator to document all AEs that occur during the study.

Adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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 considered related to the study medication. This definition includes an exacerbation of preexisting 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 9.2) 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

9.2 Serious Adverse Events (SAEs)

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

1. Death
2. A life-threatening adverse event;
3. Inpatient hospitalization or prolonging of an existing hospitalization;
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
5. A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

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: [redacted]
Belgium: [redacted]
Brazil: [redacted]
France: [redacted]
Germany: [redacted]
Israel: [redacted]
Italy: [redacted]
Netherlands: [redacted]
Spain: [redacted]
Sweden: [redacted]
United Kingdom: [redacted]

Email Address (in case of fax failure): [redacted]

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.

9.3 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.

9.4 Precautions

9.4.1 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 9.2 for contact information).

10. Statistical Methodology

10.1 Determination of Sample Size

No formal sample size calculation was made. The number of patients expected to participate in this study was calculated from estimated enrollment rates from other carcinoid cancer trials employed in the LX1606 clinical program.

10.2 Analysis Populations

Per protocol: A Per Protocol population will consist of those patients that receive study treatment and have no major protocol violation that would interfere with the collection or interpretation of the efficacy data. The primary analyses of efficacy will be based on the safety population; 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 during this study.

10.3 Study Endpoints

10.3.1 Efficacy Endpoints

The primary efficacy endpoint is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

Secondary efficacy endpoint is to evaluate changes in patients' QOL over multiple years of therapy.

10.3.2 Safety Endpoints

Safety endpoints are as follows:

- Incidence of TEAEs, suspected adverse reaction, AEs leading to discontinuation from the study, SAEs, and deaths
- Actual and change from Baseline in clinical laboratory results
- Actual and change from Baseline in vital signs results
- Actual and change from Baseline in physical examinations
- Actual and change from Baseline in ECG findings

10.4 Statistical Methods

Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values.

Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study and combined across all treated patients. All data will be listed.

Primary analyses of the data will be based on the Safety population which includes all patients treated with any fraction of study drug during this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. This dataset will include the Safety population, but limited to those patients that have at least one assessment post Day 1 and do not have any protocol violations that would interfere with collection or interpretation of the data. The Per Protocol analysis will be applied to the QOL measures, subjective global assessment, and plasma 5-HIAA values.

Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.

10.4.1 Efficacy Analyses

All efficacy and PD variables will be summarized descriptively and listed.

Statistical tests and estimates of within patient effects for these measures will be derived from application of a mixed linear model with repeated measures. The model will be generalized to handle missing data and specific to the measurement properties of the dependent variable. There is no plan to impute data for missing observations for any variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model.

Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to how patients were dosed on Day 1 of this study.

10.4.2 Safety Analyses

Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group (corresponding to the LX1606 dose given on Day 1), pooled across all patients, and as needed, by study visit. All safety data will be listed.

Treatment-emergent adverse event 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 serious adverse events.

Vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) 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 and summarized.

10.4.2.1 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.

10.4.2.2 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 using descriptive statistics. Summaries of shifts from Baseline to abnormal clinical laboratory results will also be provided. Actual and change from Baseline in chromogranin A levels will be summarized descriptively as well.

10.4.2.3 Vital Sign Measurements

Actual and changes from Baseline (Day 1) in vital signs results will be summarized by using descriptive statistics.

10.4.2.4 Electrocardiograms

Clinically significant changes in ECGs compared to Baseline, as determined by the Investigator, will be summarized by using descriptive statistics. Actual and change from Baseline (Day 1 predose values) to each time point in corrected QT interval (QTcF) will be summarized as well.

10.4.3 Pharmacodynamic Analyses

Analysis and summarization of the plasma 5-HIAA data are described in Section 10.4.1.

10.4.4 Baseline Characteristics and Other Summaries

Treatment group differences will be summarized descriptively for demographic data, prior and concomitant medications, treatment compliance, and final disposition. Data collected from assessments of tumor status, when available, will be listed.

Protocol deviations will provided as listings.

10.4.5 Interim Analysis

An independent DSMB will be charged with reviewing interim safety data on a quarterly basis 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 up to a specified data cut-off point. The second report will update the initial report by including data from the remaining portion of the study. 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.

11. Study Management

The Investigator is responsible for completing and maintaining adequate and accurate CRFs and source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, and discharge summaries.

All data on the CRF must be recorded in accordance with the CRF guidelines. If a correction is necessary, it should be made by the Investigator or a designated qualified individual as specified within the guideline. All CRFs should be completed in their entirety and stored in a secure location. The Investigator must sign the Investigator's statement in each patient's CRF indicating that the data reported are accurate.

At the study site, clinical research associates will verify 100% of CRFs in their entirety against source documentation. Computer programmed edit checks will be run against the database to check for discrepancies and reasonableness of the data, and the safety database will be reconciled with the clinical database. All issues resulting from the computer generated

checks and the safety database reconciliation will be resolved according to standard data management practices in conjunction with the Sponsor, clinical study personnel, and the study Investigators.

11.1 Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the Sponsor's study monitors will contact the study site via visits to the site, telephone calls, and/or letters in order to review study progress, CRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of patients, patient recruitment, patient compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by patients, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

The Investigator must make study data accessible to the clinical monitor, to other authorized representatives of the Sponsor, and to regulatory inspectors

11.2 Audits and Inspections

The Sponsor, regulatory authority, or IRB/ERC may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a Sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

11.3 Amendments

Any amendments to the protocol will be written and approved by the Sponsor. All amendments must be submitted to the IRB/ERC for approval prior to implementing the changes. In some instances, an amendment may require changes to the informed consent form, which also must be submitted for IRB/ERC approval prior to administration to patients. If any changes to the CRF are required, the Sponsor will issue supplemental or revised CRF pages.

11.4 Record Keeping

11.4.1 Drug Accountability

The Investigator must maintain accurate records of receipt of study drug, dispensing information (date, lot, and dose for each patient), and the prompt return or destruction of unused supplies. If the Investigator cannot account for all clinical supplies at the termination of the study, a written explanation must be provided.

11.4.2 Health Insurance Portability Accountability Act of 1996 and Subsequent Updates

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 Code of Federal Regulations (CFR) Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation and any applicable updates). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

11.4.3 Financial Disclosure

The Investigator shall provide to the Sponsor sufficient accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the FDA and/or other applicable regulatory agencies. The Investigator shall promptly update this information if any relevant changes occur in the course of the study or for 1 year following completion of the study.

11.4.4 Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 11) to ensure data integrity. “Original” in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

11.4.5 Retention of Study Documents

According to 21 CFR Part 312.62 and ICH E6, study-related records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the

investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor.

The Investigator must not destroy any study-related records without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor must be contacted to arrange alternative record storage options.

12. Administrative Structure of the Study

The study will be monitored by Sponsor personnel or Sponsor representative. The following functions for this study will be performed by organizations designated by the Sponsor: data management and statistical analysis, including PD analysis and reporting.

13. Appendix A – Schedule of Events

Procedure	Extension Period					2 Week Follow-up[4]
	Baseline Day 1[1]	Week 12	Week 24	Week 36	Week 48/ EOS	
Tolerance (days)	NA	± 5	± 5	± 5	± 5	± 5
Inclusion/Exclusion criteria	X					
Medical history	X					
Physical examination incl. weight	X	X[3]	X[3]	X[3]	X	X[5]
Urine pregnancy test[2]	X	X	X	X		X
Serum pregnancy test[2]					X	
Hematology, Blood chemistry	X	X	X	X	X	X[5]
Urinalysis	X				X	X[5]
Chromogranin A	X				X	
Vital signs	X	X	X	X	X	X
ECG	X				X	X[5]
Subjective Global Assessment	X	X	X	X	X	X
EORTC QLQ-C30 and GI.NET21	X		X		X	
Sleep and Depression Assessments	X	X	X	X	X	X
Plasma 5-HIAA	X	X	X	X	X	X
Dispensation of telotristat etiprate (LX1606)	X	X	X	X		
Concomitant medications	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X

[1]Eligibility will be determined at last visit of the original protocol; Day 1 will replace the next scheduled visit in the original protocol schedule. Visits should coincide with LAR injections for those patients receiving SSA therapy. [2]Females of child-bearing potential only. [3]Brief physical examination only (symptom-oriented, including weight). [4]Visit 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. [5]To be performed only if evaluation at Week 48/EOS is abnormal.

14. Appendix B – Amount of Blood to be Collected from Each Patient

Assessment		Sample volume (mL)	Number of samples*	Estimated total volume (mL)
Safety	Hematology	2	6	12
	Blood chemistry	6	6	36
Other	CgA	2	2	4
	Serum Pregnancy	2	1	2
Pharmacodynamic	Plasma 5-HIAA	4	6	24
			Total	78
*Maximum number of samples is indicated				

15. Appendix C – EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Lexicon

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

16. Appendix D – EORTC QLQ - GI.NET21

ENGLISH

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Did you have hot flushes?	1	2	3	4
32.	Have you noticed or been told by others that you looked flushed/red?	1	2	3	4
33.	Did you have night sweats?	1	2	3	4
34.	Did you have abdominal discomfort?	1	2	3	4
35.	Did you have a bloated feeling in your abdomen?	1	2	3	4
36.	Have you had a problem with passing wind/gas/flatulence?	1	2	3	4
37.	Have you had acid indigestion or heartburn?	1	2	3	4
38.	Have you had difficulties with eating?	1	2	3	4
39.	Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)* N/A	1	2	3	4
40.	Have you had a problem from repeated injections? *(If not having injections please circle N/A)* N/A	1	2	3	4
41.	Were you worried about the tumour recurring in other areas of the body?	1	2	3	4
42.	Were you concerned about disruption of home life?	1	2	3	4
43.	Have you worried about your health in the future?	1	2	3	4
44.	How distressing has your illness or treatment been to those close to you?	1	2	3	4
45.	Has weight loss been a problem for you?	1	2	3	4
46.	Has weight gain been a problem for you?	1	2	3	4
47.	Did you worry about the results of your tests? *(If you have not had tests please circle N/A)* N/A	1	2	3	4
48.	Have you had aches or pains in your muscles or bones?	1	2	3	4
49.	Did you have any limitations in your ability to travel?	1	2	3	4
During the past four weeks:					
50.	Have you had problems receiving adequate information about your disease and treatment?	1	2	3	4
51.	Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)* N/A	1	2	3	4

17. Appendix E – Ethical Standards

Ethics and Regulatory Considerations

This study will be conducted according to GCP, 21 CFR Part 50, (Protection of Human Subjects), 21 CFR Part 56 (Institutional Review Boards), International Conference on Harmonisation Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

General Instructions

The FDA regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to GCP regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- Current FDA Guideline for the Monitoring of Clinical Investigations
- Current Guidance for Institutional Review Boards and Clinical Investigators
- ICH E6 – Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

Studies conducted in the European Union are also regulated by Volume 10 of the publications "The rules governing medicinal products in the European Union".

Copies of these materials are available from the Sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- the study is conducted with diligence and in conformance with the protocol in such a way as to insure the integrity of the findings;
- the potential benefits of the research justify the risks.

Lexicon Pharmaceuticals, Inc. is the Sponsor of the IND. The Sponsor is responsible for the following:

- selecting qualified Investigators,
- providing Investigators with the information they need to properly conduct an investigation,
- ensuring proper monitoring of the investigation,
- ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- maintaining the IND, and
- ensuring that regulatory authorities and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied
- ensuring the study is conducted in accordance to FDA and ICH guidelines and all applicable regulations

18. Appendix F – Investigator Obligations

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56 and ICH E6, the study protocol and the final version of the subject informed consent form will be approved by the IRB/ERC before enrollment of any subjects. The opinion of the IRB/ERC will be dated and given in writing. A copy of the letter of approval from the IRB/ERC and a copy of the approved informed consent form will be received by the Sponsor prior to shipment of study medication supplies to the Investigator.

The Investigator will ensure that the IRB/ERC will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to subjects. The Investigator will also ensure that no changes will be made to the protocol without IRB/ERC approval.

As a part of the IRB/ERC requirement for continuing review of approved research, the Investigator will be responsible for submitting periodic progress reports to the IRB/ERC at intervals appropriate to the degree of subject risk involved, but no less than once per year.

Written informed consent must be given freely and obtained from every subject prior to clinical trial participation. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

As described in GCP guidelines, study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (eg, loss of medical licensure, debarment). Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

Principal Investigators must provide Lexicon with a fully executed Form FDA 1572 (statement of Investigator) and all updates on a new fully executed Form FDA 1572.

Principal Investigators must provide Lexicon with his/her own curriculum vitae and current curriculum vitae for each sub-Investigator listed on Form FDA 1572.

Protection of Human Subjects (21 CFR Part 50 and ICH E6)

Informed consent must be obtained from every subject before entry into a clinical study. It must be given freely and not under duress. Consent must be documented by use of an IRB/ERC-approved consent form and signed by the subject or the subject's legally authorized representative. The US Department of Health and Human Services suggests that when minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent, his signature should also be included. Non-English-speaking subjects must be presented with

a consent form written in a language that they understand. A copy of the signed consent form must be given to the subject signing it. Another copy must be kept in the Investigator's files and made available to regulatory authority representatives upon request. If, for any reason, subject risk is increased as the study progresses, a revised, IRB/ERC-approved consent form must be signed by the subject. Before the study begins, a sample of the consent form must be provided to the Sponsor for review. The FDA and/or other applicable regulatory agencies may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all subjects.

Only in the case of a life-threatening incident may an investigational product be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the Investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB/ERC within 5 working days. In this situation, the Investigator may not administer any subsequent product to that subject until informed consent and IRB/ERC approval are obtained.

Informed Consent

Written informed consent must be obtained from each subject prior to entry in the study. One copy of the signed informed consent document will be given to the subject, and another will be retained by the Investigator. Additionally, the subject must be allowed adequate time to consider the potential risks and benefits associated with his/her participation in the study.

In situations where the subject is not legally competent to provide consent (ie, mentally incapacitated), written consent must be obtained from a parent, legal guardian, or legal representative. In these situations, the consent must be signed and dated by a witness.

The informed consent document must have been reviewed and approved by the Sponsor and by the Investigator's IRB/ERC prior to the initiation of the study. The document must contain the 8 basic elements of informed consent and may contain the 6 additional elements described in 21 CFR Part 50. Every consent form must include the following 8 elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the subject

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility that the FDA and/or other applicable regulatory authority representatives may inspect the records
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available, or a statement describing where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research related injury
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

When appropriate, 1 or more of the following elements of information shall also be included in the consent form:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent
- Any additional costs the subject may incur from participation in the research
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject
- The approximate number of subjects involved in the study

The Declaration of Helsinki includes further details regarding the specific requirements for informed consent.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states, such as California and Oregon, require further action on the Investigator's part concerning subject consent.

Study Documentation

IRB/ERC Review/Approval

The protocol and informed consent for this study, including advertisements used to recruit subjects, must be reviewed and approved by an appropriate IRB/ERC prior to enrollment of subjects in the study. It is the responsibility of the Investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, ICH, GCP, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB/ERC approval which specifically identifies the study/protocol and a list of the committee members must be received by the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

A progress report with a request for re-evaluation and re-approval will be submitted by the Investigator to the IRB/ERC at intervals required by the IRB/ERC, and not less than annually. A copy of the report will be sent to the Sponsor.

When the Sponsor provides the Investigator with a Safety Report, the Investigator must promptly forward a copy to the IRB/ERC.

After completion or termination of the study, the Investigator will submit a final report to the IRB/ERC and to the Sponsor, if required. This report should include: deviations from the protocol, the number and types of subjects evaluated, the number of subjects who discontinued (with reasons), results of the study, if known, and significant AEs, including deaths.

Study Files

The Investigator is required to maintain complete and accurate study documentation in compliance with current Good Clinical Practice standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study. Study documents include, but are not limited to, the Investigator's Brochure, drug accountability records, Sponsor/Investigator correspondence, IRB/ERC correspondence, protocol and amendments, information regarding monitoring activities, subject exclusion records, CRFs, and data queries.

Confidentiality

The anonymity of subjects must be maintained. Patients will be identified by their initials and an assigned subject number on CRFs and other documents submitted to the clinical monitor. Documents that will be submitted to the clinical monitor and that identify the subject (eg, the signed informed consent document) must be maintained in strict confidence by the Principal Investigator, except to the extent necessary to allow auditing by regulatory authorities, the clinical monitor, or Sponsor personnel.

All information regarding the nature of the proposed investigation provided by the Sponsor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB/ERC, the subject, or the regulatory authority) must be kept in confidence by the Investigator.

Drug Accountability

The Investigator or designee is responsible for accountability of the investigational product at the site. The Investigator or designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and return to the Sponsor or alternative disposition of any unused product. These records must include dates, quantities, batch/serial/lot numbers, and expiration dates (if applicable).

The Investigator should ensure that the investigational product is used only in accordance with the protocol

19. Appendix G – Guidance on the Selection of Patients

This long-term study in France is intended for patients who experience clinical benefit in their prior experience with telotristat etiprate, either in study LX1606.1-301-CS or LX1606.303.1-303-CS.

Clinical benefit should be present for subjects to meet entry criteria #3 described in section 6.1 of the protocol: ability and willingness to provide written consent prior to participation in any study-related procedure.

In this study population, clinical benefit may be represented by any of the following:

- Reduction in bowel movement frequency, or
- A positive response on the subjective global assessment of adequate relief, or
- A reduction in urinary 5-HIAA either in study LX1606.1-301-CS or LX1606.1-303-CS.

Reduction in bowel movement frequency: a reduction of at least 30% in bowel movement frequency from baseline to the end of study LX1606.1-301-CS or LX1606.303.1-303-CS may represent clinical benefit. In patients with carcinoid syndrome, benefits of this magnitude have been associated with improvements in patient-reported outcomes.

A positive response on the subjective global assessment of adequate relief: An answer of "yes" to the 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?" at the time of completing participation in LX1606.1-301-CS or LX1606.303.1-303-CS is a clinical benefit.

A reduction in urinary 5-HIAA either in study LX1606.1-301-CS or LX1606.1-303-CS: Normalization of urinary 5-HIAA or a reduction of at least 50% in urinary 5-HIAA is a clinical benefit for patients at risk of the development of new or progressive carcinoid heart disease.

In addition to the absence of the above signs of benefit, a lack of clinical benefit may reflect itself in one of the criteria for stopping treatment or study withdrawal (section 6.3 of the protocol): withdrawal of consent, refusal of the study medication, or an investigator decision that it is not medically acceptable to continue participation in the study.

20. Appendix H - Guidance on the Use of Pro-serotonergic Drugs as Concomitant Medications

Serotonin-synthesis reuptake inhibitors (SSRis) are associated with serotonin syndrome, and patients with carcinoid syndrome may be at higher risk of this complication.

There is some experience with the use of SSRis with telotristat etiprate. In study LX1606.1-202-CS there were 8 patients on SSRis at baseline, and one patient had an SSRi added during the study. There were no reports of serotonin syndrome. However, since the experience was relatively limited, caution should be given to the use of SSRis as a concomitant medication in study LX1606.1-302-CS.

21. References

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CLINICAL PROTOCOL ADDENDUM
STUDY LX1606.302

A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)

PROTOCOL NO.:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
EudraCT Number:	2013-002596-18
INVESTIGATIONAL PHASE:	3
SPONSOR:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381 Telephone: from USA (281) 863 3000 International sites dial +1 281 863 3000 Safety Data Facsimile: +1 832 442 5917
ADDENDUM DATE:	13 April 2015 (the Netherlands only)
PROTOCOL AMENDMENT 1 DATE:	31 January 2014
ORIGINAL VERSION DATE:	14 June 2013

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Addendum

Rationale

A source of confusion has been identified in the clinical study protocol relating to terminology that is inconsistently used to identify primary objectives and endpoints versus secondary objectives and endpoints. Specifically, the term "efficacy" has been used in relation to primary parameters that pertain solely to safety and tolerability. This addendum is designed to both clarify the primary and secondary study parameters and describe the plan for correcting the errant language in an upcoming protocol amendment.

1. **Primary Objective and Secondary Objective –Synopsis – page 3: This is to clarify that study objectives are as described in the Synopsis of Amendment 1, dated 31 January 2014, and summarized below:**

Primary Objective:	To evaluate the long-term safety and tolerability of orally administered telotristat etiprate.
Secondary Objective:	To evaluate long-term changes in patients' quality of life (QOL).

2. **An amendment to the clinical study protocol is planned in the near future. Revisions will include corrections to the errant language that unintentionally associates the term "efficacy" with the primary objectives of the protocol. At minimum, the necessary corrections identified in the following comparative table will be made:**

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Section	Current Version 31 January 2014 with Proposed Revisions in Track Change Mode	Proposed Protocol Amendment New Wording
Section 4./ Study Objectives (page 19)	**4. Study Objectives** **~~4. 1 Efficacy Objectives~~** **4.1~~.1~~ Primary Objective** The primary objective of the study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate. **4.~~1.~~2 Secondary Objective(s)** The secondary objective of this study is to evaluate changes in patients' QOL. **4.~~2~~3 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	**4. Study Objectives** **4.1 Primary Objective** The primary objective of the study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate. **4.2 Secondary Objective(s)** The secondary objective of this study is to evaluate changes in patients' QOL. **4.3 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
Section 10.3.1/ Efficacy Endpoints (page 36)	**10.3.1 ~~Efficacy~~ Primary and Secondary Endpoints** The primary ~~efficacy~~ endpoint is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate. Secondary ~~efficacy~~ endpoint is to evaluate changes in patients' QOL over multiple years of therapy.	**10.3.1 Primary and Secondary Endpoints** The primary endpoint is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate. Secondary endpoint is to evaluate changes in patients' QOL over multiple years of therapy.

added text / ~~deleted text~~

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CLINICAL PROTOCOL AMENDMENT 1
STUDY LX1606.302

A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)

PROTOCOL NO.:	**LX1606.1-302-CS** **LX1606.302** (Abbreviated number)
EudraCT Number:	2013-002596-18
INVESTIGATIONAL PHASE:	3
SPONSOR:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: 001 (281) 863-3000 Safety Hotline: 001 (877) 372-3597 Safety Data Facsimile: 001 (832) 442-5917
PROTOCOL AMENDMENT 1 DATE:	31 January 2014
ORIGINAL VERSION DATE:	14 June 2013

Amendment Changes

Rationale

A protocol amendment is proposed to clarify that (1) the frequency of the Data Safety Monitoring Board (DSMB) meetings; (2) patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities are excluded from participation; (3) patients may transition into the study at the same dose level as the original protocol; (4) pregnancy tests will be conducted at each visit (5) both food and drink containing grapefruit should be avoided; (6) mobile research services will not be used for this study; and (7) interim analysis will be performed for this study.

In addition, the study name has been modified to remove 'symptoms'. As noted in the protocol the secondary objective of the long-term study is to evaluate long-term changes in patients' quality of life (QOL).

Modifications have also been made to: (1) revise the number of patients expected to participate; (2) include Depression and Sleep Assessments at each visit; (3) revise the definition of AE/SAE to be consistent with current regulatory guideline; (4) capture weight with each physical examination; (5) update Schedule of Events to reflect new assessments; (6) include contact information for the reporting SAEs in Israel and Brazil; (7) reflect current guidance documents will be used to conduct the trial.

The following administrative changes have also been made:

- The Lexicon safety hotline has been added to the Sponsor contact information
- Minor formatting, capitalization, and punctuation have been corrected
- List of Abbreviations and Definition of Terms has been updated to reflect additional abbreviations as necessary
- Due to the insertion of new sections, renumbering has occurred as appropriate
- Table of contents has been updated as appropriate

In response to these changes, the following sections have been revised as follows (changes are indicated in *italics*):

1. **CLINICAL STUDY PROTOCOL – Study Name, page 1 – The term 'Symptoms' has been removed to be consistent with the secondary objective of study. To evaluate long-term changes in patients' overall quality of life (QOL). The revised Study Name now reads:**

"TELEPATH (**Tel**otristat **E**tiprate – Expanded Treatment for **Pat**ients wit**h** Carcinoid Syndrome)"

2. **SYNOPSIS – Methodology, pages 3-4, and INVESTIGATIONAL PLAN – Overall Study Design, Section 5.1, page 19 – This section was modified to clarify that patients will continue on open-label study drug at the same dose level identified in "their" specific original study. In addition, Data Safety Monitoring Board review will occur quarterly throughout the study. The revised section now reads:**

"The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate.

Patients currently participating in any LX1606 Phase 2 CS study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original protocol to LX1060.1-302-CS.

Following confirmation of eligibility, patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label LX1606 at the same dose level identified in *their original* study.

Downward dose adjustment will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. Patients may return to *the previous* dosing at the discretion of the Investigator and in consultation with the Medical Monitor.

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

A Data Safety Monitoring Board (DSMB) will review safety data quarterly throughout the study."

3. **SYNOPSIS – Number of Patients, page 4, and STUDY POPULATION, Section 6, page 19, 2nd sentence – The number of patients expected to participate has been modified. The revised section now reads:**

"Up to *100* patients are expected to participate in this study."

4. **SYNOPSIS – Treatments, page 4 – This section has been modified to clarify that 250 mg telotristat tablets will be administered at the same dose level and regimen identified in the patient's original study. The revised section now reads:**

"Telotristat etiprate, *250 mg tablet*, administered *at the same dose level and regimen identified in the patient's original study*."

5. **SYNOPSIS – Exclusion Criteria, page 5, and STUDY POPULATION – Exclusion Criteria, Section 6.2, page 20 – This section have been modified to add Exclusion Criterion #4. The added text reads:**

"*Patients who are currently committed to an institution by virtue of an order issued either by judicial or administrative authorities.*"

6. **INTRODUCTION – Background on Telotristat Etiprate (LX1606) and Disease, Section 3.1, pages 12-13, Paragraph #4 – This paragraph was modified to clarify that the discussion referenced the human TPH2 enzyme. The revised paragraph now reads:**

"The oral TPH inhibitor, telotristat etiprate, represents a novel approach to potentially lessen the pathophysiology of CS by reducing 5-HT levels via inhibition of TPH. Telotristat etiprate was designed specifically as a prodrug in order to gain greater systemic exposure, opening the potential application for indications in which hyperserotonemia is thought to contribute to the disorder, such as CS. Preclinical pharmacology studies of telotristat etiprate were designed to evaluate the compound's mechanism of action and effects in vivo. Telotristat etiprate is the ethyl-ester prodrug of the active moiety LP-778902. Telotristat etiprate was designed as a prodrug in order to enhance peripheral exposure without crossing the blood-brain barrier. In vivo, telotristat etiprate is readily converted through esterase activity to its corresponding acid, LP-778902. LP-778902 has an in vitro potency of 0.028 μM on purified human TPH1 enzyme and 0.032 μM on purified *human* TPH2 enzyme. Therefore, telotristat etiprate is a robust inhibitor of TPH both in vitro and in vivo and has been shown in Phase 2 studies to provide clinical benefit to patients with carcinoid tumors and associated CS."

7. **INTRODUCTION – Clinical Trials of Telotristat Etiprate (LX1606) in Humans, Section 3.2, page 13, 1st paragraph – This paragraph has been modified to reflect the most current data in reference to the ulcerative colitis study. The revised paragraph now reads:**

"Telotristat etiprate has been studied in single/multiple doses in Phase 1 studies, approximately 109 healthy volunteers participated in Phase 1 trials with 88 subjects receiving telotristat etiprate and 21 subjects *receiving* placebo. In addition, *37 patients with CS* have received telotristat etiprate during the clinical development program in Phase 2. *An additional 59 patients with ulcerative colitis* have been enrolled into an ongoing Phase 2 study to evaluate telotristat etiprate versus placebo in *patients with ulcerative colitis experiencing active flares*."

8. **INTRODUCTION – Clinical Trials of Telotristat Etiprate (LX1606) in Humans, Section 3.2, pages 13-16 – Section headings for Phase 1 Studies, Phase 2 Studies, and Ongoing Studies have been inserted to provide a clear delineation between the phases of study. Sections 3.2.1 Phase 1 Studies, Section 3.2.2 Phase 2 Studies, and Section 3.2.2 Ongoing Studies have been inserted as appropriate. Section 3.2.3 Ongoing Studies has been modified to reflect current status of all ongoing studies. The revised Ongoing Studies section now reads:**

"*The open-label extension portion in LX1606.1-202-CS and LX1606.1-203-CS remains ongoing.*

LX1606.1-204-UC is currently evaluating patients with active flares of ulcerative colitis. Doses under evaluation are 500 mg once daily (*qd*) and 500 mg tid vs. placebo; *59* patients *have been* enroll*ed* for an 8-week treatment period.

LX1606.1-301-CS is intended to evaluate *patients who are currently on a background of SSA therapy and still experiencing breakthrough symptoms such as an increased frequency of BMs ≥ 4 per day on average:* (1) the efficacy of telotristat etiprate on reducing the number of BMs; (2) the efficacy of telotristat etiprate on a number of clinically relevant secondary endpoints; and, (3) the safety of telotristat etiprate over the 12-week double-blind portion (Treatment Period) of the study. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period (Extension Period).

LX1606.1-303-CS is intended to evaluate *patients with carcinoid syndrome whose primary symptoms are not GI related and may be naïve to SSA therapy:* (1) the safety of telotristat etiprate over the 12-week double-blind portion (Treatment Period) of the study; *(2) % change from Baseline in 24-hr u5-HIAA levels at Week 12;* (*3*) the effects of telotristat etiprate on a number of clinically relevant secondary endpoints. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period."

9. **INTRODUCTION – Rationale for Selection of Dose, Section 3.3.1, pages 16-17 – This section was modified to clarify that dose levels evaluated are consistent with prior clinical experience. The revised section now reads:**

"*The* dose levels of telotristat etiprate selected for this study *are consistent with prior clinical study experience and* based upon clinical safety and pharmacodynamic (PD) data from 2 Phase 2 multiple ascending-dose studies in patients with symptomatic CS (LX1606.1-202-CS and LX1606.1-203-CS).

Based upon observations noted in Section 3.2, it is anticipated that the doses to be utilized in this protocol will be safe and well tolerated and may provide clinical benefit to patients with CS."

10. INTRODUCTION – Benefit/Risk Assessment, Section 3.3.2, pages 17-18, Paragraph #5 – This section has been modified to clarify that a reduction in serotonin may help reduce the risk of carcinoid heart disease. The revised paragraph now reads:

"Treatment has the potential to improve several signs and symptoms of CS. The Phase 2 clinical trial results indicated that treatment may lead to improvements in *BM* frequency, stool consistency, urgency, abdominal pain, diarrhea, flushing, and reductions in 5-HIAA. These potential benefits relate to a unique mechanism of action. Symptomatic improvement may lead to a better quality of life (QOL) for patients with few treatment options available, and *a* reduction *in serotonin* may help reduce the risk of carcinoid heart disease. Overall the benefit/risk profile of telotristat etiprate is expected to be favorable for participation in this clinical study."

11. STUDY POPULATION – Criteria for Stopping Treatment/Study Withdrawal, Section 6.3, page 21 – This section was modified to clarify patient responsibilities following voluntary withdrawal from the study. The revised section now reads:

"A patient may also be discontinued from the study for the following medical or administrative reasons:

- Withdrawal of consent by the patient or legal guardian
- Noncompliance, including refusal of the study medication and/or failure to adhere to the study requirements as in the study protocol
- Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study
- The Sponsor terminates the study (Section 6.4)
- Pregnancy (Section 9.4.1)

Note: *If a patient voluntarily withdraws or is* discontinued from study treatment before completing the entire duration of the Treatment Period*, 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 Appendix A – Schedule of Events *and agree to report any SAEs (Section 9.2) that occur within 30 days following the last dose of telotristat etiprate.*

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 Case Report Form (CRF).

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."

12. **TREATMENT – Dose Adjustment, Section 7.4, page 24 – This section was revised to clarify dose adjustment during the study. The revised section now reads:**

"Downward dose adjustment of telotristat etiprate will be permitted if evidence of intolerability emerges. After a period at the *lowered* dose level, patients may resume *the previous* dosing *level* at the discretion of the Investigator after consultation with the Medical Monitor. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from *study treatment*. Interruptions or delays in dosing throughout the entire study may be permitted after consultation with the Medical Monitor, at which time the patient will be reassessed for study continuation, dosage reduction, or discontinuation."

13. **STUDY PROCEDURES, Section 8, page 24 – This section has been modified to remove the reference to study visits being performed by a mobile research service outside of the investigational site. No mobile research services will be utilized for this protocol. The revised section now reads:**

"A schedule of study assessments is provided in Appendix A."

14. **STUDY PROCEDURES – Restrictions during Study, Section 8.1, page 24 – This section has been modified to clarify that food and drink containing grapefruit should be avoided. The revised section now reads:**

"Patients should be advised to avoid *food and drink containing grapefruit* for 2-3 hours prior to and following dosing while participating in the study."

15. **STUDY PROCEDURES – Efficacy Assessments, Section 8.2.1, page 25 – This section was modified to indicate the EORTC QLQ-C30 and GI.NET21 and the subjective global assessment are quality of life measure. The revised section now reads:**

"Efficacy assessments include the patient reported *QOL* measures*;* EORTC QLQ-C30 (Appendix D) & GI.NET21 (Appendix E) *questionnaires* and subjective global assessment of symptoms associated with CS.

A description of the efficacy assessments is provided below."

16. STUDY PROCEDURES – Depression Detection, Section 8.2.4.4.1.1, pages 28 – This section has been inserted to include parameters for depression detection at each visit during the Treatment Period. The new section reads:

"*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.*"

17. STUDY PROCEDURES – Quality of Sleep Assessment, Section 8.3.3, pages 29 – This section has been inserted to include parameters for the assessment of the quality of sleep at each visit during the Treatment Period. The new section reads:

"*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.*"

18. SAFETY REPORTING – Adverse Events, Section 9.1, pages 30-32, Paragraphs #1-4 – These paragraphs were modified to revise the language in order to be consistent with the current regulatory definitions of Adverse Events. The revised section now reads:

"It is the responsibility of the Investigator to document all AEs that occur during the study.

Adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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 considered related to the study medication*. This definition includes an exacerbation of preexisting 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."

19. SAFETY REPORTING – Serious Adverse Events (SAEs), Section 9.2, pages 32-34 – This section has been modified to revise the language in order to be consistent with the current regulatory definitions of Serious Adverse Events and to include contact information for Israel and Brazil. The revised section now reads:

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

1. Death
2. *A life-threatening adverse event;*
3. Inpatient hospitalization or prolonging of an *existing* hospitalization;
4. *A* persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; *or*
5. A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

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: [redacted]
Belgium: [redacted]
Brazil: [redacted]
France: [redacted]
Germany: [redacted]
Israel: [redacted]

Italy: [redacted]
Netherlands: [redacted]
Spain: [redacted]
Sweden: [redacted]
United Kingdom: [redacted]

Email Address (in case of fax failure): [redacted]

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 *B*aseline, but for a minimum of 30 days after the last dose of study drug."

20. **SAFETY REPORTING – Pregnancy, Section 9.4.1, pages 34-35, 1st Paragraph – This paragraph was modified to clarify that should a patient become pregnant during the study, they must be discontinued immediately from the study treatment. The revised section now reads:**

"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."

21. **STATISTICAL METHODOLOGY – Interim Analysis, Section 10.4.5, page 38 – This section was modified to clarify the frequency of DSMB meetings and provide information regarding how the study will be reported. The revised section now reads:**

"An independent DSMB will be charged with reviewing interim safety data *on a quarterly basis* 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 up to a specified data cut-off point. The second report will update the initial report by including data from the remaining portion of the study. 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."

22. Study Management – Health Insurance Portability Accountability Act of 1996 and Subsequent Updates, Section 11.4.2, page 40 – This section and its title have been modified to clarify that all updates to HIPAA are applicable. The revised section now reads:

"The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 Code of Federal Regulations (CFR) Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation *and any applicable updates*). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor."

23. APPENDIX A – Schedule of Events, Section 13, page 42 – The Schedule of Events has been updated to reflect the following changes:

- Include weight with all Physical Examinations, including brief, symptom oriented examinations
- Remove references to visits conducted by mobile research services (MRS)
- Add urine pregnancy test to be conducted for females of child-bearing potential at Weeks 12, 24, and 36
- Add Sleep and Depression Assessments to be captured at every visit, including the Follow-up visit

Changes are indicated by highlighted cells in 'Revised Appendix A – Schedule of Events' table below.

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The Woodlands, TX 77381-1160

Revised Appendix A – Schedule of Events

Procedure	Extension Period					2 Week Follow-up[4]
	Baseline Day 1[1]	Week 12	Week 24	Week 36	Week 48/ EOS	
Tolerance (days)	NA	± 5	± 5	± 5	± 5	± 5
Inclusion/Exclusion criteria	X					
Medical history	X					
Physical examination incl. weight	X	X[3]	X[3]	X[3]	X	X[5]
Urine pregnancy test[2]	X	X	X	X		X
Serum pregnancy test[2]					X	
Hematology, Blood chemistry	X	X	X	X	X	X[5]
Urinalysis	X				X	X[5]
Chromogranin A	X				X	
Vital signs	X	X	X	X	X	X
ECG	X				X	X[5]
Subjective Global Assessment	X	X	X	X	X	X
EORTC QLQ-C30 & GI.NET21	X		X		X	
Sleep and Depression Assessments	X	X	X	X	X	X
Plasma 5-HIAA	X	X	X	X	X	X
Dispensation of LX1606	X	X	X	X		
Concomitant medications	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X

[1]Eligibility will be determined at last visit of the original protocol; Day 1 will replace the next scheduled visit in the original protocol schedule. Visits should coincide with LAR injections for those patients receiving SSA therapy. [2]Females of child-bearing potential only. [3]Brief physical examination only (symptom-oriented, including weight). [4]Visit 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. [5]To be performed only if evaluation at Week 48/EOS is abnormal.

24. Appendix E – Ethical Standards, Section 17, General Instructions, pages 47-48 – This section has been modified to reflect that current guidance documents will be used for the conduct of this study. The revised General Instructions now read:

"**General Instructions**

The FDA regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to GCP regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- *Current* FDA Guideline for the Monitoring of Clinical Investigations
- *Current* Guidance for Institutional Review Boards and Clinical Investigators
- ICH E6 – Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

Studies conducted in the European Union are also regulated by Volume 10 of the publications "The rules governing medicinal products in the European Union".

Copies of these materials are available from the Sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- the study is conducted with diligence and in conformance with the protocol in such a way as to insure the integrity of the findings;
- the potential benefits of the research justify the risks.

Lexicon Pharmaceuticals, Inc. is the Sponsor of the IND. The Sponsor is responsible for the following:

- selecting qualified Investigators,

- providing Investigators with the information they need to properly conduct an investigation,
- ensuring proper monitoring of the investigation,
- ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- maintaining the IND, and
- ensuring that regulatory authorities and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied
- ensuring the study is conducted in accordance to FDA and ICH guidelines and all applicable regulations"

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CLINICAL STUDY PROTOCOL

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
EudraCT Number	2013-002596-18
Investigational Phase:	3
Protocol Title:	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Study Name:	TELEPATH (**Tel**otristat **E**tiprate – Expanded Treatment for **Pat**ients wit**h** Carcinoid Syndrome Symptoms)
Original Version Date:	14 June 2013
Sponsor:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: 001 (281) 863-3000 Safety Data Facsimile: 001 (832) 442-5917

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8800 Technology Forest Pl.
The Woodlands, TX 77381-1160

Investigator Signature Page

Protocol Number:	LX1606.1-302-CS LX1606.302 (Abbreviated number)
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Original Version Date:	14 June 2013
Sponsor:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone:001 (281) 863-3000 Safety Data Facsimile: 001(832) 442-5917

By my signature below, I hereby attest that I have read and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol and will conduct the study in accordance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance.

Additionally, I will not initiate this study without written and dated approval from the appropriate Institutional Review Board (IRB)/ Ethic Review Committee (ERC), and I understand that any changes in the protocol must be approved in writing by the Sponsor, the IRB/ERC, and, in certain cases the Food and Drug Administration (FDA) or other applicable regulatory agencies, before they can be implemented, except where necessary to eliminate hazards to patients.

Principal Investigator's Signature — Date

Principal Investigator's Name (Print)

[redacted]

Lexicon [redacted] (Signature) — Date

[redacted] M.D

Lexicon [redacted] (Printed Name)

1. Synopsis

Name of Study Drug	Telotristat etiprate
Protocol Number	LX1606.1-302-CS LX1606.302 (Abbreviated number)
Protocol Title	A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Primary Objective	The primary objective of this study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate
Secondary Objective	To evaluate long-term changes in patients' quality of life (QOL)
Phase of Development	3
Methodology	The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate. Patients currently participating in any LX1606 Phase 2 carcinoid syndrome (CS) study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original study to LX1060.1-302-CS. Following confirmation of eligibility, patients may enter into the study at a dose level of 250 mg or 500 mg telotristat etiprate given 3 times daily (tid). Upon entering, these patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label study drug at the same dose level and regimen as identified in the previous study. Downward dose adjustment from 500 mg to 250 mg tid will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. Patients may return to 500 mg tid dosing at the discretion of the Investigator and in consultation with the Medical Monitor. Upon completion or early withdrawal from treatment, all patients

	will be required to complete a 14-day Follow-up Period, during which no study drug will be administered.
Number of Patients	Up to 160 patients are expected to participate in this study.
Patients	Eligible patients are defined as those that are currently participating in a Phase 2 or Phase 3 telotristat etiprate carcinoid syndrome study.
Number of Study Sites	Approximately 70 sites
Treatments	Telotristat etiprate tablets administered as 250 mg (1 x 250 mg) tid or 500 mg (2 x 250 mg) tid
Route of Administration	Oral
Duration of Participation	Up to 50 weeks including Treatment and Follow-up
Inclusion Criteria	Patients must meet all of the following criteria to be considered eligible to participate in the study: 1. Ongoing participation in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study 2. 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 entry are confirmatory in the absence of a clear postmenopausal history. 3. Ability and willingness to provide written informed consent prior to participation in any study-related procedure

Exclusion Criteria	Patients who meet any of the following criteria will be excluded from participating in the study: 1. Major protocol violations or tolerability concerns in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study 2. Positive pregnancy test 3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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
Statistical Methods	Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study and combined across all treated patients. Primary analyses of the data will be based on the Safety population which includes all patients treated on Day 1 of this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.
Study Assessments	<u>Safety</u> Safety assessments include monitoring of adverse events, clinical laboratory tests, vital signs measurements, 12-lead ECG, and physical examinations <u>Efficacy</u> Efficacy assessments will include patient reported quality of life measures as captured in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and the module specific for gastrointestinal symptoms of carcinoid neuroendocrine tumors (GI.NET21) and subjective global assessment of symptoms associated with CS

	Pharmacodynamics Pharmacodynamic (PD) assessments include determination of 5-HIAA levels in plasma
Efficacy Data Analysis	All efficacy and PD variables will be summarized descriptively and listed. Statistical tests and estimates of within patient effects for the efficacy and PD measures will be derived from application of a mixed linear model with repeated measures. The form of the model will be specific to measurement properties of the dependent variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model. Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to patients' LX1606 dose level on Day 1 of this study.
Safety Data Analysis	Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group, and as needed, by study visit. Treatment-emergent adverse event 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 serious adverse events. Vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) 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.

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2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ALP	alkaline phosphatase
AST	aspartate transaminase
bid	twice daily
BM	bowel movements
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CgA	chromogranin A
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CS	carcinoid syndrome
CT	computed tomography
DSMB	Data Safety Monitoring Board
EC	enterochromaffin
ECG	electrocardiogram
ERC	Ethic Review Committee
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HEENT	head, eyes, ears, nose, and throat
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonisation
IND	Investigational New Drug

Continued on the next page

Abbreviation	Definition
IRB	Institutional Review Board
ITT	intent-to-treat
IMP	Investigational Medicinal Product
IWRS	interactive web response system
LAR	long-acting release
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MCP	multiple comparison procedure
MRI	magnetic resonance imaging
NET	neuroendocrine tumor
NRS	numeric rating scale
OOR	out-of-range
OTC	over-the-counter
PD	pharmacodynamic
PK	pharmacokinetic
qd	once daily
SAE	serious adverse event
SBS	short bowel syndrome
SOP	standard operating procedure
SSA	somatostatin analog
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	treatment-emergent adverse events
tid	3 times daily
TPH	tryptophan hydroxylase
ULN	upper limit of the normal reference range
WRS	Wilcoxon rank sum

Definitions of Terms

Term	Definition
LP-778902	Active moiety of LX1606
LX1606	Ethyl-ester prodrug of the active moiety LP-778902; a serotonin synthesis inhibitor being developed by Lexicon Pharmaceuticals, Inc.
QTcF	corrected QT interval using Frederica's formula

3. Introduction

3.1 Background on Telotristat Etiprate (LX1606) and Disease

Serotonin (5-HT) plays a critical role in regulating several major physiological processes of the gastrointestinal tract, including aspects of secretion, motility, inflammation and sensation. Enterochromaffin (EC) cells release 5-HT when the intestinal wall is stimulated by intraluminal pressure or chemicals. Through multiple classes of receptors, 5-HT is believed to initiate directly, or facilitate, peristaltic and secretory reflexes. 5-HT is also reportedly involved in the pathophysiology of various types of functional gastrointestinal (GI) disorders, valvular heart disease and may play a role in the pathophysiology of inflammatory bowel disease (IBD).

Carcinoid tumors are mostly derived from EC cells of the midgut, and often produce and release large amounts of 5-HT. Such excess of 5-HT is believed to be responsible for the severe diarrhea and eventual valvular heart damage and mesenteric fibrosis in patients with carcinoid syndrome (CS).[1-3] Inhibition of tryptophan hydroxylase (TPH) activity in carcinoid tumors should lead to a reduction of peripheral 5-HT in afflicted patients and thus an amelioration of the pathophysiology and symptomology of CS. A peripheral TPH inhibitor, such as telotristat etiprate, should alleviate the symptoms due to excess 5-HT in carcinoid patients without central nervous system (CNS)-related adverse events (AEs).

Approximately 90% of the body's 5-HT is found in the EC cells of the GI tract, with the remainder distributed between the platelets and CNS.[4] TPH catalyzes the biopterin-dependent monooxygenation of tryptophan to 5-hydroxytryptophan, which is subsequently decarboxylated to form 5-HT. Expression of TPH is limited to a few specialized tissues: raphe neurons, pinealocytes, mast cells, mononuclear leukocytes, beta cells of the islets of Langerhans, and intestinal and pancreatic EC cells.[5] Two isoforms of the enzyme exist, TPH1 and TPH2. TPH1 is exclusively located in the EC cells of the GI tract and pineal gland and is the rate limiting enzyme responsible for the majority of systemic 5-HT production and is also responsible for 5-HT synthesis in carcinoid tumors. TPH2 is located in the central and enteric nervous systems and is the rate-limiting enzyme in the production of neuronal 5-HT.

The oral TPH inhibitor, telotristat etiprate, represents a novel approach to potentially lessen the pathophysiology of CS by reducing 5-HT levels via inhibition of TPH. Telotristat etiprate was designed specifically as a prodrug in order to gain greater systemic exposure, opening the potential application for indications in which hyperserotonemia is thought to contribute to the disorder, such as CS. Preclinical pharmacology studies of telotristat etiprate were designed to evaluate the compound’s mechanism of action and effects in vivo. Telotristat etiprate is the ethyl-ester prodrug of the active moiety LP-778902. Telotristat etiprate was

designed as a prodrug in order to enhance peripheral exposure without crossing the blood-brain barrier. In vivo, telotristat etiprate is readily converted through esterase activity to its corresponding acid, LP-778902. LP-778902 has an in vitro potency of 0.028 μM on purified human TPH1 enzyme and 0.032 μM on purified TPH2 enzyme. Therefore, telotristat etiprate is a robust inhibitor of TPH both in vitro and in vivo and has been shown in Phase 2 studies to provide clinical benefit to patients with carcinoid tumors and associated CS.

Telotristat etiprate is being developed to manage GI symptoms and possibly other symptoms associated with CS. Currently, the standard of care for patients with CS is symptom management using somatostatin analogs (SSA), which are available in both short- and long-acting release (LAR) formulations. Somatostatin analogs such as octreotide are indicated for the control of flushing, diarrhea, and other symptoms associated with CS. Common side effects of the long-acting depot form of the drug are pain at the site of the injection, reported in as many as 30 to 50% of carcinoid patients at the 20 and 30 mg doses, and less commonly, stomach cramps, nausea, vomiting, headaches, dizziness, and fatigue.[6] Other side effects identified in the product labeling include biliary tract abnormalities (gallstones, sludge, and dilatation), hypothyroidism, dietary fat malabsorption, and hyper or hypoglycemia.[7] In addition to the morbidity associated with parenterally administered agents, tachyphylaxis will occur in the majority of patients, resulting in recurrent symptoms.

There are currently no specific oral treatments indicated for the management of symptoms associated with CS. As a result of the morbidity associated with SSAs and the associated tachyphylaxis, there is an unmet medical need to provide symptom management and modify the pathophysiology of patients with metastatic CS. Inhibition of the excessive 5-HT produced by these tumors with an orally delivered agent such as telotristat etiprate could provide significant benefit as an additional treatment option for patients and clinicians.

3.2 Clinical Trials of Telotristat Etiprate (LX1606) in Humans

Telotristat etiprate has been studied in single/multiple doses in Phase 1 studies, approximately 109 healthy volunteers participated in Phase 1 trials with 88 subjects receiving telotristat etiprate and 21 subjects placebo. In addition, 37 CS patients have received telotristat etiprate during the clinical development program in Phase 2. To date, an additional 56 ulcerative colitis patients have been enrolled into an ongoing Phase 2 study to evaluate telotristat etiprate versus placebo in ulcerative colitis patients experiencing active flare.

LX1606.1-101-NRM utilized telotristat etiprate as a single oral dose and was noted to be safe and well tolerated up to doses of 1,000 mg. At doses of ≥1,000 mg, an increase in GI AEs was observed, which were assessed as at least possibly related to study drug. These AEs led to a decision not to escalate the dose beyond 1,500 mg. No serious adverse events (SAEs) or

deaths were reported and no patient discontinued due to an AE. Twenty-three patients experienced at least 1 AE. The majority of the AEs were assessed as mild. The most common AEs were diarrhea and nausea. Random out-of-range laboratory values at various time points in several patients occurred without any apparent trend. There were no other clinically significant vital signs, laboratory or physical examination findings.

LX1606.1-102-NRM utilized telotristat etiprate as multiple oral doses over 14 days and was tolerated up to the maximum dose assessed, 500 mg tid; 1,500 mg total dose daily. Most AEs were mild, the most common being nausea and headache; all resolved. Most AEs were at least possibly related to study treatment. Four AEs required treatment with concomitant medication, 3 AEs of constipation and 1 of headache. No deaths or SAEs were reported. One patient was discontinued due to an AE of abnormal liver function. There were no apparent trends or clinically significant findings observed upon review of vital signs and electrocardiogram (ECG) data. There were no clinically significant abnormal physical examination findings.

Overall, in LX1606.1-102-NRM, treatment with telotristat etiprate was associated with mild elevations, generally ≤2x the upper limit of normal (ULN), in alanine transaminase (ALT) and aspartate transaminase (AST), with elevations in values observed earlier in the higher dose cohorts. Results were assessed as clinically significant for only 1 patient, in Cohort 4, who was withdrawn on Day 10. The trend was most pronounced in Cohort 5, in which 5 out of 6 patients who received telotristat etiprate had increases in ALT values which were above normal range and 4 patients had increases in AST values which were above normal range at Day 14. Mean increases in ALT and AST appeared earlier in the study for Cohorts 4 and 5 than in the other cohorts, and were noted for all cohorts by Day 12. All patients had normal ALT and AST values at Baseline and most elevated transaminases returned to normal range within 48 hours after the last dose of study drug. No changes in alkaline phosphatase (ALP) or total bilirubin were observed in any patient.

LX1606.1-103-NRM evaluated 2 oral formulations of telotristat etiprate in an open-label crossover study. Each formulation was given as a single oral dose followed by a 5-day washout and then patients were given a single oral dose of the second formulation. During this study, there were no deaths or SAEs reported and no AEs lead to discontinuation. The most commonly reported AE was diarrhea. No clinically significant observations or changes in other safety parameters (eg, clinical laboratory evaluations, vital signs, physical examinations, ECGs, and AEs) were identified in the patient population during the study conduct.

LX1606.1-202-CS was a randomized, double-blind, placebo-controlled, multiple ascending dose study conducted in 2 parts in order to evaluate a total of 23 patients at a dose range of

450 to 1500 mg given as 150, 250, 350, or 500 mg tid (telotristat etiprate or matching placebo) on a background therapy of octreotide. In Part 1, 16 patients were randomly assigned 3:1 into 4 sequential cohorts. Each cohort evaluated 1 of the following daily doses given as 150, 250, 350, or 500 mg tid over a course of 4 weeks. During the study all patients continued on a stable-dose background therapy of octreotide. In Part 2, an additional 7 patients were randomly assigned 3:1 in order to evaluate 500 mg tid, the highest tolerated dose as determined in Part 1. Upon completion of the initial 4-week portion, eligible patients had the option to continue into an open-label Extension Period.

There was 1 treatment emergent SAE assessed as possibly related to study drug which occurred in the 350 mg tid dose group. The patient had a history of nausea and vomiting and was hospitalized for exacerbation of these conditions.

Telotristat etiprate was generally well tolerated with no evidence of dose-limiting tolerability. Adverse events were mostly mild to moderate and with similar frequencies between treatment groups and placebo. No significant changes in vital signs, ECG, or physical exam findings were noted after administration of telotristat etiprate at any dose level. The most common AEs were GI-related and reported as diarrhea, nausea, and abdominal pain, respectively. The modest elevations in transaminases seen in the Phase 1 multiple ascending dose study were not apparent in this 4-week study in patients with CS.

Patients that received telotristat etiprate achieved a clinical response (28%) defined as at least a 30% reduction in bowel movements (BMs) for at least 2 weeks; a biochemical response (56%) at least 50% reduction or normalization of urinary 5-hydroxyindoleacetic acid (5-HIAA); and reported adequate relief at Week 4 (46%) while no placebo patients experienced clinical response, biochemical response, or adequate relief.

LX1606.1-203 was an open-label, serial ascending, multiple dose, individual titration study that evaluated the same dose ranges as the 1606.1-202-CS study in a total of 15 patients. Patients were serially escalated to the next dose level every 2 weeks until a maximally tolerated dose or 500 mg tid was reached. Once a dose had been determined, the patient would remain on the dose for an additional 4 weeks. Patients then had the option to continue into an Extension Period.

Telotristat etiprate was generally safe and well-tolerated in subjects with CS in the LX1606.1-203 study. Most AEs were mild to moderate in severity and assessed as unrelated to study drug. Events in the Gastrointestinal Disorders SOC were common, as is anticipated with the underlying illness.

Statistically significant reductions from Baseline in the mean number of BMs/day were observed in this study throughout the entire dose-escalation and stable-dose phases, as were

associated improvements in stool form. Telotristat etiprate produced an improvement in global assessment of GI symptoms associated with CS in the majority of subjects (12 of 15 subjects, 80%) across the 12-week period. The global assessment of GI symptoms was based on 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 BM, abdominal pain or discomfort?" In addition, subjects experienced statistically significant decreases in the mean daily number of cutaneous flushing episodes.

Thirteen subjects (86.7%) experienced a complete biochemical response (defined as a ≥50% reduction from Baseline in u5-HIAA levels at 1 or more time points). Consistent with the proposed mechanism of action for telotristat etiprate, a complete biochemical response correlated closely with measures of clinical response, such as numbers of bowel movements per day.

Detailed information regarding the completed clinical studies can be found in the Investigator Brochure.[8]

3.2.1 Ongoing Studies

LX1606.1-204-UC is currently evaluating patients with active flares of ulcerative colitis. Doses under evaluation are 500 mg once daily (qd) and 500 mg tid vs. placebo; 60 patients are expected to enroll for an 8-week treatment period.

LX1606.1-301-CS is intended to evaluate (1) the efficacy of telotristat etiprate on reducing the number of BMs; (2) the efficacy of telotristat etiprate on a number of clinically relevant secondary endpoints; and, (3) the safety of telotristat etiprate over the 12-week double-blind portion (Treatment Period) of the study. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period (Extension Period).

LX1606.1-303-CS is intended to evaluate (1) the safety of telotristat etiprate over the 12-week double-blind portion (Treatment Period) of the study and (2) the effects of telotristat etiprate on a number of clinically relevant secondary endpoints. Upon completion of the Treatment Period, patients will continue into a 36-week open-label Extension Period.

3.3 Rationale for Current Study

3.3.1 Rationale for Selection of Dose

Two dose levels of telotristat etiprate (250 mg and 500 mg tid) were selected for this study based upon clinical safety and pharmacodynamic (PD) data from 2 Phase 2 multiple

ascending-dose studies in patients with symptomatic CS (LX1606.1-202-CS and LX1606.1-203-CS).

Based upon observations noted in Section 3.2, it is anticipated that the doses to be utilized in this protocol will be safe and well tolerated and may provide clinical benefit to patients with CS.

3.3.2 Benefit/Risk Assessment

Clinical experience with telotristat etiprate (treated subjects) consists of completed single and multiple ascending dose studies in 88 normal subjects (36 in single dose studies and 52 in the multiple dose study), two Phase 2 studies (37 patients with symptomatic CS) and 2 ongoing Phase 3 studies in patients with symptomatic CS.

In healthy volunteer studies, single doses up to 1000 mg were found to be generally well tolerated, while at the 1500 mg dose level GI-related adverse events increased. A similar adverse event profile was observed after multiple dose administration over 14 days with GI events predominating. Mild, dose-dependent increases in hepatic transaminase levels (≤2 x ULN) were observed with increased frequency in relation to dose, with 1 subject requiring withdrawal from therapy at the 500 mg bid dose level. Most subjects that were observed to have increased transaminase levels did not exceed >2 times upper limits of normal. No abnormalities in total bilirubin were observed at any dose level. GI events have been the most commonly observed events to date. The adverse event profile in normal subjects may differ significantly from what is observed in patients with hyperserotonemia. All adverse events resolved without sequelae. In addition, there were no significant changes in vital signs or ECG. No physical examination abnormalities were noted in studies to date. There were no serious adverse events reported in healthy volunteers.

In patients with CS, dose escalations have proceeded up to and including 500 mg tid. To date, there has been no evidence of dose-limiting intolerability. Dose levels have been generally well tolerated with no evidence to suggest elevations in hepatic transaminase levels. Discontinuations that have occurred to date have not been dose-dependent and include lack of effect (n=1, 350 mg tid) and a serious adverse event of nausea/vomiting (n=1, 350 mg tid).

Based upon observations from preclinical and clinical studies conducted to date, it is anticipated that orally administered telotristat etiprate will be well tolerated at dose levels required to influence peripheral 5-HT production in patients with symptomatic CS. Potential adverse events primarily involve the GI tract, and could include alterations in gut motility, nausea, vomiting, diarrhea, constipation, abdominal bloating, and/or pain. Regular and ongoing clinical and laboratory assessments should detect any of these events, and depending on the type of event, further dose adjustment or discontinuation from the trial would occur.

Although CNS effects are not anticipated at dose levels planned for evaluation, standard adverse event questioning and/or physical examination should reveal any subtle CNS findings. As elevations in hepatic transaminase levels were observed with multiple dosing in normal subjects, monitoring clinical laboratory tests of hepatic function will be incorporated into clinical trials conducted in CS patients.

Treatment has the potential to improve several signs and symptoms of CS. The Phase 2 clinical trial results indicated that treatment may lead to improvements in bowel movement frequency, stool consistency, urgency, abdominal pain, diarrhea, flushing, and reductions in 5-HIAA. These potential benefits relate to a unique mechanism of action. Symptomatic improvement may lead to a better quality of life (QOL) for patients with few treatment options available, and 5-HIAA reduction may help reduce the risk of carcinoid heart disease. Overall the benefit/risk profile of telotristat etiprate is expected to be favorable for participation in this clinical study.

3.4 Rationale for Study Design and Control Groups

Currently, no approved therapy exists for the treatment of symptoms driven by underlying serotonin pathophysiology of CS in patients whose disease is refractory to SSA therapy or for those patients who are unable to tolerate SSA therapy or who are unwilling to take SSA therapy.

This study will allow for continued access to telotristat etiprate after patients have completed the required study visits in ongoing Phase 2 and Phase 3 studies. Continuation of CS patients into this study will allow for the collection of additional long-term safety and efficacy data, while providing access to patients who may be receiving benefit. The treatment duration is supported by results of chronic toxicology studies (6-month rat and 9-month dog) and the current safety profile from completed and ongoing clinical trials.

4. Study Objectives

4.1 Efficacy Objectives

4.1.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

4.1.2 Secondary Objective(s)

The secondary objective of this study is to evaluate changes in patients' QOL.

4.2 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

5. Investigational Plan

5.1 Overall Study Design

The study will be conducted as a multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate.

Patients currently participating in any LX1606 Phase 2 CS study may enter into this extension study upon institutional or local approval of the protocol. Patients participating in a Phase 3 CS study may enter into this extension study at the Week 48 visit. All patients who enter into this extension study will be exempt from any follow-up visit required by the original study and will not experience an interruption in study drug due to the transition from the original protocol to LX1060.1-302-CS.

Following confirmation of eligibility, patients may enter into the study at a dose level of 250 mg or 500 mg telotristat etiprate given 3 times daily (tid). Upon entering, these patients will complete a series of visit assessments in order to establish Baseline symptoms. Patients will then continue on open-label LX1606 at the same dose level identified in the previous study.

Downward dose adjustment from 500 mg to 250 mg tid will be permitted during the study if evidence of intolerability emerges. Patients who experience intolerability at the 250 mg tid dose level must be discontinued from the study. Patients may return to 500 mg tid dosing at the discretion of the Investigator and in consultation with the Medical Monitor.

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

A Data Safety Monitoring Board (DSMB) will review safety data throughout the study.

6. Study Population

Adult patients who are currently participating in ongoing Phase 2 or Phase 3 telotristat etiprate CS clinical protocols will be enrolled into the study. Up to 160 patients are expected to enroll in this study. Approximately 70 sites worldwide will participate in the study. Patients

may continue allowed medications as background therapy provided they remain on stable-doses throughout the Treatment Period.

6.1 Inclusion Criteria

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

1. Ongoing participation in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study
2. 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.
3. Ability and willingness to provide written informed consent prior to participation in any study-related procedure.

6.2 Exclusion Criteria

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

1. Major protocol violations or tolerability concerns in a Phase 2 (eg, LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (eg, LX1606.1-301-CS, LX1606.1-303-CS) study
2. Positive pregnancy test
3. Presence of any clinically significant findings at entry for medical history, laboratory values, 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

6.3 Criteria for Stopping Treatment/Study Withdrawal

A patient may also be discontinued from the study for the following medical or administrative reasons:

- Withdrawal of consent by the patient or legal guardian
- Noncompliance, including refusal of the study medication and/or failure to adhere to the study requirements as in the study protocol
- Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study
- The Sponsor terminates the study (Section 6.4)
- Pregnancy (Section 9.4.1)

Note: Patients who are discontinued from study treatment before completing the entire duration of the Treatment Period should continue clinic visits according to the study schedule; this includes the reporting of any AEs, including SAEs (Section 9.2).

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 Appendix A – Schedule of Events.

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 Case Report Form (CRF).

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.

6.4 Criteria for Termination of the Study

If the 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; and,
- Insufficient adherence to protocol requirements.

Study termination and Follow-up would be performed in compliance with applicable governing body regulations.

6.5 Clinical Stopping Rules

Criteria for individual patient withdrawal or study termination are summarized in Sections 6.3 and 6.4, respectively.

6.6 Method of Assigning Patients to Treatment

Patients will enter the study at the same dose level and regimen as identified in the prior Phase 2 or Phase 3 CS study. Randomization will not be used to assign patients to study treatments.

6.7 Blinding and Unblinding of Study Medication

This is an open-label study.

6.8 Replacement of Patients

Patients who do not complete the study will not be replaced.

7. Treatment

7.1.1 Telotristat Etiprate (LX1606)

7.1.1.1 Identity

LX1606 hippurate is the salt form of the drug substance. LX1606 hippurate is a crystalline white to off-white to tan solid with a melting point of 147°C. LX1606 is insoluble in water within the pH range of 5 to 9 (≤2 mg/L). It undergoes hydrolysis under strongly basic or

strongly acidic conditions. The solubility of LX1606 hippurate in water is about 22 mg/L at 25°C.

Study drug dosage form consists of white coated debossed oval tablets containing 250 mg LX1606.

7.1.1.2 Packaging, Labeling, and Storage

Patients will receive 250 mg telotristat etiprate tablets packaged in 100 cc high density polyethylene bottles with child-resistant polypropylene screw caps and heat-induction seal liners.

Telotristat etiprate should be stored between 15 to 25°C (59 to 77°F).

7.2 Prior and Concomitant Medications

7.2.1 Prior Medications

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

7.2.2 Concomitant Medications

All concomitant medications taken by patients during the study will be recorded on the CRF. Treatment with prescription or over-the-counter (OTC) antidiarrheal therapy, bile acid sequestrants, or pancreatic enzyme is permitted; 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 dose(s) of all concomitant medication should remain stable. Should the need arise to modify/adjust a patient's therapy 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.

7.2.3 Prohibited Medications or Concomitant Therapy

None

7.3 Administration of Study Medication

All patients will be instructed to take the study medication with food. "With food" means taking telotristat etiprate 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.

Study medication and instructions will be dispensed to patients at each visit as described in the schedule of study procedures (Appendix A).

7.3.1 Treatment Compliance

Patients will be asked to bring their unused or unopened study medication to each visit (Appendix A). At each visit and in the presence of the patient, study site personnel will count returned tablets and reconcile the counts against planned number of doses for that interval. Site personnel will clarify any discrepancy and record this information within the CRF.

Patients must maintain at least 75% compliance in dosing to be deemed as compliant. In the event of a missed or vomited dose, patients will take their subsequent dose of study drug at the next scheduled time point, following the tid dosing regimen of approximately every 6 hours. A dose outside of a 3 hour window should be considered missed. Missed or vomited doses will not be made up.

7.4 Dose Adjustment

Downward dose adjustment of telotristat etiprate, from 500 mg to 250 mg tid, will be permitted 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 may be permitted after consultation with the Medical Monitor, at which time the patient will be reassessed for study continuation, dose reduction, or discontinuation.

8. Study Procedures

A schedule of study assessments is provided in Appendix A.

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 Appendix A.

8.1 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.

8.2 Description of Study Assessments

8.2.1 Efficacy Assessments

Efficacy assessments include the patient reported measures EORTC QLQ-C30 (Appendix D) & GI.NET21 (Appendix E) and subjective global assessment of symptoms associated with CS.

A description of the efficacy assessments is provided below.

8.2.1.1 EORTC QLQ-C30 & GI.NET21

Patients will complete the questionnaires during each visit as indicated in Appendix A.

8.2.1.2 Subjective Global Assessment

A subjective global assessment of symptoms associated with CS will be evaluated using 2 methods at each visit.

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."

8.2.2 Clinical Laboratory Assessment

Clinical laboratory assessments will consist of hematology (complete blood count [CBC] with differential and platelet counts), blood chemistry (complete metabolic panel and liver function tests), and urinalysis. 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 9.1 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.

8.2.2.1 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 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 function test values 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 continued study participation.

8.2.3 Pharmacodynamic Assessments

8.2.3.1 Plasma 5-HIAA

Fasting blood samples (of at least 6 hours) 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.

8.2.4 Safety Assessments

In addition to the clinical laboratory assessments described in Section 8.2.2, monitoring of AEs is also considered a safety assessment and is described in detail in Section 9. Clinically significant changes compared with Baseline findings for these variables should be reported as AEs on the CRF. Clinically significant changes compared with Baseline values, which are determined to be AEs, 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.

8.2.4.1 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 with 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. 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 Appendix A.

8.2.4.2 Physical Examinations

Complete physical examinations will be performed as outlined in Appendix A. 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, weight will be captured during each physical examination. Efforts should be made to standardize 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.

8.2.4.3 Electrocardiograms

Electrocardiograms (12-lead ECGs) will be performed as specified in Appendix A.

8.2.4.4 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.

8.2.4.4.1 Central Nervous System Events

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

8.3 Other Assessments

Blood samples for measurement of chromogranin A (CgA) levels will be collected as indicated in Appendix A.

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 [eg, PET, CAT, MRI scans of tumor], Investigator assessment of disease status) while the patient is enrolled in the study.

8.4 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.

8.4.1 Blood Collection

An attempt should be made to collect all samples as per the schedule outlined in Appendix A. Any portion of samples remaining after the required tests for this study have been completed will be destroyed.

The estimated amount of blood scheduled for collection per patient, over the course of the study, may be found in Appendix B.

9. Safety Reporting

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

Sites in North America:

[redacted], MD
[redacted]
INC Research
[redacted]
Phone: [redacted]

Sites outside North America:

[redacted], MD, PhD
[redacted]
INC Research
[redacted]
The Netherlands
Phone: [redacted]
Mobile: [redacted]

[redacted] MD, PhD
Medical Monitor
INC Research, LLC
[redacted]
Czech Republic
Phone: [redacted]
Fax: [redacted]

After-hours 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. **Note**: these calls are not toll-free.

9.1 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 preexisting 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 9.2) 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

9.2 Serious Adverse Events (SAEs)

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; or
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: [redacted]
Belgium: [redacted]
France: [redacted]
Germany: [redacted]
Italy: [redacted]
Netherlands: [redacted]
Spain: [redacted]
Sweden: [redacted]
United Kingdom: [redacted]

Email Address (in case of fax failure): [redacted]

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.

9.3 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.

9.4 Precautions

9.4.1 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 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 9.2 for contact information).

10. Statistical Methodology

10.1 Determination of Sample Size

No formal sample size calculation was made. The number of patients expected to participate in this study was calculated from estimated enrollment rates from other carcinoid cancer trials employed in the LX1606 clinical program.

10.2 Analysis Populations

Per protocol: A Per Protocol population will consist of those patients that receive study treatment and have no major protocol violation that would interfere with the collection or interpretation of the efficacy data. The primary analyses of efficacy will be based on the safety population; 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 during this study.

10.3 Study Endpoints

10.3.1 Efficacy Endpoints

The primary efficacy endpoint is to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

Secondary efficacy endpoint is to evaluate changes in patients' QOL over multiple years of therapy.

10.3.2 Safety Endpoints

Safety endpoints are as follows:

- Incidence of TEAEs, suspected adverse reaction, AEs leading to discontinuation from the study, SAEs, and deaths
- Actual and change from Baseline in clinical laboratory results
- Actual and change from Baseline in vital signs results
- Actual and change from Baseline in physical examinations
- Actual and change from Baseline in ECG findings

10.4 Statistical Methods

Descriptive analysis methods will be used to summarize the data. Continuous variables will be summarized by the N, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized as counts and related percentages. Data tabulations will be categorized by the treatment received on Day 1 of this study and combined across all treated patients. All data will be listed.

Primary analyses of the data will be based on the Safety population which includes all patients treated with any fraction of study drug during this study. Supportive analyses of the efficacy data will be made on a Per Protocol population. This dataset will include the Safety population, but limited to those patients that have at least one assessment post Day 1 and do not have any protocol violations that would interfere with collection or interpretation of the data. The Per Protocol analysis will be applied to the QOL measures, subjective global assessment, and plasma 5-HIAA values.

Data will be summarized per study visit as the actual (raw) outcomes and change from Baseline scores, where applicable. Day 1 of this study will serve as the Baseline assessment.

10.4.1 Efficacy Analyses

All efficacy and PD variables will be summarized descriptively and listed.

Statistical tests and estimates of within patient effects for these measures will be derived from application of a mixed linear model with repeated measures. The model will be generalized to handle missing data and specific to the measurement properties of the dependent variable. There is no plan to impute data for missing observations for any variable. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model.

Exploratory analyses of treatment group differences may be performed by use of propensity score models. The treatments groups will correspond to how patients were dosed on Day 1 of this study.

10.4.2 Safety Analyses

Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Reporting of these data will be based on the Safety population. Summaries will be prepared by treatment group (corresponding to the LX1606 dose given on Day 1), pooled across all patients, and as needed, by study visit. All safety data will be listed.

Treatment-emergent adverse event 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 serious adverse events.

Vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) 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 and summarized.

10.4.2.1 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.

10.4.2.2 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 using descriptive statistics. Summaries of shifts from Baseline to abnormal

clinical laboratory results will also be provided. Actual and change from Baseline in chromogranin A levels will be summarized descriptively as well.

10.4.2.3 Vital Sign Measurements

Actual and changes from Baseline (Day 1) in vital signs results will be summarized by using descriptive statistics.

10.4.2.4 Electrocardiograms

Clinically significant changes in ECGs compared to Baseline, as determined by the Investigator, will be summarized by using descriptive statistics. Actual and change from Baseline (Day 1 predose values) to each time point in corrected QT interval (QTcF) will be summarized as well.

10.4.3 Pharmacodynamic Analyses

Analysis and summarization of the plasma 5-HIAA data are described in Section 10.4.1.

10.4.4 Baseline Characteristics and Other Summaries

Treatment group differences will be summarized descriptively for demographic data, prior and concomitant medications, treatment compliance, and final disposition. Data collected from assessments of tumor status, when available, will be listed.

Protocol deviations will provided as listings.

10.4.5 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.

11. Study Management

The Investigator is responsible for completing and maintaining adequate and accurate CRFs and source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, and discharge summaries.

All data on the CRF must be recorded in accordance with the CRF guidelines. If a correction is necessary, it should be made by the Investigator or a designated qualified individual as specified within the guideline. All CRFs should be completed in their entirety and stored in a secure location. The Investigator must sign the Investigator's statement in each patient's CRF indicating that the data reported are accurate.

At the study site, clinical research associates will verify 100% of CRFs in their entirety against source documentation. Computer programmed edit checks will be run against the database to check for discrepancies and reasonableness of the data, and the safety database will be reconciled with the clinical database. All issues resulting from the computer generated checks and the safety database reconciliation will be resolved according to standard data management practices in conjunction with the Sponsor, clinical study personnel, and the study Investigators.

11.1 Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the Sponsor's study monitors will contact the study site via visits to the site, telephone calls, and/or letters in order to review study progress, CRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of patients, patient recruitment, patient compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by patients, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

The Investigator must make study data accessible to the clinical monitor, to other authorized representatives of the Sponsor, and to regulatory inspectors

11.2 Audits and Inspections

The Sponsor, regulatory authority, or IRB/ERC may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a Sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

11.3 Amendments

Any amendments to the protocol will be written and approved by the Sponsor. All amendments must be submitted to the IRB/ERC for approval prior to implementing the changes. In some instances, an amendment may require changes to the informed consent form, which also must be submitted for IRB/ERC approval prior to administration to patients.

If any changes to the CRF are required, the Sponsor will issue supplemental or revised CRF pages.

11.4 Record Keeping

11.4.1 Drug Accountability

The Investigator must maintain accurate records of receipt of study drug, dispensing information (date, lot, and dose for each patient), and the prompt return or destruction of unused supplies. If the Investigator cannot account for all clinical supplies at the termination of the study, a written explanation must be provided.

11.4.2 Health Insurance Portability Accountability Act of 1996

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 Code of Federal Regulations (CFR) Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

11.4.3 Financial Disclosure

The Investigator shall provide to the Sponsor sufficient accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the FDA and/or other applicable regulatory agencies. The Investigator shall promptly update this information if any relevant changes occur in the course of the study or for 1 year following completion of the study.

11.4.4 Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 11) to ensure data integrity. “Original” in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

11.4.5 Retention of Study Documents

According to 21 CFR Part 312.62 and ICH E6, study-related records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least

2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor.

The Investigator must not destroy any study-related records without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor must be contacted to arrange alternative record storage options.

12. Administrative Structure of the Study

The study will be monitored by Sponsor personnel or Sponsor representative. The following functions for this study will be performed by organizations designated by the Sponsor: data management and statistical analysis, including PD analysis and reporting.

13. Appendix A – Schedule of Events

Procedure	Extension Period					2 Week Follow-up[5]
	Baseline Day 1[1]	Week 12[2]	Week 24	Week 36[2]	Week 48/ EOS	
Tolerance (days)	NA	± 5	± 5	± 5	± 5	± 5
Inclusion/Exclusion criteria	X					
Medical history	X					
Physical examination	X	X[4]	X[4]	X[4]	X	X[6]
Urine pregnancy test[3]	X					X
Serum pregnancy test[3]					X	
Hematology, Blood chemistry	X	X	X	X	X	X[6]
Urinalysis	X				X	X[6]
Chromogranin A	X				X	
Vital signs	X	X	X	X	X	X
ECG	X				X	X[6]
Subjective Global Assessment	X	X	X	X	X	X
EORTC QLQ-C30 & GI.NET21	X		X		X	
Plasma 5-HIAA	X	X	X	X	X	X
Dispensation of LX1606	X	X[7]	X	X[7]		
Concomitant medications	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X

[1]Eligibility will be determined at last visit of the original protocol, Day 1 will replace the next scheduled visit in the original protocol schedule. Visits should coincide with LAR injections for those patients receiving SSA therapy. [2]Visits 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. [3]Females of child-bearing potential only. [4]Brief physical examination only (symptom-oriented) [5]Visit 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. [6]To be performed only if evaluation at Week 48/EOS is abnormal. [7]If visit is conducted by MRS drug dispensation will not occur. Study drug dispensation will only occur during visits to Investigator study site.

14. Appendix B – Amount of Blood to be Collected from Each Patient

Assessment		Sample volume (mL)	Number of samples*	Estimated total volume (mL)
Safety	Hematology	2	6	12
	Blood chemistry	6	6	36
Other	CgA	2	2	4
	Serum Pregnancy	2	1	2
Pharmacodynamic	Plasma 5-HIAA	4	6	24
			Total	78
*Maximum number of samples is indicated				

15. Appendix C – EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Lexicon

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

16. Appendix D – EORTC QLQ - GI.NET21

ENGLISH

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31. Did you have hot flushes?		1	2	3	4
32. Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33. Did you have night sweats?		1	2	3	4
34. Did you have abdominal discomfort?		1	2	3	4
35. Did you have a bloated feeling in your abdomen?		1	2	3	4
36. Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37. Have you had acid indigestion or heartburn?		1	2	3	4
38. Have you had difficulties with eating?		1	2	3	4
39. Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40. Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41. Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42. Were you concerned about disruption of home life?		1	2	3	4
43. Have you worried about your health in the future?		1	2	3	4
44. How distressing has your illness or treatment been to those close to you?		1	2	3	4
45. Has weight loss been a problem for you?		1	2	3	4
46. Has weight gain been a problem for you?		1	2	3	4
47. Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48. Have you had aches or pains in your muscles or bones?		1	2	3	4
49. Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:					
50. Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51. Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

17. Appendix E – Ethical Standards

Ethics and Regulatory Considerations

This study will be conducted according to GCP, 21 CFR Part 50, (Protection of Human Subjects), 21 CFR Part 56 (Institutional Review Boards), International Conference on Harmonisation Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

General Instructions

The FDA regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to GCP regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- FDA Guideline for the Monitoring of Clinical Investigations, January 1988
- FDA Information Sheets – Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update
- ICH E6 – Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

Studies conducted in the European Union are also regulated by Volume 10 of the publications "The rules governing medicinal products in the European Union".

Copies of these materials are available from the Sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- the study is conducted with diligence and in conformance with the protocol in such a way as to insure the integrity of the findings;

- the potential benefits of the research justify the risks.

Lexicon Pharmaceuticals, Inc. is the Sponsor of the IND. The Sponsor is responsible for the following:

- selecting qualified Investigators,
- providing Investigators with the information they need to properly conduct an investigation,
- ensuring proper monitoring of the investigation,
- ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- maintaining the IND, and
- ensuring that regulatory authorities and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied
- ensuring the study is conducted in accordance to FDA and ICH guidelines and all applicable regulations

18. Appendix F – Investigator Obligations

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56 and ICH E6, the study protocol and the final version of the subject informed consent form will be approved by the IRB/ERC before enrollment of any subjects. The opinion of the IRB/ERC will be dated and given in writing. A copy of the letter of approval from the IRB/ERC and a copy of the approved informed consent form will be received by the Sponsor prior to shipment of study medication supplies to the Investigator.

The Investigator will ensure that the IRB/ERC will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to subjects. The Investigator will also ensure that no changes will be made to the protocol without IRB/ERC approval.

As a part of the IRB/ERC requirement for continuing review of approved research, the Investigator will be responsible for submitting periodic progress reports to the IRB/ERC at intervals appropriate to the degree of subject risk involved, but no less than once per year.

Written informed consent must be given freely and obtained from every subject prior to clinical trial participation. The rights, safety, and well being of the trial subjects are the most important considerations and should prevail over interests of science and society.

As described in GCP guidelines, study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (eg, loss of medical licensure, debarment). Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

Principal Investigators must provide Lexicon with a fully executed Form FDA 1572 (statement of Investigator) and all updates on a new fully executed Form FDA 1572.

Principal Investigators must provide Lexicon with his/her own curriculum vitae and current curriculum vitae for each sub-Investigator listed on Form FDA 1572.

Protection of Human Subjects (21 CFR Part 50 and ICH E6)

Informed consent must be obtained from every subject before entry into a clinical study. It must be given freely and not under duress. Consent must be documented by use of an IRB/ERC-approved consent form and signed by the subject or the subject's legally authorized representative. The US Department of Health and Human Services suggests that when minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent, his signature should also be included. Non-English-speaking subjects must be presented with

a consent form written in a language that they understand. A copy of the signed consent form must be given to the subject signing it. Another copy must be kept in the Investigator's files and made available to regulatory authority representatives upon request. If, for any reason, subject risk is increased as the study progresses, a revised, IRB/ERC-approved consent form must be signed by the subject. Before the study begins, a sample of the consent form must be provided to the Sponsor for review. The FDA and/or other applicable regulatory agencies may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all subjects.

Only in the case of a life-threatening incident may an investigational product be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the Investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB/ERC within 5 working days. In this situation, the Investigator may not administer any subsequent product to that subject until informed consent and IRB/ERC approval are obtained.

Informed Consent

Written informed consent must be obtained from each subject prior to entry in the study. One copy of the signed informed consent document will be given to the subject, and another will be retained by the Investigator. Additionally, the subject must be allowed adequate time to consider the potential risks and benefits associated with his/her participation in the study.

In situations where the subject is not legally competent to provide consent (ie, mentally incapacitated), written consent must be obtained from a parent, legal guardian, or legal representative. In these situations, the consent must be signed and dated by a witness.

The informed consent document must have been reviewed and approved by the Sponsor and by the Investigator's IRB/ERC prior to the initiation of the study. The document must contain the 8 basic elements of informed consent and may contain the 6 additional elements described in 21 CFR Part 50. Every consent form must include the following 8 elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the subject

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility that the FDA and/or other applicable regulatory authority representatives may inspect the records
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available, or a statement describing where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research related injury
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

When appropriate, 1 or more of the following elements of information shall also be included in the consent form:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent
- Any additional costs the subject may incur from participation in the research
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject
- The approximate number of subjects involved in the study

The Declaration of Helsinki includes further details regarding the specific requirements for informed consent.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states, such as California and Oregon, require further action on the Investigator's part concerning subject consent.

Study Documentation

IRB/ERC Review/Approval

The protocol and informed consent for this study, including advertisements used to recruit subjects, must be reviewed and approved by an appropriate IRB/ERC prior to enrollment of subjects in the study. It is the responsibility of the Investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, ICH, GCP, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB/ERC approval which specifically identifies the study/protocol and a list of the committee members must be received by the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

A progress report with a request for re-evaluation and re-approval will be submitted by the Investigator to the IRB/ERC at intervals required by the IRB/ERC, and not less than annually. A copy of the report will be sent to the Sponsor.

When the Sponsor provides the Investigator with a Safety Report, the Investigator must promptly forward a copy to the IRB/ERC.

After completion or termination of the study, the Investigator will submit a final report to the IRB/ERC and to the Sponsor, if required. This report should include: deviations from the protocol, the number and types of subjects evaluated, the number of subjects who discontinued (with reasons), results of the study, if known, and significant AEs, including deaths.

Study Files

The Investigator is required to maintain complete and accurate study documentation in compliance with current Good Clinical Practice standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study. Study documents include, but are not limited to, the Investigator's Brochure, drug accountability records, Sponsor/Investigator correspondence, IRB/ERC correspondence, protocol and amendments, information regarding monitoring activities, subject exclusion records, CRFs, and data queries.

Confidentiality

The anonymity of subjects must be maintained. Patients will be identified by their initials and an assigned subject number on CRFs and other documents submitted to the clinical monitor. Documents that will be submitted to the clinical monitor and that identify the subject (eg, the signed informed consent document) must be maintained in strict confidence by the Principal Investigator, except to the extent necessary to allow auditing by regulatory authorities, the clinical monitor, or Sponsor personnel.

All information regarding the nature of the proposed investigation provided by the Sponsor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB/ERC, the subject, or the regulatory authority) must be kept in confidence by the Investigator.

Drug Accountability

The Investigator or designee is responsible for accountability of the investigational product at the site. The Investigator or designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and return to the Sponsor or alternative disposition of any unused product. These records must include dates, quantities, batch/serial/lot numbers, and expiration dates (if applicable).

The Investigator should ensure that the investigational product is used only in accordance with the protocol

19. References

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