SAP Title: An Observational Study to Evaluate the Real-World Experience of Patients who are Initiating Treatment with Telotristat Ethyl (XERMELO™): The RELAX Study (Protocol Number LX1606.1-401-CS)

NCT Number: 03223428

SAP Approval Date: 19 September 2019

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An Observational Study to Evaluate the Real-World Experience of Patients who are Initiating Treatment With Telotristat Ethyl (XERMELO™): The RELAX Study (Protocol Number LX1606.1-401-CS)

Statistical Analysis Plan [redacted]

September 19, 2019

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ABBREVIATIONS

CL	confidence limit
CS	carcinoid syndrome
ER	emergency room
N/A	not applicable
NANETS	North American Neuroendocrine Tumor Society
NET	neuroendocrine tumor
PGIC	patient global impression of change
QC	quality control
RELAX	Real-World Experience of Patients Who Are Initiating Treatment With XERMELO
RTI-HS	RTI Health Solutions
SD	standard deviation
SSA	somatostatin analog
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire—Specific Health Problem

1 INTRODUCTION

Carcinoid syndrome (CS) is a paraneoplastic condition that can develop in patients who have functional carcinoids, a type of neuroendocrine tumor (NET). Although carcinoids can occur anywhere in the body, approximately two-thirds occur in the gastrointestinal system, most commonly in the small intestine or appendix, and these may be associated with CS when hepatic metastasis occurs (Modlin et al., 2003). Carcinoid tumors are rare, with an incidence of approximately 2.47 to 4.48 cases per 100,000 persons, depending on race and gender (Modlin et al., 2003). Carcinoid syndrome occurs in about 10% of patients with carcinoid tumors and is most often associated with tumors in the midgut (Kulke and Mayer, 1999; Robertson et al., 2006).

On February 28, 2017, the United States (US) Food and Drug Administration approved telotristat ethyl (XERMELO) 250 mg as the first and only orally-administered therapy for the treatment of CS diarrhea in combination with somatostatin analog (SSA) therapy in adult patients who are inadequately controlled by SSA therapy alone (Lexicon, 2017). XERMELO offers a novel approach to ameliorating the pathophysiology of CS by reducing circulating serotonin levels. Inhibition of intracellular serotonin production by XERMELO complements the extracellularly mediated action of SSAs, potentially providing a more complete inhibition of serotonin's adverse effects than with SSA therapy alone. Treatment with XERMELO has led to reductions in bowel movement frequency and has been associated with improvements in stool consistency, reductions in days with urgency, and improvements in the diarrhea domain of the European Organisation for Research and Treatment of Cancer questionnaire, resulting in clinically meaningful control of the symptoms of CS (Anthony et al., 2015; Pavel et al., 2016).

The RELAX study is a longitudinal patient registry of XERMELO users that is designed to collect long-term patient-reported outcomes and to better understand patients' experiences in real-world settings. This statistical analysis plan describes the data that will be collected and the analyses that will be performed to address the objectives of the RELAX study.

2 STUDY DESIGN AND OBJECTIVES

2.1 Study Design

This observational, noninterventional, single-arm study will include adult patients with CS who are initiating XERMELO as a new treatment. A minimum of 643 patients are expected to enroll.

A specialty pharmacy tasked with distributing XERMELO to patients will be responsible for the identification and recruitment of patients, and all eligible patients who are initiating treatment with XERMELO will be invited to participate in this study. Patients who enroll will be asked to complete up to 7 longitudinal, web-based surveys, including a Baseline assessment at enrollment, and a Follow-up survey every 6 months for up to 3 years. The Baseline questionnaire may be completed any time within a 30-day window following the electronic mail invitation to a patient to participate in the survey. The Follow-up surveys at 6-month intervals may be completed at any time within a ± 14-day window.

Prescription fill data, type of insurance, and reasons for discontinuation, including mortality, will be collected directly from the specialty pharmacy using a process that is still being determined and will be described in a separate document.

A full description of the study design is found in the study protocol dated 19 May 2017 (Lexicon Pharmaceuticals, Inc.).

2.2 Study Objectives

2.2.1 Primary Objective

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

2.2.2 Secondary Objectives

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 the 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 the Patient Global Impression of Change (PGIC)
- To estimate the proportion of patients who had reduction in work-related absenteeism, presenteeism, activity impairment, and overall productivity loss after initiating XERMELO based on Work Productivity and Activity Impairment Questionnaire: Specific Health Problem v.2.0 (WPAI-SHP)
- To estimate the proportion of patients reporting weight gain

2.2.3 Exploratory Objectives

To explore the association between satisfaction with overall and CS symptom control (ie, diarrhea, flushing) at month 6 and long-term health outcomes such as, CS-related hospitalization, CS-related emergency room (ER) visits, and mortality over the study period

2.3 Study Endpoints

2.3.1 Primary Endpoint

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

2.3.2 Secondary Endpoints

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

- The proportion of patients reporting satisfaction of CS-related diarrhea control
- The proportion of patients reporting satisfaction of CS-related flushing control
- The proportion of patients reporting reduction in rescue SSA use
- The proportion of patients reporting reduction in the dose of long-acting SSA injection
- The proportion of patients reporting reduction in the frequency of long-acting SSA injection
- The proportion of patients reporting an overall improvement in CS control after initiating XERMELO based on PGIC

- The proportions of patients who had reduction in work-related absenteeism, presenteeism, activity impairment, and overall productivity loss after initiating XERMELO based on the WPAI-SHP
- The proportion of patients reporting weight gain

2.3.3 Other Endpoints

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

Another endpoint, not described in the protocol, is the proportion of patients with a reduction in the number of bowel movements. This endpoint will be assessed at the 6-month Follow-up after initiation of treatment with XERMELO.

2.4 Sample Size Determination

The sample size was derived by satisfying design assumptions for the primary study endpoint of the proportion of patients with CS 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". This proportion will be estimated as x/n, where x is the number of patients in the study who are either "Very satisfied" or "Somewhat satisfied", and n is the number of patients with a non-missing response for the primary endpoint. Two-sided 95% confidence limits (CLs) will be calculated for this proportion using normal approximation. The true proportion may be approximately 50%; hence, an expected proportion of 50% was used in the sample size calculation as it requires the largest n. It is desired for the proportion to be known with a precision, ω, of 5%, that is, for the CLs to be (x/n) ± ω. Based on the expected proportion of 50% and the precision requirement of 5%, n = 385 patients are needed to have a non-missing response for the primary endpoint. Assuming that 40% of the patients who participate in the study will drop out prior to the 6-month survey, then a minimum of N = 643 patients, with CS who initiate treatment with XERMELO, should be entered into the study.

3 DATA SOURCES AND VARIABLES

3.1 Data Sources

Data will be collected from patients electronically using web-based questionnaires. Patients who enroll in the study will complete a Baseline questionnaire within 30 days of enrollment and up to 6 Follow-up questionnaires at 6-month intervals after Baseline.

Prescription fill data, type of insurance, and reasons for discontinuation, including mortality, will be collected directly from the specialty pharmacy using a process that is still being determined and will be described in a separate document.

3.2 Variables for Analysis

3.2.1 Demographics, Medical History, and Change in Weight

Several demographic and medical history variables will be collected as part of the Baseline questionnaire. These include:

- Age and sex
- Highest level of education
- Race and ethnicity
- Geographic region
- Height (in feet and inches) and weight (in pounds)
- Diagnosis date for CS
- Site and diagnosis date of primary NET causing CS

Patients will also be asked to qualitatively assess their weight change since initiating XERMELO at each 6-month Follow-up ("I weigh less," "I weigh about the same," "I weigh more," "I don't know").

3.2.2 Prior and Concomitant Treatments for Carcinoid Syndrome

Patients' use of other treatments for CS, specified below, will be assessed at Baseline and/or at each 6-month Follow-up:

- Recent or concomitant use of short-acting or long-acting somatostatin analog medications at Baseline
- Changes in SSA use (frequency and dose) at each Follow-up
- NET-related surgery for CS within 6 months of Baseline and the reason for the surgery

- Additional concomitant treatments for CS (radionuclide therapy, radiation, chemotherapy, embolization, chemoembolization directly into liver)

3.2.3 Symptom Control

Satisfaction with control of diarrhea, flushing, and overall CS symptoms will be assessed at Baseline. Satisfaction with how XERMELO has controlled diarrhea, flushing, and overall CS symptoms will be assessed at the initial 6-month Follow-up only. The questionnaire items allow patients to choose a response on a 5-level Likert scale ranging from "Very dissatisfied" (level 1) to "Very satisfied" (level 5). For the assessments of satisfaction with control of diarrhea and flushing, "Not applicable" (level 0) is also 1 of the response options, for those patients who do not have the symptom that is being assessed.

At the initial 6-month Follow-up, patients will also be asked to assess the change in the number of bowel movements on a 7-level Likert scale from "A great deal worse" to "A great deal better." This assessment is not described in the study protocol.

3.2.4 Patient Global Impression of Change

At the initial 6-month Follow-up, patients will be asked to rank their impression of their CS symptoms on a 7-level Likert scale from "Very much worse" to "Very much improved."

3.2.5 Work Productivity and Activity Impairment Questionnaire—Specific Health Problem (WPAI-SHP)

The WPAI–SHP is a self-administered questionnaire (Reilly et al., 1993) comprising 6 questions that measure the effect of health problems on participants' ability to work and participate in regular activities based on their experiences in the previous 7 days. This questionnaire will be administered at Baseline and at the initial 6-month Follow-up.

The WPAI–SHP includes 4 domains (absenteeism, presenteeism, work productivity loss, and activity impairment). All participants will be asked whether they are employed (Q1) and how their CS-related problems affected their regular activities (Q6). Employed participants will be asked about hours of work missed due to CS-related problems (Q2), hours of work missed for any reason (eg, vacation, holidays, time off to participate in this study) (Q3), hours actually worked (Q4), and the degree that CS affected their productivity while working (Q5). An integer scale from 0 to 10 is used for Q5 and Q6, where 0 corresponds to no effect and 10 corresponds to complete effect.

Responses to the items are scored to produce the following 4 domains:

- Absenteeism: work time missed due to CS = [redacted]
- Presenteeism: impairment while working due to CS = [redacted]

- Work productivity loss: overall work impairment due to CS = [redacted]
- Activity impairment: activity impairment due to CS = [redacted]

Each score is then multiplied by 100 to express domains in terms of impairment percentages, with higher numbers indicating greater impairment and less productivity (ie, worse outcomes).

3.2.6 Carcinoid Syndrome-related Health Care Resource Utilization

At Baseline and at each Follow-up, questionnaire items will ask patients about ER visits and hospitalizations during the prior 6-month period. Data collected will include the following:

- The number of ER visits and the CS-related reason for each visit
- The number of hospitalizations, the number of nights for each stay, and the CS-related reason for each hospitalization

3.2.7 Study Discontinuation and Mortality

Patients will be terminated from the study if they discontinue the use of XERMELO, withdraw consent for participation, or are lost to follow-up. Information on reasons for discontinuation will be provided by the specialty pharmacy.

Information on patient deaths during the study will be collected by the specialty pharmacy and transferred to RTI-HS for analysis. This information may be aggregated (ie, counts of patients who die during each 6-month interval) or patient-level, with or without actual dates of death.

4 PLANNED ANALYSIS SCHEDULE

4.1 Interim Analyses

A number of interim analyses will be performed while data collection is ongoing. The planned analyses are outlined below, along with the estimated dates of completion. 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.

4.1.1 Year 1 Analysis

Around the end of the first year of the study, descriptive analyses of questionnaire responses and Baseline patient characteristics will be performed using all available data. Interim analyses of all primary and secondary endpoints for patients who have completed the 6-month Follow-up will also be conducted. [redacted]

4.1.2 Baseline Analysis

After the last patient enrolled in the study completes a Baseline questionnaire [redacted] an analysis will be performed to summarize the burden of CS for all patients (n = 643) at the time that XERMELO was initiated as a new treatment. This analysis will include summaries of all questionnaire items as well as interim analyses of all primary and secondary endpoints for patients who have completed the 6-month Follow-up.

4.1.3 Year 2 (Primary Endpoint) Analysis

Around the time that the last patient enrolled in the study completes the initial 6-month Follow-up questionnaire, the analysis of endpoints associated with the primary study objective and all secondary study objectives will be conducted. All descriptive analyses conducted at Year 1 will also be repeated. Interim analyses of other study endpoints will be conducted for subgroups of patients having 12, 18, and 24 months of Follow-up data. [redacted]

4.1.4 Year 3 Analysis

The same summary analyses performed at Year 1 will be performed around the time when the first enrolled patient completes 3 years of Follow-up. Interim analyses of other study

endpoints will be conducted for subgroups of patients having 12, 18, 24, and 30 months of Follow-up data. [redacted]

4.2 Final Analysis

When data collection is completed [redacted] the final analysis will be performed. This analysis will include all full questionnaire summaries for Baseline and each Follow-up, as well as all analyses that correspond to the exploratory objectives for the study. A dry run of the final analysis will be conducted prior to database lock using a preliminary cut of the study data, and the results from this dry run will be reviewed by RTI-HS and Lexicon before database lock.

After database lock, topline results for the remaining study objectives will be produced and provided to Lexicon for review. All remaining tables and figures for the final analysis will then be produced and provided to Lexicon for review prior to the preparation of the study report.

5 STATISTICAL ANALYSIS

5.1 Statistical Methods

5.1.1 General Considerations

Derivation of analytic variables will be detailed in a separate analytic variable specification document to be produced in Microsoft Excel. This document will be developed at the time of the first interim analysis and will be maintained through the final analysis. It will be provided to Lexicon at the end of the study, along with the corresponding SAS data sets.

All analyses will be descriptive in nature. For continuous and ordinal variables, the number of available observations, means, standard deviations (SDs), medians, minimums, and maximums will be provided. For categorical variables, the frequency and percentage in each category will be displayed. For computation of percentages, missing values and "Prefer not to answer" responses will not be included in the denominator. Results will be presented by study time point, where applicable. Additionally, all questionnaire data will be displayed in listings. Height and weight information will be collected in feet and inches and in pounds but will be summarized in the tables in centimeters and kilograms, respectively. By convention, dates will be displayed in DDMMMYYYY format (eg, 17JAN2017). For the times since diagnosis of CS and diagnosis of primary NET and all time-to-event analyses, the date of Baseline questionnaire completion will be considered as Day 1, and times will be expressed in months or years, as appropriate. The day before the date of Baseline questionnaire completion will be considered Day –1; there will be no Day 0.

All analyses will be performed in SAS, Version 9.4 or higher (SAS Institute, Cary, NC).

5.1.2 Analysis Population

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

5.1.3 Summary Analyses

5.1.3.1 Patient Disposition

For each analysis, current patient disposition as of the database lock date will be summarized in tabular format. This table will report the number of completed Baseline and Follow-up questionnaires, the number and percentage of enrolled patients who discontinued the study after each Follow-up time point and overall, and the reasons for study discontinuation.

5.1.3.2 Demographics, Medical History, and Carcinoid Syndrome Treatments

Patient demographics and medical history information collected at Baseline, including prior treatments received for CS, will be summarized in separate tables. Age will be summarized both as a continuous variable and as a categorical variable (18-30 years, 31-40 years, 41-50 years, 51-64 years, 65 years or older, 75 years or older).

Information on treatments received for CS during study Follow-up, including changes in frequency and dose for short- and long-acting SSAs and additional treatments for CS (Section 3.2.2), will be summarized in tabular format for each Follow-up time point.

5.1.4 Primary and Secondary Endpoint Analyses

Responses to questionnaire items related to the primary and secondary endpoints will be summarized as categorical variables, as described in Section 5.1.1. Items having ordinal response scales consisting of at least 5 categories will also be summarized as ordinal variables. Estimates of proportions for all primary and secondary endpoints at the initial 6-month Follow-up will be accompanied by 2-sided 95% CLs based on the normal distribution approximation.

For estimation of the proportions for the primary and secondary endpoints, patients will be categorized based on their responses to the corresponding questionnaire items as described in Table 1. Responses of "Not applicable" will be excluded from the denominator for computation of each proportion. Missing data will not be imputed, with the exception of a sensitivity analysis on the primary endpoint, whereby a patient with a missing response will be imputed as a non-responder (ie, neither "Very satisfied" nor "Somewhat satisfied"). Some endpoints will have supplemental/sensitivity analyses in addition to the main analysis, and specifications for those analyses are also shown in Table 1.

In addition to the proportions of patients reporting reduction from Baseline in the 4 domains of the WPAI-SHP, domain scores will be summarized at Baseline and at the initial 6-month Follow-up. The change in score for each domain over this 6-month interval will also be summarized as a continuous variable.

Table 1. Primary and Secondary Endpoint Definitions

	Definition for Main Analysis	Definition for Supplemental Analyses
Primary Endpoint (proportion of patients at 6 months after initiating treatment with XERMELO)		
Satisfaction with overall control of CS symptoms	"Very satisfied" or "Somewhat satisfied"	▪ "Very satisfied" only ▪ [redacted]
Secondary Endpoints (proportions of patients at 6 months after initiating treatment with XERMELO)		
Satisfaction with control of CS-related diarrhea	"Very satisfied" or "Somewhat satisfied"	"Very satisfied" only
Satisfaction with control of CS-related flushing	"Very satisfied" or "Somewhat satisfied"	"Very satisfied" only
Reduction in rescue SSA use	"Less frequent"	N/A
Reduction in dose of long-acting SSAs	"Decreased"	N/A
Reduction in frequency of long-acting SSA injection	"Decreased"	N/A
Improvement in overall CS symptom control based on PGIC	"Very much improved", "Much improved", or "Somewhat improved"	"Very much improved" or "Much improved" only
WPAI-SHP		
Reduction in absenteeism	[redacted]	N/A
Reduction in presenteeism	[redacted]	N/A
Reduction in activity impairment	[redacted]	N/A
Reduction in overall productivity loss	[redacted]	N/A
Weight gain	[redacted]	N/A

5.1.5 Other Endpoint Analyses

5.1.5.1 Analyses of Incidence of Emergency Room Visits, Hospitalizations, and Mortality

Incidence proportions for patients with at least 1 ER visit, at least 1 hospitalization, and mortality during each 6-month Follow-up interval will be reported along with 95% CLs. The denominator for each incidence proportion will be the number of patients enrolled in the

study at the beginning of that particular 6-month interval who also provide a non-missing response to the questionnaire item for each type of event.

The time to the first occurrence of a CS-related ER visit, time to the first occurrence of a CS-related hospitalization, time to the first occurrence of a CS-related ER visit or hospitalization, and time to mortality will be analyzed using the nonparametric Turnbull estimation method (Turnbull, 1976) for interval-censored data available in SAS PROC ICLIFETEST for each 6-month interval during Follow-up. These tables will display the number of patients still at risk at the beginning of the interval along with the number of events and censored observations within each interval. Estimates of the survival probability (the proportion of patients without the event) will be provided for the upper boundary of each interval, and these probabilities will also be displayed as figures. Estimated quartiles for event-free time (with 95% CLs) will be reported.

If death dates are available for the analysis of mortality, this analysis will be performed using the Kaplan-Meier method instead of the Turnbull method. Estimated quartiles for survival time (with 95% CLs) will be reported, and estimated survival probabilities will be displayed as Kaplan-Meier curves.

Details for all ER visits and hospitalizations, including the reason for the visit or hospitalization, will be provided in data listings.

5.1.5.2 Analysis of Reduction in Bowel Movements

An analysis of the proportion of patients reporting a reduction in bowel movements will be conducted at the 6-month Follow-up. This endpoint is not described in the study protocol. For the main analysis of this endpoint, the proportion of patients who respond that the number of bowel movements since starting XERMELO is "A great deal better," "Much better," or "A little better" will be computed. As a supplemental analysis, the proportion of patients who respond that the number of bowel movements is "A great deal better" or "Much better" only will be computed.

5.1.5.3 Subgroup Analyses

Subgroup analyses of study endpoints based on categories of sociodemographics or clinical characteristics of patients may be conducted on a post hoc basis. These analyses will not be prespecified in this statistical analysis plan, and will be considered exploratory in nature.

5.1.5.4 Exploratory Analyses

Exploratory analysis of the association between patient satisfaction with overall CS symptom control at the initial 6-month Follow-up and the incidence of at least 1 ER visit, at least 1 hospitalization, and mortality will be performed as part of the final analysis. Only patients with non-missing data on satisfaction with overall CS symptom control at 6 months

will be included in the analysis. The satisfaction categories correspond to the binary categories used in the main analysis of the primary endpoint.

- Contingency table analysis to compare the incidence proportions of ER visits, hospitalizations, and mortality for each Follow-up interval and for the entire study period by satisfaction category, with chi-square tests for association. The satisfaction categories correspond to the binary categories used in the primary endpoint.
- Logistic regression models for the incidence of at least 1 ER visit and/or at least 1 hospitalization during the study period, with satisfaction category as a predictor variable. Covariates may be included in the models.

Additional or alternative exploratory analyses to be performed after data collection is complete will be determined in consultation with Lexicon and described in the final study report. The feasibility of each additional analysis will depend on the extent of data availability. Examples of additional analyses that may be considered are as follows:

- Kaplan-Meier analysis of mortality data, stratified by satisfaction category, including log-rank tests for differences between the strata.
- Kaplan-Meier analysis of time to first hospitalization, first ER visit, or mortality.
- Cox models for times to first ER visit, first hospitalization, and mortality, with satisfaction category as a predictor variable. Covariates may be included in the models.

Statistical tests will be 2-sided and have an associated alpha level of 0.05. The p-values from these tests will be considered descriptive rather than inferential.

5.2 Missing Data

No imputations will be performed, except as noted for the sensitivity analysis for the primary endpoint as described in Table 1 (Section 5.1.4). In all other cases, missing data will be excluded and variables will be analyzed using the available observed data.

5.3 Quality Control

Per RTI-HS' standard operating procedure on analytic programming and quality control (QC), all analysis programs, whether used for creating analysis datasets or outputs (eg, table or listings), will undergo QC review prior to delivery to Lexicon. The exact method of QC to be performed is determined by the lead statistician and/or project director. Methods of QC include 100% independent programming, spot checking, and code review. For this study, a mix of QC methods has been budgeted. Specifically, 100% independent QC programming via SAS PROC COMPARE will be employed to review all analytic datasets. For tables, a mix of spot checking and independent QC programming will be implemented depending on the type and complexity of the table. For data listings, code review by an

independent programmer will be used. Regardless of the level of QC, all outputs will be checked for formatting and consistency.

Quality control will be documented in detail in a separate document and, if requested, can be delivered to Lexicon at the end of the study.

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