Title: An Observational Study to Evaluate the Real-world Experience of Patients who are Initiating Treatment with Telotristat Ethyl (XERMELO™)

NCT Number: 03223428

Protocol Approval Date: 06 January 2020

Certain information within this protocol has been redacted (ie, Specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

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- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
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REGISTRY PROTOCOL

Protocol Number:	LX1606.1-401-CS LX1606.401 (Abbreviated number)
Investigational Phase:	4
Protocol Title:	An Observational Study to Evaluate the Real-world Experience of Patients who are Initiating Treatment with Telotristat Ethyl (XERMELO®)
Study Name:	**R**eal-world **E**vidence Study Eva**L**uating P**A**tient-Reported Outcomes with **X**ERMELO (**RELAX**)
Amendment 1 Date:	06 January 2020
Original Version Date:	19 May 2017
Sponsor:	Lexicon Pharmaceuticals, Inc.
Medical Director:	[redacted] EVP and CMO Lexicon Pharmaceuticals, Inc. [redacted]

Investigator Signature Page

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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 Council for 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 US Food and Drug Administration (FDA) or other applicable regulatory agencies, before they can be implemented, except where necessary to eliminate hazards to participants.

Principal Investigator's Signature	Date
Principal Investigator' Name (Print) [redacted]	
Lexicon Executive Vice President and Chief Medical Officer (Signature) [redacted]	[redacted] Date
Lexicon Executive Vice President and Chief Medical Officer [redacted]	

1. Synopsis

Name of Study Drug	Telotristat ethyl (XERMELO®)
Protocol Number	LX1606.1-401-CS LX1606.401 (Abbreviated number)
Protocol Title	An Observational Study to Evaluate the Real-world Experience of Patients who are Initiating Treatment with Telotristat Ethyl (XERMELO)
Primary Objective	The primary objective of the study is to estimate the proportion of carcinoid syndrome (CS) patients who are satisfied with their overall symptom control, 6 months after initiating treatment with telotristat ethyl (XERMELO).
Secondary Objective	The following secondary objectives will be assessed 6 months after initiating treatment with telotristat ethyl (XERMELO): • To estimate the proportion of patients reporting satisfaction of CS- related diarrhea control • To estimate proportion of patients reporting satisfaction of CS- related flushing control • To estimate the proportion of patients reporting reduction in rescue somatostatin analog (SSA) use • To estimate the proportion of patients reporting reduction in the dose of long-acting SSA injection • To estimate the proportion of patients reporting reduction in the frequency of long-acting SSA injection • To estimate the proportion of patients reporting an overall improvement in CS control after initiating XERMELO based on patient global impression of change (PGIC) • To estimate the proportion of patients that had a reduction in work-related absenteeism, presenteeism, activity impairment, and overall productivity loss after initiating XERMELO based on Worker Productivity and Activity Impairment: Specific Health Problem v2.0 (WPAI- SHP) • To estimate the proportion of patients reporting weight gain
Exploratory Objectives	[redacted]
Phase of Development	4

Methodology	This observational, noninterventional, single-arm study will include patients with CS and who are initiating treatment with XERMELO. Patients will be asked to complete up to 7 web-based surveys including a Baseline assessment and then every 6 months for a total of up to 3 years. Each survey is anticipated to take no more than 20 minutes on average. All assessments, except mortality, will be patient-reported; medical records will not routinely be requested or reviewed as part of this observational study unless required for safety reporting purposes. XERMELO prescription fill data will be collected directly from the specialty pharmacies, for all study patients that enter this study. Upon entering the study, patients will be asked to provide sociodemographic information, current medical history (specifically date of CS and neuroendocrine [NET] diagnosis, NET location, CS-related hospitalization and/or ER visits, and NET-related surgery), height, weight, concomitant medications (specifically those related to SSA therapy, systemic therapy, and liver-directed therapy). In addition, patients will be asked to complete a work productivity and activity impairment (WPAI) assessment and describe satisfaction with CS, CS-related diarrhea and/or flushing prior to initiating treatment with XERMELO. Patients will complete a survey every 6 months, describing changes to previously reported data and/or new occurrence of pre-specified events. Data that may be collected at the 6 month time point includes changes in weight, concomitant medications (specifically those related to SSA therapy, systemic therapy, and liver-directed therapy), WPAI assessment, and satisfaction with CS, CS-related diarrhea and/or flushing following the initiation of treatment with XERMELO, as well as, new occurrence(s) of CS-related hospitalization and/or ER visit(s) will also be collected. Following the month 6 time point, long-term assessments are to include changes in weight, concomitant medications (specifically those related to SSA therapy, systemic therapy, and liver-directed therapy), as well as, new occurrence(s) of CS-related hospitalization and/or ER visit(s) will also be collected. Throughout the study information related to mortality will be collected through indirect sources.
Number of Patients	A minimum of 643 patients with CS who initiate treatment with XERMELO are expected to participate in this study.
Patients	Eligible patients are defined as adult patients (≥18 years) diagnosed with CS and initiating XERMELO as a new treatment.

Number of Study Sites	2
Treatments	250-mg XERMELO tablet administered as directed
Route of Administration	Oral
Duration of Participation	Up to 3 years
Inclusion Criteria	Patients must meet **all** of the following criteria to be considered eligible to participate in the study: 1. Adult, ≥18 years of age at the time of informed consent 2. A new, valid prescription for XERMELO 3. Initiating XERMELO for the treatment of carcinoid syndrome 4. Able and willing to provide informed consent prior to participation in the study
Exclusion Criteria	Patients who meet **any** of the following criteria will be excluded from participating in the study: 1. Unable to understand and read English 2. Unable to access the internet 3. Prior exposure to XERMELO
Statistical Methods	The analysis population is comprised of all patients who provide consent, are enrolled into the study, and have data available for 1 or more of the primary and secondary endpoints. Descriptive statistics will be used to summarize the data. Continuous and ordinal variables will be summarized by n, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by patient counts and related percentages. Confidence limits (CLs) corresponding to point estimates of the proportions or means corresponding to the study endpoints will be 2-sided and calculated with 95% confidence coefficient. Statistical tests will be 2-sided and have an associated α-level=0.05. For the primary endpoint, the proportion of CS patients who are at least somewhat satisfied with their overall symptom control at 6 months, a point estimate and the corresponding 95% CLs will be calculated based on the assumption of approximate normal distribution. Secondarily, a point estimate and corresponding 95% CLs will be calculated for the proportion of CS patients who are very satisfied with their overall symptom control at 6 months. All the secondary endpoints correspond to proportions and will be summarized through point estimates and 95% CLs, as described above for the primary endpoint. In addition, for the primary and secondary endpoints, the frequency distributions of the categorical

	responses and summary statistics of the corresponding ordinal values of the categories will be presented. The incidences of at least 1 CS-related hospitalization, at least 1 CS-related ER visit, and mortality Baseline will be calculated at each 6-month interval. Kaplan-Meier estimates of each time-to-event variable, including quartiles, medians, and their corresponding 95% CLs, will be presented. The association or relationship between the primary endpoint and each long-term health outcome will be evaluated through descriptive statistics and the use of statistical models, as appropriate.
Assessments	Assessments include the following measures: patient satisfaction with CS, CS-related diarrhea and/or flushing control; PGIC; rescue SSA use; long-acting SSA dose and frequency; weight; productivity (WPAI-SHP); incidence of CS-related hospitalization(s), incidence of CS-related ER visit(s), and incidence of mortality.

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2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	adverse event
BM	bowel movement
CFR	Code of Federal Regulations
CL	confidence limit
CS	carcinoid syndrome
e-mail	electronic mail
ER	emergency room
ERC	Ethics Review Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GINA	Genetic Information Nondiscrimination Act
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
ID	Identification
IND	Investigational New Drug
IRB	Institutional Review Board
INCA	International Neuroendocrine Cancer Alliance
LAR	long-acting release
NET	neuroendocrine tumor
NRI	non-responder imputation
PGIC	Patient Global Impression of Change
RTI	Research Triangle Institute
SAP	Statistical Analysis Plan
SSA	somatostatin analog
TPH	tryptophan hydroxylase
US	United States
u5-HIAA	urinary 5-hydroxyindoleacetic acid
WPAI-SHP	Work Productivity and Activity Impairment – Specific Health Problem

3. Introduction

3.1 Background on Telotristat Ethyl (XERMELO®) and Carcinoid Syndrome (CS)

Well differentiated neuroendocrine tumor (NET), formerly known as carcinoid tumor, is a relatively rare tumor type that arises from cells of the neuroendocrine system (Kulke, 2011; Turaga, 2011; Yao 2008).

Carcinoid syndrome (CS) occurs when well differentiated NETs secrete large amounts of serotonin and other vasoactive products into the systemic circulation. By one estimate, CS develops in approximately 10% of adult patients with well differentiated NET and, with a few exceptions, only manifests itself in the presence of liver metastasis (Tomassetti, 2001). By another estimate, approximately 8% to 35% of patients with NET have associated CS, with tumors of the small intestine carrying the highest risk (Rorstad, 2005). Classically, symptoms associated with CS include flushing, diarrhea, wheezing, abdominal pain, and valvular heart disease, although, a variety of other symptoms can occur. Roughly 75% of patients with CS experience diarrhea, which can occur either with or without other manifestations of the syndrome, and has perhaps the most direct impact on activities of daily living (Moertel, 1987).

Valvular heart disease has been associated with high serotonin levels (as measured by its metabolite, urinary 5-hydroxyindoleacetic acid [u5-HIAA]). Due to the slow growing nature of NETs and the prolonged course of disease, about 50% of patients with CS will eventually develop heart disease. Usually only metastatic NETs result in pathological changes to the heart as a result of the hypersecretion of vasoactive substances; in these cases, the development of cardiac pathology heralds a more precipitous decline in clinical course (Fox, 2004; Gustafsson, 2008; Turaga, 2011).

In epidemiological studies, high levels of u5-HIAA in patients with NETs have been associated with poor survival. van der Horst Schrivers, et al prospectively studied 76 patients with midgut well differentiated NETs (van der Horst Schrivers, 2007). Urine collected over a 24 hour period every 3 months was tested for u5 HIAA levels. Patients with high u5-HIAA levels (>20 mmol/mol creatinine) had a median survival of 33 months compared with 90 months for patients with a moderately high level (≤20 mmol/mol creatinine) (hazard ratio=3.33; 95% confidence limit [CL]: 1.66 6.66; p=0.001) (Turaga, 2011).

Morbidity Associated with Carcinoid Syndrome

For the patient with CS, severe diarrhea can lead to weight loss, electrolyte imbalance, malnutrition, and anxiety often resulting in social isolation. In a study of health-related

quality of life (QOL) using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 (version 3.0), patients with CS in Sweden reported a lower health-related QOL than the Swedish general population. A majority of patients reported higher levels of emotional distress, fatigue, and diarrhea, as well as worries about their prognosis, their families, and medical examinations (Fröjd, 2007). Issues with flushing, an intense reddening of the skin, produce considerable discomfort and impair social function. A higher bowel movement (BM) frequency is strongly associated with more reports of fatigue, sleep disturbance, anxiety, depression, pain, and worsening social and physical function. In a cross-sectional survey, undesirable associations were observed between a high number of BMs/day and domains including physical function, anxiety, depression, fatigue, pain impact, sleep disturbance, and social role, suggesting that a reduction in BMs could lead to a much better quality of life (Beaumont, 2012; Turaga, 2011).

The burden of symptoms associated with CS has been recently described in a global survey of 1,928 patients with NET (International Neuroendocrine Cancer Alliance [INCA], 2014; Turaga, 2011). According to the president of the INCA, the survey "...confirms for us the devastating impact this rare cancer can have on patients' lives". Diarrhea and flushing were prominent issues for patients in the survey. The majority of patients (92%) reported a lifestyle change as a result of their neuroendocrine cancer and 60% reported a negative effect on their emotional health. Patients commonly reported that their cancer led them to stop or to cut back on physical activity (49%) or on social life (43%).

Available Treatment Options

Somatostatin analogs (SSAs), like lanreotide and octreotide, are the cornerstone of therapy for the relief of CS and tumor stasis. Somatostatin analogs inhibit the release of serotonin by NETs and have become first line therapy for CS providing the most efficient treatment for the control of flushing, diarrhea, and other symptoms (Modlin, 2010).

Common side effects of SSAs are back pain, fatigue, headache, abdominal pain, nausea, and dizziness. Other side effects identified include biliary tract abnormalities (jaundice, gallstones, sludge, and dilatation), hyper- or hypoglycemia, hypothyroidism, and cardiac changes (sinus bradycardia, conduction abnormalities, and arrhythmias) (Novartis Pharmaceuticals Corp., Sandostatin® LAR Depot package insert, 2016).

Recently, results from the PROMID and CLARINET studies demonstrated the antiproliferative effects of octreotide and lanreotide autogel® (Caplin, 2014; Rinke, 2009).

Therefore, use of SSAs to reduce tumor proliferation has become increasingly common in the treatment paradigm for many patients with NET with or without symptoms.

In a substantial number of NET patients with CS, a tachyphylaxis to SSA treatment may occur as soon as 1 week and as long as 12.5 months after starting therapy (Garland, 2003; Moertel, 1987), possibly due to desensitization of the SSAs' effect on the somatostatin receptors (Hofland, 2003). This desensitization to SSAs may be overcome in some patients by increasing the dosage of SSA above the approved label; however, the efficacy and safety of higher doses is not yet established (Broder, 2015). Significant tumor progression might also contribute to the decrease in efficacy of SSAs over time.

Patients whose symptoms are generally controlled using long-acting SSA therapy may require supplemental doses of short acting SSA therapy when symptoms become exacerbated. Results of a 93 patient study with octreotide indicate approximately 35% to 40% of the patients who received the long-acting release (LAR) Depot formulation still require supplemental subcutaneous (rescue) therapy to control exacerbation of CS symptoms. After 6 months of treatment with octreotide, the number of patients requiring "rescue" doses increased to approximately 50% to 70% of patients. When a patient's response to SSA therapy declines, it is accepted practice to continue SSA therapy while initiating additional treatments, including additional prescribed and over the counter medications (Oberg, 2004).

Surgical debulking of tumors, radiation, various liver directed therapies, and chemotherapy may be attempted as a way of addressing overall tumor burden and reducing associated serotonin production (Kulke, 1999; Kulke, 2011; Öberg, 2012; Turaga, 2011).

Scientific Background for Development of XERMELO

Given the established role of serotonin in CS, inhibiting activity of tryptophan hydroxylase (TPH), the rate limiting enzyme responsible for the production of serotonin, should ameliorate symptoms and could perhaps avoid longer term disease sequelae.

XERMELO is a tryptophan hydroxylase inhibitor indicated for the treatment of carcinoid syndrome diarrhea in combination with SSA therapy in adults inadequately controlled by SSA therapy. Through inhibition of tryptophan hydroxylase, XERMELO reduces the production of peripheral serotonin, and the frequency of carcinoid syndrome diarrhea (Lexicon Pharmaceuticals, Inc., XERMELO™ package insert, 2017).

3.2 Rationale for Current Study

This observational study will capture patient experience with XERMELO in a real-world setting. XERMELO is the first orally available drug to be indicated for the treatment of CS diarrhea.

The clinical development program provided experience in more than 200 patients with CS and demonstrated statistically significant reductions in daily BM frequency, as well as an acceptable safety and tolerability profile. Data from 2 clinical studies, TELESTAR and TELECAST, support that the mechanism of action for XERMELO holds an important role in the treatment of CS. By reducing the production of peripheral serotonin, XERMELO is able to significantly reduce the frequency of CS diarrhea.

Patient satisfaction with XERMELO was not thoroughly studied in the clinical program and is not readily available in medical records. Results of a 35-patient interview sub-study conducted in TELESTAR after 12 weeks of blinded treatment indicated that nearly all patients reporting reductions in BM frequency during the Double-blind Treatment Period described them as meaningful, allowing them to better enjoy life and participate more in social and physical activities. Among interview participants (n=33) answering the question about satisfaction with the ability of the blinded study drug to treat CS, 50% of patients (12/24) on active treatment reported “very satisfied” while 0 patients in the placebo group reported the same term. The Sponsor assumes that satisfied patients will continue XERMELO to avoid the complications of CS, leading to better long-term outcomes (Lexicon Pharmaceuticals, Inc., Clinical Study Report, 2017).

Real-world experience with pharmaceutical products may only be evaluated once the product is available within the marketplace. In capturing patient experience, this study will also assess the patient journey though medical diagnosis of NET and treatment for CS in the clinical setting.

4. Study Objectives

4.1 Primary Objective

The primary objective of the study is to estimate the proportion of CS patients who are satisfied with their overall symptom control, 6 months after initiating treatment with telotristat ethyl (XERMELO).

4.2 Secondary Objective

The following secondary objectives will be assessed 6 months after initiating treatment with telotristat ethyl (XERMELO):

- To estimate the proportion of patients reporting satisfaction of CS-related diarrhea control
- To estimate proportion of patients reporting satisfaction of CS- related flushing control
- To estimate the proportion of patients reporting reduction in rescue SSA use
- To estimate the proportion of patients reporting reduction in the dose of long-acting SSA injection
- To estimate the proportion of patients reporting reduction in the frequency of long-acting SSA injection
- To estimate the proportion of patients reporting an overall improvement in CS control after initiating XERMELO based on patient global impression of change (PGIC)
- To estimate the proportion of patients that had reduction in in work-related absenteeism, presenteeism, activity impairment, and overall productivity loss after initiating XERMELO based on Worker Productivity and Activity Impairment: Specific Health Problem v2.0 (WPAI- SHP)
- To estimate the proportion of patients reporting weight gain

4.3 Exploratory Objective(s)

[redacted]

5. Investigational Plan

5.1 Overall Study Design

In this study, the 2 specialty pharmacies, tasked with distributing XERMELO to patients, will be responsible for the identification and recruitment of patients. All eligible patients initiating treatment with XERMELO will be invited to participate in this study.

Individuals assigned by the specialty pharmacies (the 'site staff') will be responsible for describing the study to patients. An initial verbal consent will be obtained to collect personal contact information and to share it with the [redacted] and/or Research Triangle Institute (RTI) (collectively, the 'study team') for the purpose of providing additional information about the study, collecting informed consent, and managing access and/or support for the web-based survey.

The specialty pharmacies will send contact information to the study team, for patients who express interest in participation, via an approved method of communication noting the patient's unique specialty pharmacy identification (ID) number, first name, phone number, electronic mail (e-mail) address, and preferred time of contact (eg, morning, mid-day, evening). For patients who do not provide consent for further contact, the specialty pharmacies will be asked to provide aggregate data to the study team including patient(s) age, sex, geographic region, insurance type, reason for refusal to participate, and total number of patients who refused to provide consent.

As this study will be completed via an online survey and patients are to complete the enrollment process independently, electronic consent will be utilized for this study. Enrollment will be self-directed through a unique survey link sent directly to the patient's e-mail address. Each patient receiving an invitation to the survey will be assigned a numerical patient ID code; the patient ID will be assigned by the study team, based on a subject ID log at each specialty pharmacy. If successful enrollment is not logged within 30 days of the initial survey e-mail invitation or within 14 days of the subsequent survey e-mail invitations, the study team will make up to 3 attempts to contact the patient via e-mail and/or telephone to complete the enrollment process for study participation. The enrollment process and Baseline survey may be completed anytime within the 30-day window, at a time convenient for the patient.

If the study team is unsuccessful in reaching the patient, the patient will be considered lost-to-follow up and the study team will update the enrollment status as appropriate.

Upon completion of the electronic consent and successful enrollment, the patient will be prompted to complete an online survey at Baseline, then every 6 months for a period of up to 3 years. All surveys will be completed online, at the patient's convenience, and in accordance with Appendix A. The study team will provide technical support and reminder prompts, as described above, throughout the duration of participation.

At any time after Baseline, if the study team is unable to reach a patient after 3 attempts and the patient does not complete the survey within the prespecified window, the patient will be considered lost-to-follow up and the study team will disable the patient's unique study link as appropriate. Awareness by the specialty pharmacy of any change in the patient's status (ie, withdrawal of consent, treatment discontinuation) must be communicated to the study team. Should the specialty pharmacy communicate a patient's status change during the 3-year Follow-up Period, the study team will disable the patient's unique study link upon notification and no further survey invitations or reminders will be triggered.

Information regarding a patient's initial prescription and refill(s) will also be collected from the specialty pharmacies for all enrolled patients.

5.1.1 Survey Conduct

An electronic consent and survey questionnaire approved by an Institutional Review Board (IRB) will be used by RTI to program the online survey for the purpose of standardizing responses among patients.

Each patient will complete up to 7 web-based surveys over the duration of the study. Each survey is anticipated to take no more than 20 minutes on average.

All assessments, except mortality, will be patient-reported; medical records will not routinely be requested or reviewed as part of this observational study unless required for safety reporting purposes. As patient recall over time may be limited, partial responses as in the case of dates of onset, and/or estimates of numerical information will be accepted.

Participation in the study is contingent on continued use of XERMELO. Each survey will establish ongoing treatment with XERMELO and continued consent to study participation prior to subsequent data collection.

The initial survey is intended to gather Baseline information, which may include:

- Sociodemographics (age, year of birth, sex, race, ethnicity, education, geographic region)
- Current medical history as it relates to CS, NET burden, NET location, and related conditions
    - Location of NET
    - Date of diagnosis; CS and NET
    - CS-related hospitalization(s)
    - CS-related ER visit(s)
    - NET-related surgery (eg, tumor debulking, lysis of adhesions)
- Satisfaction with CS, CS-related diarrhea and/or flushing control prior to starting XERMELO, where applicable
- Height and weight
- Concomitant medication as it relates to the following:
    - Long-acting SSA therapy

- Use of rescue medication - short-acting SSA
- Systemic tumor-directed therapy
- Liver-directed therapy (eg, chemoembolization)

- WPAI-SHP

The initial survey should be completed no later than 30 days, and subsequent surveys should be completed no later than 14 days, after the unique survey link has been provided to the patient via e-mail. Patients will be asked to complete a survey every 6 months for up to 3 years. The following patient-reported data may be collected as described in Appendix A:

- Satisfaction with CS, CS-related diarrhea and/or flushing control after initiating XERMELO, where applicable
- PGIC
- Concomitant medication as it relates to the following:
  - Change in use of rescue medication - short-acting SSA
  - Change in long-acting SSA therapy
  - Systemic tumor-directed therapy
  - Liver-directed therapy (eg, chemoembolization)
- Change in weight
- WPAI-SHP
- Incidence of CS-related hospitalization(s)
- Incidence of CS-related ER visit(s)

The incidence of mortality will be tracked indirectly based upon information received by RTI through secondary sources of information (eg, available pharmacy records).

6. Study Population

This observational, noninterventional, single-arm study will include patients with CS and who are initiating treatment with XERMELO.

The recruitment period was anticipated to be approximately 18 months from first patient enrolled; however, due to slow enrollment, the recruitment period has been extended to 6 months before data collection end. Each patient will be followed for up to 3 years; the last patient enrolled will be eligible to complete a Baseline survey and the first 6 month survey.

6.1 Inclusion Criteria

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

1. Adult, ≥18 years of age at the time of informed consent
2. A new, valid prescription for XERMELO
3. Initiating XERMELO for the treatment of carcinoid syndrome
4. Able and willing to provide informed consent prior to participation in the study

6.2 Exclusion Criteria

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

1. Unable to understand and read English
2. Unable to access the internet
3. Prior exposure to XERMELO

6.3 Criteria for Stopping/Study Withdrawal

Study participation will continue for up to 3 years or until

- withdrawal of consent by the patient or legal guardian
- the patient is lost-to-follow-up
- death
- data collection ends

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

- Noncompliance, including failure to adhere to the study requirements
- The Sponsor terminates the study

One missed survey completion in the period of 1 year will automatically withdraw the patient from the study, unless otherwise indicated the patient will be categorized as lost-to-follow up.

6.4 Criteria for Termination of the Study

If the Sponsor or regulatory officials discover conditions arising during the study that indicate that the study should be halted or that a specialty pharmacy's participation in the study should

be terminated, action may be taken at the discretion of the Sponsor. 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 evaluation of the product
- Failure to enroll patients into the study at an acceptable rate
- Failure to comply with pertinent Food and Drug Administration (FDA) regulations
- Submission of knowingly false information to the Sponsor, or the FDA
- Insufficient adherence to protocol requirements

Study termination and follow up would be performed in compliance with the conditions set forth in the following sections of the Code of Federal Regulations: 21 CFR 312.50 and 21 CFR 312.56.

7. Treatment

7.1 Telotristat Ethyl (XERMELO)

Treatment with XERMELO 250-mg tablets is a requirement of this study. However, XERMELO will not be supplied to participants of this study. XERMELO is available by prescription and patients are expected to take XERMELO as directed by the prescribing physician.

7.2 Prior and Concomitant Medications

7.2.1 Prior Medications

Information relating to SSA therapy, systemic tumor-directed therapy, and/or liver-directed therapy intended to treat NET, CS, individual symptoms, and/or related conditions taken by patients within 1 month of enrolling into the study will be collected.

7.2.2 Concomitant Medications

Information relating to SSA therapy, systemic tumor-directed therapy, and/or liver-directed therapy intended to treat NET, CS, individual symptoms, and/or related conditions taken by patients during the study will be collected.

7.3 Prohibited Medications or Concomitant Therapy

None

8. Study Procedures

A schedule of study assessments is provided in Appendix A.

8.1 Restrictions during Study

None

8.2 Description of Study Assessments

8.2.1 Assessments

Assessments will include the following: satisfaction with CS control, CS-related diarrhea control and/or flushing control, PGIC, change in use of short-acting SSA as rescue medication, change in long-acting SSA dose or frequency, change in weight, incidence of CS-related hospitalization(s), incidence of CS-related ER visit(s), incidence of mortality, and WPAI-SHP.

All responses will be collected electronically via a web-based survey in accordance with Appendix A.

A description of the study assessments is provided below.

8.2.1.1 Satisfaction with Overall Carcinoid Syndrome Control, Carcinoid Syndrome-related Diarrhea Control, Carcinoid Syndrome-related Flushing Control

Patient satisfaction with treatment prior to initiating XERMELO and satisfaction at the month 6 interval will be assessed.

8.2.1.2 Rescue Short-Acting Somatostatin Analogs (SSAs) and Long-acting SSAs

Beginning with the month 6 survey, patients will be asked to describe changes (ie, frequency, dosage) in the use of short and long-acting SSA therapy, where applicable, since initiating XERMELO.

8.2.1.3 Patient Global Impression of Change (PGIC)

At the month 6 survey, patients will be asked to describe change in overall status since the start of treatment with XERMELO.

8.2.1.4 Work Productivity and Activity Impairment – Specific Health Problem (WPAI-SHP)

At Baseline and at month 6, patients will complete the WPAI-SHP questionnaire. The WPAI-SHP has 6 items and yields 4 types of scores: (1) Absenteeism (work time missed); (2) Presenteeism (impairment at work / reduced on-the-job effectiveness); (3) Work productivity loss (overall work impairment / absenteeism plus presenteeism); and, (4) Activity impairment. WPAI-SHP outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (ie, worse outcomes).

8.2.1.5 Change in Weight

Beginning with the month 6 survey, patients will be asked to describe perceived changes in weight, where applicable.

8.2.1.6 Incidence of CS-related Hospitalizations and Emergency Room (ER) Visit

The incidence of CS- related hospitalization and/or ER visits will be collected at Baseline and at each of the subsequent time points. Patients will be asked to provide additional information, including but not limited to the date(s), reason for each CS-related hospitalization or ER visit, action taken, outcome, dosage, and dose regimen of XERMELO.

8.2.1.7 Incidence of Mortality

The incidence of mortality will be tracked indirectly based upon information received by RTI.

8.2.2 Other Assessments

Additional information will include sociodemographic information, current medical history, height, weight, prior and concomitant medications, and prescription fill data.

8.2.2.1 Sociodemographics

Age, year of birth, sex, race, ethnicity, education, geographic region, and insurance type will be collected for all enrolled patients.

Aggregate demographic information (eg, age, sex, geographic region, insurance type) for all patients invited to participate but chose to opt-out will be provided by the specialty pharmacies in a de-identified format.

8.2.2.2 Height and Weight

Patient reported height and weight will be captured at Baseline.

8.2.2.3 Current Medical History

Patient-reported dates and diagnosis will be captured for all ongoing medical conditions related to CS, NET burden, and related conditions:

- Location of NET
- Date of diagnosis; CS and NET
- NET-related surgery (eg, tumor debulking, lysis of adhesions)

8.2.2.4 Prior and Concomitant Medications

Patients will be asked to provide information on the following taken within 1 month of study enrollment:

- Long-acting SSA therapy
- Use of rescue medication – short-acting SSA
- Systemic tumor-directed therapy
- Liver-directed therapy (eg, chemoembolization)

Patients will be asked to provide an update on therapy usage every 6 months.

8.3 Prescription Fill Data

Information regarding a patient's initial prescription fill and subsequent refill(s) will be collected.

8.4 Appropriateness of Assessments

The assessments used in this study conform to accepted standards for observational studies.

9. Safety Reporting

9.1 Adverse Events

This is an observational, noninterventional study assessing patients initiating treatment of XERMELO via web-based surveys. Given the indirect contact with patients, adverse event (AE) collection will be limited by the questions included in the survey.

Explorative objectives of CS-related hospitalizations and CS-related ER visits will be reported as AEs. All information will be captured as part of the web-based survey and will be reported to Sponsor using a format agreed by the Sponsor and RTI. Information related to these events will be patient reported, unless the event is designated by the Sponsor as requiring additional follow-up as described in Section 9.4.

The AEs will be forwarded by the study team to the Sponsor within 24 hours of the completion of a survey using the following e-mail address.

E-mail address (in case of fax failure): [redacted]

Patient mortality will be collected outside of this study as part of routine practice at the specialty pharmacies and will be received by the Sponsor on an ongoing basis as spontaneous reports and reported as such. These data will be reported in this study only as the study endpoint.

In case where an AE is received outside of the web-based surveys by the study team, an AE Report form will be completed and sent to the Sponsor at the above e-mail address within 24 hours of the study team's awareness of the AE.

Exposure (either maternal or paternal) to XERMELO during pregnancy, received either through or outside the web-based surveys, will be reported following the same process as that for the AEs, and additional information will be collected following the process described in Section 9.5.1.

9.2 Definition of an Adverse Event

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

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. Anticipated day-to-day fluctuations of preexisting conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Medication error, overdose, misuse/abuse, and off-label use should also be reported and followed according to the same timeline and process as those for AEs.

9.3 Assessment of Adverse Events

The Sponsor will be responsible for assessing AEs collected for seriousness, expectedness, and causality using standard definitions and categories for safety reporting purpose.

9.4 Follow-up of Adverse Events

For events designated by the Sponsor as requiring additional information, consent will be obtained from the patient for additional contact and access to medical records as applicable. The follow-up action will be directed by the Sponsor and carried out by the study team and/or site staff. All actions will be in accordance with local and/or federal reporting requirements.

9.5 Special Situations

9.5.1 Pregnancy

Exposure of an embryo or infant to study medication during pregnancy or lactation (ie, in utero through either maternal exposure or transmission via semen following paternal exposure, or after birth via breast milk) should be reported and followed for the outcome of the pregnancy and/or development of the child, following the same timeline and process as those for AEs; see Section 9.1 for contact information. 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 Good Clinical Practice (GCP) and International Council for Harmonisation (ICH) guidelines and the Sponsor's SOPs. Patients should report if they become pregnant or father a child within 30 days after last dose of XERMELO.

10. Statistical Methodology

10.1 Determination of Sample Size

The sample size was derived by satisfying design assumptions for the primary study endpoint of proportion of CS patients who are satisfied with their overall symptom control, 6 months after initiating treatment with telotristat ethyl (XERMELO). Of specific interest is the proportion of patients with CS who are at least somewhat satisfied with their control of CS at 6 months, defined as those patients with a response of either "very satisfied" or "somewhat satisfied". [redacted] where [redacted] Two-sided 95% confidence limits (CLs) will be calculated for this proportion using normal approximation. [redacted] hen a minimum of N=643 patients with CS,

who initiate treatment with XERMELO, should be entered into the study. Table 10.1-1 shows precision estimates with the expected 95% confidence intervals (CIs) assuming various combinations of sample size.

Table 10.1-1: Expected 95% Confidence Intervals

Sample size	Estimated proportion	Sides on CI	LCL (Exact)	UCL (Exact)	Width of exact interval	LCL (Wald)	UCL (Wald)	Width of Wald interval
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

10.2 Analysis Populations

The analysis population is comprised of all patients who provide consent, are enrolled into the study, and have data available for 1 or more of the primary and secondary endpoints.

10.3 Study Endpoints

10.3.1 Primary and Secondary Endpoints

The primary study endpoint is the proportion of CS patients who are satisfied with their overall symptom control, 6 months after initiation of treatment with telotristat ethyl (XERMELO).

Secondary endpoints include the following outcomes, assessed at 6 months among patients with CS after initiation of treatment with telotristat ethyl (XERMELO):

- Proportion of patients reporting satisfaction of CS-related diarrhea control
- Proportion of patients reporting satisfaction of CS-related flushing control

- Proportion of patients reporting reduction in rescue SSA use
- Proportion of patients reporting reduction in the dose of long-acting SSA injection
- Proportion of patients reporting reduction in the frequency of long-acting SSA injection
- Proportion of patients reporting an overall improvement in CS control after initiating XERMELO based on PGIC
- Proportion of patients that had improvement reduction in work-related absenteeism, presenteeism activity impairment, and overall productivity loss after initiating XERMELO based on WPAI- SHP
- Proportion of patients reporting weight gain

10.3.2 Other Endpoints

Other endpoints include incidence of CS-related hospitalizations, incidence of CS-related ER visits, and incidence of mortality at 6-month intervals for up to 3 years after initiation of treatment with XERMELO.

10.4 Statistical Methods

Descriptive statistics will be used to summarize the data. Continuous and ordinal variables will be summarized by n, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by patient counts and related percentages. Summaries will be by study time point, as applicable.

Confidence limits corresponding to point estimates of the proportions or means corresponding to the study endpoints will be 2-sided and calculated with 95% confidence coefficient. Statistical tests will be 2-sided and have an associated α-level=0.05. As there is no specified hierarchy for the statistical tests and a potentially large number of tests may be performed without adjustments for multiplicity, the p-values from these tests will be considered descriptive rather than inferential.

All data will be provided in by-patient listings.

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

10.4.1 Analyses of Study Endpoints

For the primary endpoint, the proportion of CS patients who are at least somewhat satisfied with their overall symptom control at 6 months, a point estimate and the corresponding 95% CLs will be calculated. Secondarily, a point estimate and corresponding 95% CLs will be calculated for the proportion of CS patients who are very satisfied with their overall symptom control at 6 months. The 95% CLs will be unadjusted and based on the assumption of approximate normal distribution. Missing data will not be imputed in the main analysis of the primary endpoint. As a sensitivity analysis, a patient with a missing response at 6 months will be imputed as a non-responder. This approach corresponds to non-responder imputation.

In addition to the point estimates and 95% CLs for the primary endpoint, the frequency distribution of the categorical responses, on a 5-point Likert scale, to patient satisfaction with overall symptom control at 6 months will be presented. The patient satisfaction measure will also be summarized as an ordinal variable with a value of 1 corresponding to "very dissatisfied" up to 5 corresponding to "very satisfied".

All the secondary endpoints correspond to proportions and will be summarized through point estimates and 95% CLs, as described above for the primary endpoint. Frequency distributions of the categorical responses and summary statistics of the corresponding ordinal values of the categories will be presented. The handling of patients with a response of "not applicable" to patient satisfaction with CS-related diarrhea control or patient satisfaction with CS-related flushing control in the analysis will be described in the SAP.

The 4 WPAI-SHP scores at Baseline and month 6 will be summarized, as well as the change from Baseline to month 6.

The incidences of at least 1 CS-related hospitalization, at least 1 CS-related ER visit, and mortality after Baseline will be calculated at each 6-month interval. Kaplan-Meier estimates of each time-to-event variable, including quartiles, medians, and their corresponding 95% CLs, will be presented. The association or relationship between the primary endpoint and each long-term health outcome will be evaluated through descriptive statistics and the use of statistical models, as appropriate. Any statistical models that will be used and the appropriateness and/or limitations of their use will be described in the SAP.

For any other study endpoints assessed at 12 months and thereafter, descriptive statistics will be presented and 95% CLs will be calculated.

Subgroup analyses of study endpoints based on categories of sociodemographics or clinical characteristics of patients may be performed, but will serve as exploratory assessments only.

10.4.2 Safety Analyses

10.4.2.1 Adverse Events

Since AEs will not be actively solicited during the study, there are no planned summaries of AEs. Descriptions of AEs in the study report will be based on a medical review of the data reported in the AE Reporting forms.

10.4.3 Baseline Characteristics and Other Summaries

Sociodemographics and clinical characteristics of patients collected at Baseline will be summarized through descriptive statistics.

10.4.3.1 Protocol Deviations

Protocol deviations will be listed in the study report.

10.4.4 Interim Analysis

The study may be analyzed and reported in multiple phases. Analyses will be conducted yearly upon the anniversary of the first patient's initial survey completed for the purposes of summarizing available data.

In addition, an analysis will be performed after the last patient completes the Baseline assessments in order to assess the baseline burden of patients initiating XERMELO. A primary endpoint analysis will be performed after the last patient completes the online survey at 6 months and will include the analysis of the data corresponding to the primary and secondary endpoints at 6 months.

Since the study is an observational, noninterventional, single-arm study, no statistical adjustments will be made to the results of any of the interim or final analysis. The reporting of data in multiple phases while the study is still ongoing may be taken as an interim analysis in terms of procedural efforts needed to summarize these data, but it will not serve as a means to modify the study conduct.

11. Study Management

The study will be conducted as described in Section 5. The study team will be responsible for maintaining adequate documentation as provided by the specialty pharmacies.

Issues resulting from data reconciliation will be resolved according to standard data management practices in conjunction with the Sponsor and the study team. As survey data is patient-reported, no changes to the data will occur.

11.1 Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, operating 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 will contact the study team via visits, telephone calls, and/or letters in order to review study progress and address any concerns or questions regarding the study conduct. During these monitoring activities, the following aspects of study conduct will be carefully reviewed: informed consent of patients, patient recruitment, patient compliance with the study procedures, and AE documentation and reporting. Records pertaining to these aspects are expected to be kept current.

All parties must make study data accessible to the Sponsor, to other authorized representatives of the Sponsor, and to regulatory inspectors

11.2 Protocol Deviations

A protocol deviation is any noncompliance with the protocol, GCP, or other procedural requirements. The noncompliance may be either on the part of the participant, site staff, or the study team. As a result of deviations, corrective actions are to be developed and implemented promptly.

It is the responsibility of the study team and/or site staff to use continuous vigilance to identify and report deviations within 3 working days of identification, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, and reported to the Sponsor. Protocol deviations must be sent to the local IRB as per their guidelines. All parties are responsible for knowing and adhering to their applicable IRB requirements. Further details about the handling of protocol deviations will be included in the study plans.

11.3 Audits and Inspections

The Sponsor, regulatory authority, or IRB may visit the study team and/or the specialty pharmacies 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.

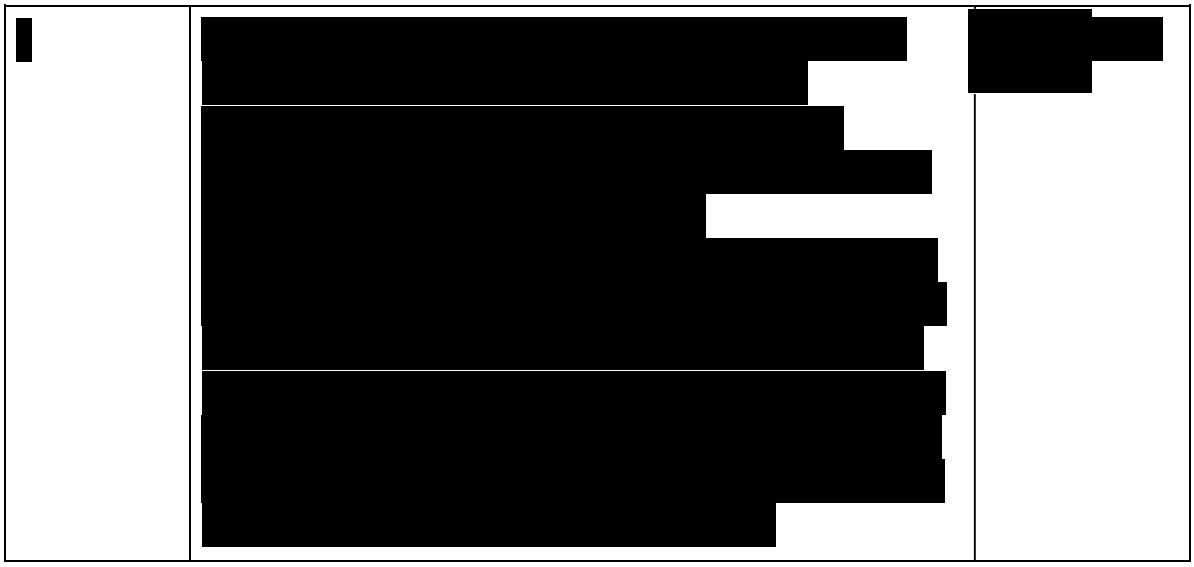
11.4 Amendments

Any amendments to the protocol will be written and approved by the Sponsor. All amendments must be submitted to the IRB 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 approval prior to administration to patients. Table 11.4-1 summarizes the IRB submissions and approvals for the study to date.

Table 11.4-1: IRB Submissions and Approvals

Submission Number	Summary of Changes	Date of Approval
1	Full study implementation	07 June 2017
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]



11.5 Record Keeping

11.5.1 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 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.

The Department of Health and Human Services updated a final rule to modify HIPAA. The new rule has been in effect since 26 Mar 2013, and strengthens the privacy and security protection for individual's health information; modify the rule for Breach Notification for Unsecured Protected Health Information (Breach Notification Rule) under the HITECH Act to address public comment received on the interim final rule; modify the HIPAA Privacy Rule to strengthen the privacy protections for genetic information by implementing section 105 of Title I of the Genetic Information Nondiscrimination Act of 2008 (GINA); and make certain other modifications to the HIPAA Privacy, Security, Breach Notification, and Enforcement Rules (the HIPAA Rules) to improve their workability and effectiveness and to increase flexibility for and decrease burden on the regulated entities.

The full text of the rule can be found at:
https://www.federalregister.gov/documents/2013/01/25/2013-01073/modifications-to-the-hipaa-privacy-security-enforcement-and-breach-notification-rules-under-the

11.5.2 Access to Original Records

It is an expectation of regulatory authorities that the Sponsor, 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.

11.5.3 Retention of Study Documents

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: recruiting, data collection, data management, statistical analysis, and reporting.

13. Appendix A – Schedule of Events

	Baseline	Follow-up Period					
	Day 1	6 months	12 months	18 months	24 months	30 months	36 months
Tolerance (days)	*+30*	*±14*	*±14*	*±14*	*±14*	*±14*	*±14*
Informed consent	X						
Review and assess entry criteria (Section 6.1 and Section 6.2)	X						
Sociodemographics (Section 8.2.2.1)	X						
Height and weight (Section 8.2.2.2)	X						
Change in weight (Section8.2.1.5)		X	X	X	X	X	X
Medical history: (Section 8.2.2.3)	X						
• Location of NET	X						
• Date of diagnosis; CS/NET	X						
• CS-related hospitalization and/or ER visit	X						
• NET-related surgery	X						
Satisfaction with CS control (Section 8.2.1.1) 0	X	X					
Satisfaction with CS-related diarrhea control (Section 8.2.1.1)	X	X					
Satisfaction with CS-related flushing control (Section 8.2.1.1)	X	X					
Patient Global Impression of Change (PGIC) Section 8.2.1.3		X					
Work Productivity and Activity Impairment – Specific Health Problem instrument (WPAI-SHP) Section 8.2.1.4	X	X					
Patient-reported CS-related hospitalization and emergency room visit (Section 8.2.1.6)	X	X	X	X	X	X	X
Review of Concomitant Medications: (Section 8.2.2.4)	X	X	X	X	X	X	X
• Rescue short-acting somatostatin analogs (SSAs)	X	X	X	X	X	X	X
• Long-acting SSAs	X	X	X	X	X	X	X
• Systemic tumor-directed therapy	X	X	X	X	X	X	X
• Liver-directed therapy	X	X	X	X	X	X	X

14. Appendix B – 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(s); including updates or revisions:

- 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

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, the Sponsor is responsible for the following:

- 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,
- ensuring that FDA and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied.

15. Appendix C – Investigator Obligations

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56, the study protocol and the final version of the patient informed consent form will be approved by the IRB/ERC before enrollment of any patients. The opinion of the IRB/ERC will be dated and given in writing.

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 patients. 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 patient risk involved, but no less than once per year.

Informed consent must be given freely and obtained from every patient prior to participation. The rights, safety, and well being of the participants 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 the Sponsor with their own curriculum vitae.

Informed Consent

Informed consent must be obtained from every patient before entry into this study. It must be given freely and not under duress. The participant must be allowed adequate time to consider the potential risks and benefits associated with their participation in the study.

Consent must be documented by use of an IRB/ERC-approved method and in a manner consistent with the IRB/ERC approval expectations. If, for any reason, patient risk is increased as the study progresses, the new information must be presented to the patient.

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 patient'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 patient
- A description of any benefits to the patient 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 patient
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA and 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 patient'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 patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient 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 patient (or to the embryo or fetus, if the patient is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the patient's participation may be terminated by the Investigator without regard to the patient's consent
- Any additional costs the patient may incur from participation in the research
- The consequences of a patient's decision to withdraw from the research and procedures for orderly termination of participation by the patient

- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients 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 patient consent.

Study Documentation

The protocol and informed consent for this study, including advertisements used to recruit participants, must be reviewed and approved by an appropriate IRB/ERC prior to enrollment of participants 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 reevaluation and reapproval 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 may include: deviations from the protocol, the number and types of participants evaluated, the number of participants 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 GCP 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, Sponsor/Investigator correspondence, IRB/ERC correspondence, protocol and amendments, information regarding monitoring activities, patient records, and data queries.

Confidentiality

The anonymity of participating patients must be maintained. Patients will be identified by their year of birth and an assigned patient number on documents submitted to the Sponsor. Documents that may be submitted to the Sponsor and that identify the patient must be maintained in strict confidence, except to the extent necessary to allow auditing by the FDA 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 patient, or the FDA) must be kept in confidence by the Investigator.

16. Appendix D[redacted]

[redacted]

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