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

NCT Number: NCT02026063

Document Date: SAP Amendment/Version 1: 24 November 2014

16.1.9 Documentation of statistical methods

Statistical Analysis Plan Amendment 1 dated 24Nov2014*

Note to File dated 03Nov2015: Calculation of Extent of Exposure for Open Label Studies

Revised Note to File dated 03Nov2015: Calculation of Extent of Exposure for Open Label Studies

Note to File dated 23Nov2015: Handling of the Week 84/End of Study (EOS) Efficacy Data in the Statistical Analysis for Patients who Discontinued from the Study Prior to Week 84

Note to File dated 23Nov2015: Race Information for Patient [redacted] from [redacted] LX1606.302

Note to File dated 30Nov2015: Baseline Data for 302

Note to File dated 05Feb2016: Subject Numbers from Phase II Studies

Note to File dated 05Feb2016: Correcting Error in SAP Regarding Scoring Algorithm for GI.NET21 Scales and Single Items

* Excludes SAP attachments 1-3, which were for review purposes only.

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Statistical Analysis Plan

Sponsor Name:	Lexicon Pharmaceuticals, Inc.
Protocol Number and Title:	LX1606.1-302-CS LX1606.302 (Abbreviated number) A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)
Protocol Version and Date:	Original version, 14 June 2013 Amendment 1, 31 January 2014 Amendment 2, 08 October 2014
INC Research Project Code:	1003157
Author(s):	[redacted] Biostatistician INC Research, LLC
SAP Version:	Final V1.0
SAP Version Date:	24-Nov-2014

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Lexicon Pharmaceuticals, Inc.

LX1606.302

Final V1.0

Statistical Analysis Plan

Version Control

Version	Date	Revision Summary
Draft 0.1	26 Sep 2014	Initial version
Draft 0.2	12 Nov 2014	Incorporate Lexicon's review comments
Final V1.0	24 Nov 2014	Update version number and date

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inc Research

Statistical Analysis Plan

I confirm that I have reviewed this document and agree with the content.

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Statistical Analysis Plan

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1 GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
5-HIAA	5-hydroxyindoleacetic acid
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CgA	Chromogranin A
CL	Confidence limit
eCRF	Electronic case report form
CS	Carcinoid syndrome
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EOS	End of study
EORTC	European Organisation for Research and Treatment of Cancer
ICH	International Conference on Harmonisation
LP-778902	Active moiety of LX1606
LS	Least square
LX1606	Telotristat ethyl, (the ethyl-ester prodrug of the active moiety LP-778902); a serotonin synthesis inhibitor being developed by Lexicon Pharmaceuticals, Inc.
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model with repeated measurement
NET	Neuroendocrine tumor
NRS	Numeric rating scale
PP	Per-protocol
PT	Preferred term
QoL	Quality of life
QLQ	Quality of life questionnaire
QTc	Corrected QT interval

Statistical Analysis Plan

Abbreviation	Description
QTcF	Corrected QT interval using Fridericia's formula
SAE	Serious adverse event
SAF	Safety population
SAP	Statistical analysis plan
SD	Standard deviation
SI	Standard international system of units
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
tid	3 times daily
TLFs	Tables, listings and figures
ULN	Upper limit of normal

2 PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions to be drawn regarding the study objectives.

2.1 RESPONSIBILITIES

INC Research will perform the statistical analyses and are responsible for the production and quality control of all analysis datasets, tables, listings, and figures (TLFs).

2.2 TIMINGS OF ANALYSES

The study will be analyzed and reported in 2 phases. The first report will summarize data obtained from all patients providing information up to a specified data cut-off point. The second report will update the initial report by including data from the remaining portion of the study. The first reporting of the data may be taken as an interim analysis in terms of the procedural efforts needed to summarize these data, but it will not serve as a means to modify the analysis/study conduct.

An independent Data Safety Monitoring Board (DSMB) will be charged with reviewing interim safety data on a quarterly basis and reporting its recommendations to Sponsor. Appropriate procedures will be detailed in a DSMB charter that defines accessibility and disclosure of the interim safety results.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

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

3.2 SECONDARY OBJECTIVES

The secondary objective of this study is to evaluate long-term changes in patients' quality of life (QoL).

3.3 SAFETY OBJECTIVES

Evaluation of overall safety will be assessed as:

- Incidence of treatment-emergent adverse events (TEAEs)

- Changes from Baseline in clinical laboratory results, vital signs results, and electrocardiogram (ECG) findings

4 STUDY DESIGN

4.1 BRIEF DESCRIPTION

This is a Phase 3, multicenter, open-label, long-term extension study to further evaluate long-term safety and tolerability of telotristat etiprate for patients with carcinoid syndrome (CS).

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

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

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

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

A DSMB will review safety data quarterly throughout the study.

4.2 PATIENT SELECTION

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

4.2.1 Inclusion Criteria

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

1. Ongoing participation in a Phase 2 (e.g., LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (e.g., LX1606.1-301-CS, LX1606.1-303-CS) study

2. Patients of childbearing potential must agree to use an adequate method of contraception (defined as having a failure rate of <1% per year) during the study and for 12 weeks after the Follow-up visit. Adequate methods of contraception for patients or partner include condoms with spermicide gel, diaphragm with spermicide gel, coil (intrauterine device), surgical sterilization, vasectomy, oral contraceptive pill, depot progesterone injections, progesterone implant, and abstinence during the study and for 12 weeks after the Follow-up visit.

    a. Childbearing potential is defined as those who have not undergone surgical sterilization, or those who are not considered postmenopausal. Postmenopause is defined as absence of menstruation for at least 2 years. If necessary, follicle-stimulating hormone results > 50 IU/L at Baseline Day 1 are confirmatory in the absence of a clear postmenopausal history.

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

4.2.2 Exclusion Criteria

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

1. Major protocol deviations or telotristat etiprate tolerability concerns in a Phase 2 (e.g., LX1606.1-202-CS, LX1606.1-203-CS) or Phase 3 (e.g., LX1606.1-301-CS, LX1606.1-303-CS) study

2. Positive pregnancy test

3. Presence of any clinically significant findings at entry for medical history, laboratory values, or physical examination (relative to patient population) that, in the Investigator's or Medical Monitor's opinion, would compromise patient safety or the outcome of the study

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

4.3 CRITERIA FOR STOPPING TREATMENT/STUDY WITHDRAWAL

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

1. Withdrawal of consent by the patient or legal guardian
2. Noncompliance, including refusal of the study drug and/or failure to adhere to the study requirements as in the study protocol
3. Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study
4. The Sponsor terminates the study
5. Pregnancy

4.4 CRITERIA FOR TERMINATION OF THE STUDY

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

1. The discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study
2. A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product for carcinoid syndrome or any other indication for any reason
3. Failure of the Investigator to enroll patients into the study at an acceptable rate
4. Failure of the Investigator to comply with pertinent governing body regulations
5. Submission of knowingly false information from the research facility to the Sponsor, study monitor, medical officer, or regulatory official
6. Insufficient adherence to protocol requirements

4.5 DETERMINATION OF SAMPLE SIZE

No formal sample size calculation was made. The number of patients expected to participate in this study was calculated from estimated enrollment rates from other trials of carcinoid syndrome employed in the LX1606 clinical program. Up to 100 patients are expected to enroll in this study.

4.6 TREATMENT ASSIGNMENT AND BLINDING

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

4.7 ADMINISTRATION OF STUDY DRUG

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

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

4.8 STUDY PROCEDURES

A schedule of study events is provided in Table 1.

Table 1 Schedule of Events

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

[1]Eligibility will be determined at last visit of the original protocol; Day 1 will replace the next scheduled visit in the original protocol schedule. Visits should coincide with LAR injections for those patients receiving SSA therapy. [2]Females of child-bearing potential only. [3]Brief physical examination only (symptom-oriented, including weight). [4]Visit to be performed for subjects who withdraw early and will not return for a 2-week follow-up visit; in all other cases the EOS visit should be performed followed by the follow-up visit 2 weeks postdose. [5]To be performed only if evaluation at Week 84/EOS is abnormal.

5 ENDPOINTS

5.1 EFFICACY ENDPOINTS

Efficacy endpoints are the long-term changes in patients' QoL, including:

- Change from Baseline in overall and domain scores of the European Organisation for Research and Treatment of Cancer QoL questionnaire (EORTC QLQ)-C30 and GI.NET21 at each study visit
- Proportion of patients that report adequate relief of CS symptoms at each study visit
- Change from Baseline in subjective global assessment of CS symptoms on an 11-point Numeric Rating Scale (NRS) at each study visit

5.2 PHARMACODYNAMIC ENDPOINT

The pharmacodynamic endpoint is the change from Baseline in plasma levels of 5-hydroxyindoleacetic acid (5-HIAA) at each study visit

5.3 SAFETY ENDPOINTS

Safety endpoints are as follows:

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

5.4 OTHER ENDPOINTS

Other endpoints are as follows:

- Chromogranin A (CgA) levels

- Disease progression
- Quality of sleep assessment

6 ANALYSIS POPULATIONS

The primary analyses of the data will be based on the safety population (SAF). Supportive analyses of the efficacy data will be performed on a per-protocol (PP) population.

6.1 ENROLLED POPULATION

The enrolled population includes all patients who sign the informed consent form. Unless specified otherwise, this population will be used for patient listings and for summaries of patient disposition.

6.2 PER-PROTOCOL POPULATION

The PP population will consist of those patients who receive telotristat etiprate and have no major protocol deviation(s) that would interfere with the collection or interpretation of the efficacy data. Patients with significant protocol deviations will be excluded from the PP population. Determination of the PP population will be made before database lock. The primary analyses of efficacy will be based on the SAF; the PP population will be used in a supplemental manner.

6.3 SAFETY POPULATION

The SAF consists of all patients receiving any fraction of a dose of telotristat etiprate during the study.

7 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

7.1 GENERAL METHODS

Statistical methodology and analyses are in accordance with the principles outlined by the International Conference on Harmonisation (ICH) E9 guidelines[1].

Patient listings of all data represented in the electronic case report form (eCRF) will be provided. Measurements from patients excluded from the predefined analysis populations or extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables unless specified otherwise, but will be included in the patient listings. In general, the patient listings will be sorted by treatment group,

patient number, and assessment date (and time), if applicable. For most summary statistics, data will be analyzed and displayed by the order of the treatment groups and overall, where treatment groups correspond to how patients were dosed on Day 1 of this study.

Unless otherwise specified, continuous/quantitative variables will be summarized using descriptive statistics, which will include the number of patients with data to be summarized (n), mean, standard deviation (SD), median, minimum, and maximum. The same number of decimal places as in the raw data will be presented when reporting the minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting the mean and median, and 2 more decimal places than in the raw data will be presented when reporting the SD.

All categorical/qualitative data will be presented using frequency counts and percentages. The total number of patients in the treatment group overall (N) will be used as the denominator for percentage calculations, unless stated otherwise in the table shell. All percentages will be presented as 1 decimal point, unless otherwise specified. Percentages equal to 100 will be presented as 100%, and percentages will not be presented for zero frequencies.

All statistical tests will be 2-sided and have an associated α-level = 0.05 unless mentioned otherwise. Confidence limits (CLs) will be 2-sided and calculated with a 95% confidence coefficient.

All statistical analyses will be done using SAS statistical software version 9.3 or higher.

In the case of multiple or repeat assessments at a scheduled visit, the latest value at the visit will be used for summarization and analyses.

7.2 KEY DEFINITIONS

7.2.1 Baseline Values

Day 1 of this study will serve as the baseline assessment. The Baseline value is defined as the last non-missing measurement or assessment for safety and efficacy parameters assessed on Day 1 of this study.

7.2.2 First Dose Date

The first dose date will be the date that the first dose of telotristat etiprate is administered during the study. The first dose date will be obtained from the eCRF.

7.2.3 Study Day

There is no study day 0. Study day for an event occurring prior to first dose date is defined as Event Date – First Dose Date. The study day for an event occurring on or after first dose date is defined as Event Date – First Dose Date + 1.

7.2.4 Last Dose Date

The last dose date will be the date that the last dose of telotristat etiprate was taken during the study. The last dose date will be obtained from the CRF.

7.2.5 Duration

Treatment duration in weeks will be determined as Duration = (Last Dose Date – First Dose Date + 1)/7, rounding to 1 decimal place.

7.2.6 End of Study

The end of study (EOS) is defined as date of early termination or the date of completion of treatment for enrolled patients. It will be obtained from the eCRF. The EOS value is defined as the last non-missing measurement or assessment on or before the EOS.

7.3 MISSING DATA

There is no plan to impute data for missing observations for any variable.

7.4 HANDLING OF PARTIAL DATES

Complete dates will be imputed from partial dates of AEs and medications solely for the purpose of defining treatment emergence for AEs and prior/concomitant status for medications. Dates will be defined using the hierarchy of derivations below.

<u>Adverse Events</u>

- For missing start day where month and year are present, the start day will be set to the 1st of the month, unless the 1st of the month is before the first dose date, in which case, the start day will be set to the first dose date.
- For missing start day and month where year is present, the start day and month will be set to January 1st, unless January 1st is before the first dose date, in which case, the start day and month will be set to the first dose date.
- For missing end day where month and year present, the end day will be set to the last day of the month, unless the month is the trial termination month, in which case, the end day will be set to the trial termination date.

- For missing end day and month, where year is present, the end day and month will be set to the trial termination date, unless the trial termination year is greater than the end year, in which case, the end day and month will be set to December 31st.

Concomitant Medication

If the start date of a concomitant medication is missing, then the start date will be estimated using the first dose date. If the stop date of a concomitant medication is missing, then the medication will be treated as ongoing. Other non-complete dates will use the same algorithm as above for TEAEs.

7.5 ANALYSIS VISIT WINDOW

In general, all efficacy and safety data will be summarized by study week based on the schedule of events in Table 1. The visits indicated on the eCRF (Baseline Day 1, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84/EOS, and 2 Week Follow-up) will be used as the analysis visits for analysis of most safety parameters including vital signs, laboratory examinations, and ECGs.

After mapping the data to the analysis visits as shown, the following rules will apply unless other handling is specified for a particular analysis.

- If multiple records are available within a single analysis visit window, the record closest to the planned assessment day will be selected for analysis.
- If two records are equidistant from the target day, then the later record will be selected.
- If a subject has no record in an analysis window, the subject's data will be considered missing at that time-point.

7.6 POOLING OF CENTERS

Study sites will be pooled by country. Countries may be pooled by region if necessary to support the proposed methods of analysis, as specified in Section 8.

8 PLANNED ANALYSES

8.1 PATIENT DISPOSITION AND WITHDRAWALS

Disposition will be summarized for all enrolled patients. The number and percentage of patients who complete or discontinue prematurely from the study will be summarized

by treatment group and overall. In addition, the number and percentage of patients who discontinue from the study will be summarized by reason for discontinuation.

The number and percentage of patients included in each analysis population (SAF and PP) will be summarized by treatment group. The number of patients enrolled from each parent study will also be summarized.

A listing of disposition will be provided for all patients. The start and stop dates for each patient will be listed.

8.2 PROTOCOL DEVIATIONS

Protocol deviations will be captured during monitoring visits. Before database lock, the study Sponsor will review all protocol deviations and determine whether or not they are significant protocol deviations. Additional deviations may be identified through programmatic check or during clinical review of the data.

Significant protocol deviations include, but are not limited to, the following:

- Patient did not meet all inclusion or met any of the exclusion criteria
- Patient's study drug compliance rate was <75%

All significant protocol deviations by treatment group will be listed.

8.3 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be listed and summarized by treatment group and overall for all patients in the SAF. Demographic characteristics will include age, sex, race, ethnicity, country, and region. Baseline characteristics summarized will include childbearing potential status. Age will be categorized as <65 years or ≥65 years.

All information including inclusion/exclusion criteria and pregnancy test(s) will be listed.

8.4 MEDICAL HISTORY

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 15.1. The version of the coding dictionary used will be included in a footnote on the output. Coded medical history terms will be summarized for the safety population by treatment group, MedDRA system organ class (SOC), and preferred term (PT). SOC terms will be sorted alphabetically and then PT will be sorted in order of frequency of the total column within each SOC.

Patient listings of coded medical history terms will be provided.

8.5 MEDICATIONS AND PROCEDURES

Medications (prior, concomitant) will be coded based on the World Health Organization Drug dictionary, version September 2012. The version number will be included in a footnote on the output. Medications will be summarized by presenting the frequency and percentage of patients using medications for each treatment group for the SAF based on Anatomical Therapeutic Chemical (ATC) Level 2 and the PT. Medications will be sorted alphabetically and patients will be counted only once for each medication class and each PT.

For patient listings, medications will be reported based on therapeutic subgroup (ATC Level 2) and PT; multiple medications for an individual patient will be listed by start date and then by stop date, from earliest to latest medications.

8.5.1 Prior Medications

All medications and other treatments taken by patients within 30 days prior to the Day 1 visit will be recorded on the eCRF. Prior medications are defined as medications taken prior to the first dose of telotristat etiprate. Partial date imputation for medications is described in Section 7.4.

Prior medication use will be summarized by level 2 ATC and PT using the number and percentage of patients by treatment group. Medications will be sorted alphabetically by ATC and preferred name within ATC. Patients with multiple occurrences of a medication in ATC and preferred name will only be counted once within each ATC and preferred name.

8.5.2 Concomitant Medications

Concomitant medications are defined as medications that are taken on or after the first dose date of telotristat etiprate. Partial date imputation for medications is described in Section 7.4. Concomitant medications will be summarized for the SAF by level 2 ATC and PT.

8.5.3 Treatment Compliance

Patients will be instructed to take telotristat etiprate tablets tid during the treatment period. Treatment compliance, as a percentage, will be calculated as Compliance = (actual doses taken in tablets) / (expected doses in tablets) x 100. The treatment compliance is recorded on the eCRF.

Patients will be considered compliant overall for telotristat etiprate if the compliance is ≥75%. Descriptive statistics (number of patients, mean, SD, minimum, median, and maximum) for treatment compliance will be summarized by treatment group and overall for the safety population. In addition, treatment compliance will be categorized as <75%, 75% - 125%, or >125%.

8.5.4 Concomitant Procedures

Concomitant procedures are defined as procedures that are conducted on or after the first dose date of telotristat etiprate. Disease progression is also recorded under concomitant procedures. All data will be presented by patient listing.

8.6 EFFICACY

Analyses of the efficacy data will be performed on the PP population, and the analysis will be applied to the QoL measures, adequate relief of CS symptoms, subjective global assessment, and plasma 5-HIAA values. Majority of patients enrolled in this study may have progressive disease, and their symptoms (not governed by inhibition of serotonin synthesis) may get worse due to disease progression.

The primary analysis will be based on the observed data and missing data will not be imputed, unless stated otherwise for specific analyses. All efficacy and pharmacodynamic variables (plasma 5-HIAA) will be summarized descriptively per study visit as the actual outcomes and change from Baseline scores where applicable, and listed.

Statistical tests and estimates of within patient effects for these measures will be derived from application of a mixed model with repeated measures (MMRM). The model will be generalized to handle missing data and specific to the measurement properties of the dependent variables. Non-parametric methods will be used to supplement the tests and estimates from the mixed linear model. Analysis of efficacy endpoints will be made using statistical tests each with a 2-sided α-level = 0.05.

8.6.1 Change from Baseline in Overall and Domain Scores of the EORTC QLQ-C30 and GI.NET21 at Each Study Visit

The EORTC QLQ is an integrated system for assessing the health related QoL of cancer patients participating in international clinical trials. The QLQ-C30[2] version 3.0 is composed of both multi-item scales and single-item measures. These include 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 3 symptom scales (fatigue, nausea and vomiting, and pain), a global health status / QoL scale, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). All of the

scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + \ldots + I_n)/n$$

Then for functional scales:

$$Score = \left\{1 - \frac{RS - 1}{range}\right\} \times 100$$

And for symptom scales / items and global health status /QoL:

$$Score = \{(RS - 1)/range\} \times 100$$

Missing data rules will be applied such that the scale/item scores will be computed based on the non-missing item responses, as long as at least half of the items in the scale had non-missing values. If responses to more than half of the items in the scale are missing, the scale score will be recorded as missing.

Table 2: Items and Scale Structure of QLQ-C30

	Number of Items	Item Range	Item Numbers
Global health status/QoL	2	6	29, 30
Functional scales			
Physical functioning	5	3	1 to 5
Role functioning	2	3	6, 7
Emotional functioning	4	3	21 to 24
Cognitive functioning	2	3	20, 25
Social functioning	2	3	26, 27
Symptom scales / items			
Fatigue	3	3	10, 12, 18

Nausea and vomiting	2	3	14, 15
Pain	2	3	9, 19
Dyspnea	1	3	8
Insomnia	1	3	11
Appetite loss	1	3	13
Constipation	1	3	16
Diarrhea	1	3	17
Financial difficulties	1	3	28

The GI.NET21[3] module for patients with gastrointestinal-related neuroendocrine tumors includes 21 items, conceptualized as consisting of 5 scales and 4 single items.

The scoring algorithm for the GI.NET 21 scales and single items follows the same rule as the EORTC QLQ-C30 functional scales calculation.

Table 3: Items and Scale Structure of GI.NET21

	Number of Items	Item Range	Item Numbers
Scales			
Endocrine scale	3	3	31, 32, 33
Gastrointestinal symptoms scale	5	3	34, 35, 36, 37, 38
Treatment scale	3	3	39, 40, 46
Social function scale	3	3	42, 44, 49
Disease related worries scale	3	3	41, 43, 47
Single Items			
Muscle /bone pain symptom	1	3	48
Sexual function	1	3	51
Information/communication function	1	3	50
Body image	1	3	45

Statistical Analysis Plan

The change from Baseline in overall and each domain score of EORTC QLQ-C30 and GI.NET21 at each study visit will be analyzed using a MMRM for the PP population. The model will use the change from Baseline in overall or each domain score of EORTC QLQ-C30/GI.NET21 as the dependent variable and will include a fixed effect of time (Baseline Day 1 up to Week 84/EOS). The Baseline QLQ-C30/GI.NET21 value will be included in the model as a covariate. The Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. A first-order heterogeneous autoregressive covariance structure will be assumed initially to model the within-patient errors; however, other covariance structures will be tested and may be used in the final model if a better fit is evident. The least squares (LS) means, 95% 2-sided CLs, and the p-values of LS means at each visit will be reported to evaluate the within-patient treatment effect. The null hypothesis is that there is no treatment effect (no difference from Baseline values) over time. A sample SAS code for the model is shown below.

```
*USUBJID:  unique patient ID
AVISITN:   analysis visit (e.g., week 24, week48, week 72 and week 84)
RESP:      non-count data (e.g., change from Baseline in Global health status/QOL
           score)
BASE:      non-count data (e.g., Baseline Global health status/QOL score);

ods output lsmeans=estimates;
proc mixed data=adef method=reml;
   class USUBJID AVISITN;
   model RESP = AVISITN BASE/ ddfm=kr;
   repeated AVISITN / subject=USUBJID type=ARH(1);
   random intercept / subject=USUBJID;
   lsmeans TRT01PN*AVISITN / cl;
run;
ods output close;
```

Friedman's nonparametric method for testing treatment group differences will be used to supplement the MMRM. Friedman's test uses the ranks of the data rather than their raw values to calculate the statistic, and the test does not make a distribution assumption of the data. The null hypothesis of the test is that the change from Baseline in Global health status/QOL score are the same over time, and the alternative hypothesis is that the change from Baseline in Global health status/QOL score are different over time. Friedman's test cannot handle missing data, so patients with incomplete measurements will be dropped when applying Friedman's test. A sample SAS code for the model is shown below.

```
*USUBJID:  unique patient ID
AVISITN:   analysis visit (eg, week 24, week48, week 72 and week 84)
RESP:      change from Baseline in Global health status/QOL score;

proc freq data=adef;
```

```
    tables USUBJID*AVISITN*RESP / cmh2 scores=rank noprint;
    output out = FriedRes (keep=group p_cmhrms) cmh2;
run;
```

A graphic display of the change from Baseline value and its 95% CLs over time for each treatment group will be provided.

8.6.2 Subjective Global Assessment

8.6.2.1 Proportion of Patients that Report Adequate Relief of CS Symptoms at Each Study Visit

At each study visit, patients will be asked to respond to the following question: "In the past 7 days, have you had adequate relief of your carcinoid syndrome bowel complaints such as diarrhea, urgent need to have a bowel movement, abdominal pain, or discomfort?" Patients are regarded as reporting adequate relief of CS symptoms during the previous week if the result to the question answered is "yes".

The number of patients that report adequate relief of CS symptoms and its percentage along with the corresponding exact 95% CIs will be summarized by study visit.

Generalized linear mixed model can be used to fit the binary response with repeated measurements. The odds ratio of each telotristat etiprate group versus its Baseline, its associated 95% CI and p-value will be reported for each post-Baseline visit. A sample SAS code for the model is shown below:

```
 *USUBJID:  unique patient ID
AVISITN:    analysis visit (eg, week 12, 24, 36, 48, 60, 72, 84 and Follow-up)
RESP:       binary response data (eg, 'Yes' for adequate relief of CS symptoms)
BASE:       Baseline response;

proc glimmix data=adef;
   class USUBJID AVISITN PLA5HIAA;
   model RESP = AVISITN BASE /
            solution dist=binomial link=logit ddfm=kr oddsratio;
   random intercept / subject=USUBJID ;
   random AVISITN / subject=USUBJID type=ARH(1);
run;
```

A graph of the percentage of patients that report adequate relief of CS symptoms by study visit and treatment group will be plotted.

8.6.2.2 Change from Baseline in subjective global assessment of CS symptoms on an 11-point NRS at each study visit

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

Analysis of this endpoint is similar to that applied in Section 8.6.1*Change from Baseline in Overall and Domain Scores of the EORTC QLQ-C30 and GI.NET21 at Each Study Visit*. A graphic display of the change from Baseline value and its 95% CLs over time for each treatment group will be provided.

8.6.3 Change from Baseline in Plasma Levels of 5-HIAA at Each Study Visit

Fasting (of at least 6 hours) blood samples, for measurement of 5-HIAA in plasma, will be collected and analyzed by a specialty laboratory based on the scheduled of visits in Table 1.

The change from Baseline in plasma 5-HIAA levels will be analyzed using a MMRM. The model will use the change from Baseline in plasma 5-HIAA levels as the dependent variable, and will include patient as a random effect, Baseline plasma 5-HIAA levels as a covariate, timeas fixed effect. The Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. A first-order heterogeneous autoregressive covariance structure will be assumed initially to model the within-patient errors; however, other covariance structures will be tested and may be used in the final model if a better fit is evident. The LS means, a 95% 2-sided CLs and the p-values of LS means at each visit will be reported for each study visit to evaluate the treatment effect. A sample SAS code for the model is shown below.

```
*USUBJID:  unique patient ID
AVISITN:   analysis visit (eg, week 12, 24, 36, 48, 60, 72, 84 and follow-up visit)
PLA5HIAA: Baseline plasma 5-HIAA levels
RESP:      non-count data (eg, change from Baseline in plasma 5-HIAA level)

ods output lsmeans=estimates;
proc mixed data=adef method=reml;
   class USUBJID AVISITN;
   model RESP = PLA5HIAA AVISITN / ddfm=kr;
   repeated AVISITN / subject=USUBJID type=ARH(1);
   random intercept / subject=USUBJID;
   lsmeans TRT01PN*AVISITN / cl;
run;
ods output close;
```

Descriptive summary statistics will be provided for the observed value and change from Baseline value of the plasma 5-HIAA levels. A graphic display of the parameter estimates and the 95% CLs for the plasma 5-HIAA levels over time will be provided.

Friedman's test for repeated measures will be used to supplement the MMRM, which is similar to that applied in Section **Error! Reference source not found.Error! Reference source not found.**.

9 SAFETY

Statistical analysis of the safety data will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Safety will be evaluated from concomitant medications, study drug exposure, TEAEs, SAEs, deaths, physical examinations, ECG, clinically laboratory test results, and vital signs. Reporting of these data will be based on the SAF population. Summaries will be prepared by treatment group (corresponding to the LX1606 dose given on Day 1), pooled across all patients, and as needed, by study visit. All safety data will be listed.

9.1 STUDY DRUG EXPOSURE

Duration of exposure in weeks will be summarized using descriptive statistics by treatment group for the SAF. A listing including study drug administration information from the eCRF will be presented.

The numbers of actual dose taken in tablets, expected dose in tablets, and compliance during the study are recorded on eCRF, and will be summarized using descriptive statistics by treatment group for the SAF.

9.2 ADVERSE EVENTS

Adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Treatment-emergent AEs are defined as any AEs not present at before first administration of study drug, but occurring after the start of study drug, or if existing before first administration of study drug, increasing in intensity after initiation of study drug. Since this study provides continued access to telotristat etiprate after patients have completed the required study visits in Phase 2 and Phase 3 studies, all AEs reposted in this study will be considered TEAEs. Treatment-emergent AEs will be coded by SOC and PT using the MedDRA, version 15.1. All reported TEAEs will be listed, and the verbatim term will be included in the AE listings.

An overall summary of TEAEs will provide, by treatment group and overall, the number and percentage of patients who reported:

- Any TEAE
- Any treatment-related TEAE (definitely related, possibly related, or probably related)
- Any serious TEAE (SAE)
- Any treatment-related SAE
- Any TEAE leading to study drug discontinuation
- Any TEAE leading to study discontinuation
- Any TEAE leading to death

A set of summary tables of TEAEs by SOC and PT will also be presented for the following categories.

- TEAEs
- TEAEs experienced by ≥5% of patients in any treatment group
- Severe TEAEs
- Treatment-related and severe TEAEs
- TEAEs leading to study drug discontinuation
- TEAEs leading to study discontinuation
- SAEs
- TEAE of special interests

- Treatment-related SAEs
- TEAEs resulting in death

In addition, TEAEs will be summarized separately by the intensity and relationship to study drug. An additional summary of TEAEs will be presented by PT, but not by SOC. This table will be sorted in descending order of overall number of patients reporting PT.

In the summary tables patients may be counted under multiple SOCs and PTs, but for each SOC and PT, patients are only counted once. If a patient has the same AE on multiple occasions, the highest severity (severe > moderate > mild) or drug relationship (definitely related > probably related > possibly related > not-related) recorded for the event will be presented. If severity of AE is missing in the database, it will be programmed to be 'severe' for the counts in the summary table. If drug relationship is missing then the AE will be considered as 'related' for the summary table.

Central nervous system events of special interest may include any clinically significant changes in mood, physical affect, or exacerbation of preexisting central nervous system conditions, for example, depression and migraine headaches. Patients will be evaluated beginning at Baseline Day 1 and at each subsequent visit for indications of depression. During each visit the patient will first be asked to respond to the question "During the past month, have you often been bothered by feeling down, depressed, or hopeless?" Followed by "During the past month, have you often been bothered by little interest or pleasure in doing things?" A positive response prior to Baseline Day 1 dosing will be captured on the medical history eCRF page. Positive responses following the first dose will be captured as a TEAE and will be followed as a TEAE of special interest.

Listings will be provided for all TEAEs, SAEs, TEAEs leading to study drug discontinuation, TEAEs leading to study discontinuation, deaths, and TEAEs of special interest.

9.3 LABORATORY EVALUATIONS

Laboratory results will be reported in standard international system (SI) of units in all TLFs. Clinical laboratory test results (hematology, chemistry, urinalysis, and CgA) and their changes from Baseline value will be summarized by treatment group and analysis visit using descriptive statistics. The laboratory test results (hematology, chemistry, and urinalysis) will be reported as "High", "Low", or "Normal" with respect to relevant reference ranges. A shift table comparing the laboratory test results over the analysis visits to Baseline measure will be presented.

All laboratory data will be listed. The laboratory results falling out of the normal range will be marked as "High" or "Low" in the listings. Pregnancy results will be presented in patient listings only.

9.4 VITAL SIGNS

Measurement of vital signs will include assessment of blood pressure, respiratory rate, pulse, and oral temperature. The visit-specific average value of the multiple measurements at these scheduled study visits will be calculated and used in the summary table.

For each vital sign parameter, the observed value and change from Baseline value will be summarized using descriptive statistics by study visit and treatment group.

All vital signs data will be presented in the patient listings.

9.5 ECG

Electrocardiograms (12-lead ECGs) will be performed as specified in Table 1. The following ECG parameters will be recorded: heart rate (bpm), RR interval (msecs), PR interval (msecs), QRS interval (msecs), QT interval (msecs), and corrected QT (QTc) intervals (msecs). QT will be corrected for heart rate using Fridericia's (QTcF) interval.

For each ECG parameter, the observed value and change from Baseline value will be summarized using descriptive statistics by study visit and treatment group for all patients in the safety population.

In addition, count and percentage of patients with outlying QTcF values (i.e., value >450, >480 or >500 msec, increase from Baseline value of >30 or >60 msec) based on ICH Guidance E14[4] will be presented by study visit and treatment group.

All ECG data will be included in patient listings.

9.6 PHYSICAL EXAMINATION

Complete physical examinations will be performed at Baseline Day 1, Week 48, Week 84/EOS visit, and 2 Week Follow-up visit if evaluation at Week 84/EOS is abnormal. Complete physical examinations will include a minimum of a review of the patient's general appearance, head, eyes, ears, nose, and throat, neck, heart, lungs, abdomen, back and extremities, skin, and general neurological system. Symptom-oriented physical examinations including weight will be performed at all other time points as well and as clinically indicated.

The complete physical examination result will be reported as “Normal”, “Abnormal, Not Clinically Significant”, or “Abnormal, Clinically Significant” with respect to relevant abnormalities by the Investigator. The number and percentage of patients with abnormal physical examination results will be summarized by body system and treatment group over time. The symptom-oriented physical examination result will be reported as “Clinically Significant Change since Previous Exam, Yes”, or “Clinically Significant Change since Previous Exam, No”. The number and percentage of patients with each result will be summarized by treatment group over time.

Physical examination results will be also presented in a data listing.

9.7 QUALITY OF SLEEP

Quality of sleep will be evaluated at each study visit. Patients will be asked to respond to the following question, “Since your last visit, how many times a night (on average) do you wake up due to your carcinoid syndrome symptoms?” based on the following scale 0, 1, 2, 3, 4, >4. Results will be presented in a data listing.

10 DSMB

An independent DSMB will review interim safety data on a quarterly basis and provide its recommendations to the Sponsor on whether to continue the study or to terminate the study. Appropriate procedures will be detailed in a DSMB charter that defines accessibility and disclosure of the interim safety results.

11 INTERIM ANALYSES

The study may be analyzed and reported in multiple phases. The first report will summarize data obtained from all patients providing information up to a specified data cut-off point. The following reports will update the initial report by including data from the remaining portion of the study. The first reporting of the data may be taken as an interim analysis in terms of the procedural efforts needed to summarize these data, but it will not serve as a means to modify the analysis/study conduct.

12 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

There are no changes from the analysis planned in the protocol.

13 REFERENCE LIST

1. ICH Harmonised Tripartite Guideline "E9 Statistical principles for clinical trials" http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

2. EORTC QLQ-C30 Scoring Manual, Third edition, 2001 http://groups.eortc.be/qol/eortc-qlq-c30

3. EORTC QLQ – GINET21 Quality of Life Questionnaire (module specific for gastrointestinal symptoms of carcinoid neuroendocrine tumors) http://groups.eortc.be/qol/sites/default/files/img/slider/specimen_gi.net21_english.pdf

4. ICH Guidance "E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs". http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073153.pdf

5. ICH Guidance "E3 Structure and Content of Clinical Study Reports". http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf

14 PROGRAMMING CONSIDERATIONS

The following conventions will hold for programming of outputs:

- SAS (SAS Institute, Cary, NC) Version 9.3 or higher will be used for programming and production
- The format of the table shells will be followed as closely as possible; however, in the course of programming and familiarization with the database, some changes may become necessary. All changes will be documented. Major changes will be documented through a formal amendment to this document.
- Patients in this study will be identified as "Patients."
- Descriptive statistics will be displayed in the following order:

n
Mean
SD
Median
Min, Max

- Decimal places: For summary statistics, the minimum and maximum will be reported with the same number of decimal places as the collected measure, the mean, LS mean (if applicable) and median will have 1 more decimal place than the measure collected, and the standard deviation and CI will have 2 more decimal places than the collected measure. For frequency distributions, percentages will be reported to 1 decimal place. For p-values, 3 decimal places will be reported with the following rules:
    - If p-value < 0.001, then use "p < 0.001"
    - If 0.001 ≤ p-value ≤ 0.05, then use "p = x.xxx"
    - If 0.05 < p-value ≤ 0.999, then use "p = x.xx"
    - If p-value > 0.999, then use "p > 0.999"
- Unless otherwise noted, the denominator for percentages is the number of patients in the applicable analysis population and treatment group.
- If the frequency for a particular table cell is zero, then "0", properly aligned, will be displayed (i.e., "0 (0.0%)" will not be displayed.)
- Non-numeric values: where variables are recorded using < (e.g., "<10" or "≤10") the numeric portion of the result divided by 2 will be used (e.g., <10 and ≤10 becomes 5) for summary; where variables are recorded using > (e.g., ">10" or " ≥10") the numeric portion of the result will be used (e.g., >10 and ≥10 become 10) for summary; the actual recorded results, (e.g., "<10" or ">10") will appear in listings.

14.1 GENERAL CONSIDERATIONS

The following conventions will be used.

- Each output will be stored in a separate file.
- Output files will be delivered in rich-text file format.
- Numbering of TLFs will follow ICH E3 guidance[5]

14.2 TABLE, LISTING, AND FIGURE FORMAT

14.2.1 General

- All TLFs will be produced in landscape format, unless otherwise specified.

- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a 1-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.2.2 Headers and Footers

- All output should have the following header at the top left of each page:

  <Lexicon Pharmaceuticals, Inc.>
  Protocol LX1606.302
  Draft/Final Run <date>

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date (date output was generated) should appear along with program name and location as the last footer on each page.

14.2.3 Display Titles

- All TLFs should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3[5] numbering is strongly recommended but Sponsor preferences should be obtained prior to final determination. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Analysis Set

14.2.4 Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.

- For numeric variables, include “unit” in column or row heading when appropriate.

- Analysis set sizes will be presented for each treatment group in the column heading as (N = xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of patients in the analysis set.

- The order of treatments in the tables and listings will be lowest dose first then higher doses, followed by a total column (if applicable).

14.2.5 Body of the Data Display

14.2.5.1 General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

14.2.5.2 Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n = 0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, 0 percentage will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).
- If the categories are not ordered (e.g., Medical History, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X

Statistical Analysis Plan

SD	X.XX
Median	XXX.X
Min, Max	XXX, XXX

- Percentage values should be printed to 1 decimal place, in parentheses with no spaces, 1 space after the count (e.g., 7 (12.8), 13 (5.4)). Predetermine how to display values that round down to 0.0. A common convention is to display as '< 0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after 0 counts should not be displayed and percentages equating to 100% should be presented as 100, without any decimal places.

- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of AE data should be presented by the body system, treatment class, or SOC alphabetically, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC1 code), and AEs (by PT) should be displayed with the highest occurrence in the total column in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as "-".

- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of patients) where a patient can be included in more than 1 category, describe in a footnote or programming note if the patient should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as SOC) has to be split over more than 1 page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

14.2.5.3 Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time.
- Missing data should be represented on patient listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

14.2.5.4 Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

14.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or a, b, c, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Footnotes will be present on the page where they are first referenced and thereafter on each page of the table, unless the footnote is specific only to certain pages. Patient specific footnotes should be avoided.

- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than 6 lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

15 QUALITY CONTROL

- SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. INC Research Standard Operating Procedure (SOP) 03.010.01 and 03.013.01 provide an overview of the development of such SAS programs.

- INC Research SOP 03.009.01 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.

16 APPENDICES

Attachment 1: Table shells

Attachment 2: Listing shells

Attachment 3: Figure shells

Lexicon

Note to File

Subject: Addendum to Statistical Analysis Plan for Studies LX1606.301, 302, 303, and for the LX1606 Integrated Safety Summary (ISS)

RE: Calculation of Extent of Exposure for Open Label Phases of Studies LX1606.301 and LX1606.303, and Study LX1606.302, and in the LX1606 ISS

Date: November 3, 2015

CC: Lexicon- [redacted] INC- [redacted] Ipsen- [redacted] InStat Services: [redacted]

Background:

This note to file is intended to document the methodology to be used in estimating duration of exposure to LX1606 in the above studies and in the ISS for the interim summaries of data which are being provided for inclusion in regulatory submissions.

Study 302 and the Extension Periods of Studies 301 and 303 The referenced studies all provide open label treatment of 500 mg tid for all patients In these studies, the electronic Case Report Form (eCRF) design includes a single page (Study Drug Accountability Extension Period; SDAEP) which records information about study drug administration during the open-label period, including first dose date, last dose date, and compliance calculation. The SDAEP eCRF is intended to be completed when the patient completes or terminates early from the study. Because many of the patients in the open-label studies are currently continuing treatment, and will not have completed SDAEP forms, it is not possible to accurately estimate study drug exposure based on these pages for such patients.

Plan:

The following approach has been agreed:

- Where the SDAEP eCRF includes both the first dose and last dose dates, the patient's duration of open label treatment exposure will be calculated using these dates. If the page also includes study drug compliance information, these patients will also be included in the reporting of study drug compliance.
- Any patient without a last dose date will have their duration of exposure estimated by using the date of the last recorded visit in the eCRF (scheduled or unscheduled), up to and including the week 48 visit (ie, excluding Follow Up visits). The time on study drug will be estimated for these patients, but no estimation will be performed that includes study drug compliance, dose, or amount of drug received during the study.
- A review has been completed of all adverse events for all patients in the open-label extension periods to ascertain if any patients may have been identified on the AE eCRF as having discontinued the study, discontinued study drug, or interrupted study drug due to an adverse event, but do not have a last dose date on the SDAEP eCRF.

  All such patients, with the exception of one (LX1606.301, Patient [redacted]) have last dose dates entered. In this case, the patient developed acute renal failure (onset date [redacted]) and died on [redacted]. The AE eCRF indicates the study drug was interrupted, and the End of Study page was completed identifying the date of death as the end of study. However, no last dose date is recorded. In this case, the onset date of the AE ([redacted]) will be assumed to be the last dose date.

Signed: [redacted]

[redacted] MD

[redacted], Clinical Operations

Lexicon

REVISED: Note to File

Subject: Addendum to Statistical Analysis Plan for Studies LX1606.301, 302, 303, and for the LX1606 Integrated Safety Summary (ISS)

RE: Calculation of Extent of Exposure for Open Label Phases of Studies LX1606.301 and LX1606.303, and Study LX1606.302, and in the LX1606 ISS

Date: November 3, 2015

CC: Lexicon- [redacted] NC- [redacted] Ipsen- [redacted] InStat Services [redacted]

Background:

This note to file is intended to document the methodology to be used in estimating duration of exposure to LX1606 in the above studies and in the ISS for the interim summaries of data which are being provided for inclusion in regulatory submissions.

Study 302 and the Extension Periods of Studies 301 and 303 The referenced studies all provide open label treatment of 500 mg tid for all patients In these studies, the electronic Case Report Form (eCRF) design includes a single page (Study Drug Accountability Extension Period; SDAEP) which records information about study drug administration during the open-label period, including first dose date, last dose date, and compliance calculation. The SDAEP eCRF is intended to be completed when the patient completes or terminates early from the study. Because many of the patients in the open-label studies are currently continuing treatment, and will not have completed SDAEP forms, it is not possible to accurately estimate study drug exposure based on these pages for such patients.

Plan:

The following approach has been agreed:

- Where the SDAEP eCRF includes both the first dose and last dose dates, the patient's duration of open label treatment exposure will be calculated using these dates. If the page also includes study drug compliance information, these patients will also be included in the reporting of study drug compliance.
- Any patient without a last dose date will have their duration of exposure estimated by using the date of the last recorded visit in the eCRF (scheduled or unscheduled), up to and including the week 48 visit (ie, excluding Follow Up visits). The time on study drug will be estimated for these patients, but no estimation will be performed that includes study drug compliance, dose, or amount of drug received during the study.
- A review has been completed of all adverse events for all patients in the open-label extension periods to ascertain if any patients may have been identified on the AE eCRF as having discontinued the study, discontinued study drug, or interrupted study drug due to an adverse event, but do not have a last dose date on the SDAEP eCRF. Within the data extracted for these studies at this time, no such AEs exist.

Signed: [redacted]

[redacted], MD

[redacted], Clinical Operations

Lexicon Pharmaceuticals, Inc.
8800 Technology Forest Pl.
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Lexicon

NOTE TO FILE

To: LX1606-1.302-CS Trial Master File (TMF)

From: [redacted] of Biostatistics and Data Management
[redacted] of Biostatistics

Re: Study LX1606-1.302-CS: Handling of the Week 84/End of Study (EOS) Efficacy Data in the Statistical Analysis for Patients who Discontinued from the Study Prior to Week 84

Date: November 23, 2015

I. **Incident/Finding(s):** According to Section 7.5 of the Final Statistical Analysis Plan (dated 24Nov2014), efficacy data are to be summarized by study week based on the study's schedule of events (in Table 1 of the SAP; also in Appendix A of the protocol). However, the efficacy data recorded at Week 84/EOS include not only efficacy data assessed at the Week 84 visit for patients who completed the study, but also efficacy data assessed at the last visit (ie, EOS visit) for patients discontinued from the study prior to Week 84. This Note-to-File (NTF) describes how the EOS visit for the latter patients will be mapped, for purposes of tabular summaries and statistical analyses, to the appropriate analysis visit based on the EOS' actual study day (where Study Day 1 = day of first dose of study drug in this study).

II. **Analysis Visits for EORTC QLQ-C30 and GI.NET21:** For patients who discontinued from the study and had EORTC data recorded at the Week 84/EOS visit, these data will be assigned to analysis visits as follows:

Analysis Visit	Target Study Day	Actual Study Day of the EOS Visit
Week 24	Day 168	Day 84 to 251
Week 48	Day 336	Day 252 to 419
Week 72	Day 504	Day 420 to 545
Week 84	Day 588	Day 546 to 588

III. **Analysis Visits for Subjective Global Assessment (SGA) (11-point Numeric Rating Scale and Yes/No response to adequate relief question) and Plasma 5-HIAA:** For patients who discontinued from the study and had SGA data recorded at the Week 84/EOS visit, these data will be assigned to analysis visits as follows:

Analysis Visit	Target Study Day	Actual Study Day of the EOS Visit
Week 12	Day 84	Day 42 to 125
Week 24	Day 168	Day 126 to 209
Week 36	Day 252	Day 210 to 293
Week 48	Day 336	Day 294 to 377
Week 60	Day 420	Day 378 to 461

Analysis Visit	Target Study Day	Actual Study Day of the EOS Visit
Week 72	Day 504	Day 462 to 545
Week 84	Day 588	Day 546 to 588

IV. If after applying II or III above, the Week 84/EOS visit with the efficacy data gets assigned to a visit that already contains data for the same efficacy parameter group (ie, EORTC or SGA or plasma u5-HIAA) for the patient, the rules described in Section 7.5 of the SAP for selecting among multiple records within the same analysis visit will be applied.

V. **Action(s) Taken:** The Week 84/EOS efficacy data for patients who discontinued from the study prior to Week 84 will be assigned to appropriate analysis visits as specified in II and III above. The decision was made by Lexicon Biostatistics after review of the Draft 1 tables/listings based on the 16Oct2015 interim database extraction. It should be noted that this study is open-label, and there is no randomization to treatment. Patients are to continue on open-label telotristat etiprate at the dose level they are on at the end of their parent study.

[redacted] MS FRS/ [redacted] of Biostatistics Date

[redacted] MS, [redacted] of Biostatistics Date

110 ALLEN ROAD Basking Ridge, NJ
Tel: 908-360-4784

MEMORANDUM

To: [redacted]

From: [redacted], MD

CC: TMF for LX1606.302, [redacted]

RE: Race Information for Patient [redacted] from [redacted] in LX1606.302

Date: November 23, 2015

Dear [redacted],

As discussed, please prevent race information for patient [redacted], as well as any other subjects from [redacted] from being displayed in any tables or listings for any interim or final study report for LX1606.302.

Thank you,

[redacted]

[redacted], MD
[redacted], Clinical Operations
Lexicon Pharmaceuticals

110 ALLEN ROAD Basking Ridge, NJ
Tel: 908-360-4784

MEMORANDUM

To: [redacted]

From: [redacted], MD

CC: TMF for LX1606.302, [redacted]

RE: Baseline Data for 302

Date: November 30, 2015

Dear [redacted],

As discussed, for any Study LX1606.302 patients missing baseline PPD Laboratory or Frontage (Plasma 5-HIAA) data, please link the Week 48/EOS visit in studies LX1606.301 or LX1606.303 to the Day 1 Visit in Study LX1606.302 in order for us to have complete data set.

Thank you

[redacted]
MD
[redacted], Clinical Operations
Lexicon Pharmaceuticals

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Note to File

Study Number: LX1606.302

Regarding: Subject Numbers from Phase II Studies

Summary of Situation:

Seven participants completed the LX1606.202 and LX1606.203 Phase II studies and enrolled in the LX1606.302 Phase III extension study. These participants retained their Subject Number from the Phase II study when entering the Phase III study. The table below describes the Subject Numbers and the Investigative site at which they participated in the Phase II and Phase III studies.

Subject Number	Site Name	LX1606.302 Site Number	Investigator Name
[redacted]	[redacted]	[redacted]	[redacted]

[redacted], [redacted], Clinical Operations
Lexicon Pharmaceuticals Inc.

[redacted]
Date

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NOTE TO FILE

To: LX1606-1.301-CS Trial Master File (TMF)
LX1606-1.302-CS Trial Master File (TMF)
LX1606-1.303-CS Trial Master File (TMF)

From: [redacted] of Biostatistics and Data Management
[redacted] of Biostatistics

Re: Studies LX1606-1.301-CS, LX1606-1.302-CS, and LX1606-1.303-CS (or Studies 301, 302, and 303, for short) – Correcting the Error in the Statistical Analysis Plans (SAPs) Regarding the Scoring Algorithm for the GI.NET21 Scales and Single Items

Date: February 5, 2016

I. **Incident/Finding(s)**

The following incorrect sentence appears in the SAPs for Studies 301, 302, 303:

> The scoring algorithm for the GINET 21 scales and single items follows the same rule as the EORC QLQ-C30 functional scale scores.

The correct sentence should have been:

> The scoring algorithm for the GINET 21 scales and single items follows the same rule as the EORC QLQ-C30 symptom scale scores.

Specifically, the correct calculation for each GI.NET21 scale score or single item score is as follows:

$$\text{GI.NET21 Scale or Single Item Score} = \{(RS-1)/range\}\times 100,$$

where RS=Raw Score, as defined in the SAPs.

The affected SAPs and sections within the SAPs are: 301 SAP Amendment 1 Final V1.0 (dated 18May2015), Section 8.6.4.2; 302 SAP Final V1.0 (dated 24Nov2014), Section 8.6.1; and 303 SAP Amendment 1 Final V1.0 (dated 24Aug2015), Section 8.6.4.14.

The incorrectly calculated GI.NET21 scores were used in the GI.NET21 tables/listings/figures (TLFs) produced using interim data extractions from the 3 studies. These TLFs were finalized on 13Jan2016 for 301, 22Jan2016 for 302, and 15Jan2016 for 303.

II. **Action(s) Taken:** Lexicon Biostatistics has made the decision to correct the calculation of the GI.NET21 scores in the ADQS3 analysis dataset and rerun the previously final GINET.21 TLFs using the corrected ADQS3 for each of the 3 studies. The rest of the TLFs, which are not affected by the error, are not to be rerun. The TLFs to be rerun are listed below:

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	301	303	302
Tables	14.2.8.1	14.2.15.1	14.2.2
	14.2.8.2	14.2.15.2	
	14.2.8.3.1	14.2.15.3.1	
	14.2.8.3.2	14.2.15.3.2	
Listings	16.2.6.13.7	16.2.6.13.7	16.2.6.1.7
Figures	None	None	14.2.6.2

Lexicon Biostatistics' decision was made subsequent to the finalization of the TLFs, which means after unblinding for 301 and 303. Study 302 was an open-label study. The correction in the calculation of GI.NET21 scores will result in the change in the directionality, but not the magnitudes, of the mean changes in GI.NET21 scores from Baseline within each treatment group and the differences between treatment groups. As such, the previous findings of statistical significance or lack thereof will not change.

[redacted], MS/FRS, [redacted] of Biostatistics and Data Management — Date [redacted]

[redacted], MS, [redacted] of Biostatistics — Date [redacted]