CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208794Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	208-794
Supplement #:	000
Drug Name:	Xermelo (telotristat ethyl) Oral Tablets
Indication(s):	Carcinoid Syndrome
Applicant:	Lexicon Pharmaceuticals, Inc.
Date(s):	Date Submitted: March 29, 2016
	PDUFA Due Date: February 28, 2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
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Keywords: clinical studies, NDA review, nonparametric tests, multiple comparisons

Reference ID: 4022296

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1 EXECUTIVE SUMMARY

The sponsor submitted an original New Drug Application 208-794 for telotristat ethyl oral tablets (b) (4) for the treatment of carcinoid syndrome (CS) in combination with somatostatin analog (SSA) therapy. The efficacy of telotristat ethyl has been evaluated in two Phase 3 short-term, double-blind, placebo-controlled multi-national studies in adults: LX1606.1-301-CS and LX1606.1-303-CS (hereafter referred to as LX301 and LX303). Studies LX301 and LX303 focused on different primary objectives and used different inclusion/exclusion criteria.

The primary objective of the pivotal Phase 3 study LX301 was to confirm that telotristat etiprate compared with placebo was effective in reducing the number of bowel movements/day in patients not adequately controlled by current SSA therapy. Hence, study LX301 enrolled subjects with CS who were currently experiencing >4 BMs/day and who were on a stable-dose of SSA therapy. The primary efficacy endpoint was the change from baseline in the bowel movement (BM) frequency/day averaged over the 12-week double-blind treatment period. Also, the change in the urinary 5-hydroxyindoleacetic acid (u5-HIAA) levels (mg/24 hours) at Week 12 was included in multiple testing procedure as a secondary efficacy endpoint. Based on the pre-specified primary analysis, the Wilcoxon rank sum statistic stratified by the baseline urinary 5-HIAA levels, telotristat ethyl 250 mg and 500 mg were statistically significantly different from placebo in both endpoints.

Study LX303, the companion study to the LX301 study was designed to enroll patients who were either receiving SSA therapy and had <4 BMs/day with ≥1 signs/symptoms of CS or were not receiving SSA therapy and had ≥1 signs/symptoms of CS. Patients who were previously screened for the LX301 study and did not meet the entry criteria may have been eligible for study LX303. The primary objectives of LX303 were to evaluate the effect of telotristat etiprate versus placebo on the incidence of treatment-emergent adverse events, and on 24-hour u5-HIAA levels. The primary efficacy endpoint in LX303 was percent (%) change from baseline in 24-hour u5-HIAA levels at Week 12 (end of the double-blind period). Both telotristat ethyl doses (250 mg and 500 mg) were statistically significantly different from placebo in the primary endpoint based on the Wilcoxon rank sum statistic stratified by the baseline urinary 5-HIAA levels. The change from baseline in the BM frequency/day averaged over the 12-week double-blind treatment period was one of six secondary endpoints in study LX303 and was not included in the multiple testing procedure. Statistical analysis results for comparison of telotristat ethyl doses (250 mg and 500 mg) versus placebo using stratified Wilcoxon rank sum test were also in favor of telotristat ethyl.

After confirming the sponsor's pre-specified primary analysis results, we agreed that telotristat ethyl showed statistically significant reductions in the number of daily bowel movements (counts/day) and the urinary 5-hydroxyindoleacetic acid (u5-HIAA) levels (mg/24 hours) comparing with placebo. However, treatment effect in u5-HIAA is difficult to interpret due to very high variability at all visits including baseline and observed baseline imbalance. In

particular, in study LX301, we found that baseline u5-HIAA levels in the three treatment arms were statistically significantly different based on stratified Wilcoxon rank sum test (overall p=0.04).

2 INTRODUCTION

2.1 Overview

The sponsor submitted clinical study reports of two Phase 3 short-term double-blind studies LX1606.1-301-CS and LX1606.1-303-CS (hereafter referred to as LX301 and LX303). The studies were designed to be randomized, placebo-controlled, parallel-group with 12 week double-blind treatment period to evaluate the efficacy and safety of telotristat ethyl (LX1606) in patients with carcinoid syndrome (CS). Both studies included three treatment arms: telotristat ethyl 250 mg, 500 mg, and placebo.

2.2 Data Sources

The electronic links to relevant sponsor's submissions and to the datasets are included below.

- Original submission: \\CDSESUB1\evsprod\NDA208794\0001 ;
- Data sets: \\CDSESUB1\evsprod\NDA208794\0001\m5\datasets ;
- Sponsor's responses to FDA Information Request (dated October 04, 2016) in regards to the u5-HIAA data \\CDSESUB1\evsprod\NDA208794\0040 and \\CDSESUB1\evsprod\NDA208794\0043 ;
- Sponsor's responses to FDA Information Request (dated November 07, 2016) in regards to baseline imbalance: \\CDSESUB1\evsprod\NDA208794\0042 .

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This reviewer found the data and analysis quality of this submission acceptable and was able to replicate the primary results from the sponsor's clinical study reports (CSR) for both studies.

3.2 Evaluation of Efficacy

3.2.1 Study Descriptions for LX301 and LX303

3.2.1.1 Study Design and Endpoints

Clinical studies LX301 and LX303 focused on different primary objectives and used different inclusion/exclusion criteria.

The primary objective of the pivotal Phase 3 study LX301 was to confirm that at least 1 or more treatment groups of telotristat ethyl compared with placebo was effective in reducing the number of bowel movements/day in patients not adequately controlled by current SSA therapy. Hence, study LX301 enrolled subjects with CS who were currently experiencing >4 BMs/day and who were on a stable-dose of SSA therapy.

Study LX303, the companion study to the LX301 study was designed to enroll patients who were either receiving SSA therapy and had <4 BMs/day with ≥1 signs/symptoms of CS or were not receiving SSA therapy and had ≥1 signs/symptoms of CS. Patients who were previously screened for the LX301 study and did not meet the entry criteria may have been eligible for study LX303. The primary objectives of LX303 were to evaluate the effect of telotristat etiprate versus placebo on the incidence of treatment-emergent adverse events, and on 24-hour u5-HIAA levels.

In both studies, patients were to enter into a Screening/Run-in Period of at least 3 weeks to establish baseline symptoms. During the Run-in Period, no changes to SSA therapy were to occur. Patients receiving SSA therapy were to continue to receive stable-dose SSA therapy and those not currently receiving SSA therapy were to remain without SSA therapy in order to establish baseline characteristics and symptomatology.

After the Screening/Run-in Period, eligible patients were to be randomly assigned (1:1:1 ratio) on Day 1 to receive 1 of 2 oral dose levels of telotristat ethyl (250 or 500 mg) or placebo, each given tid for 12 consecutive weeks. A blinded titration was to occur during the first 7 days for patients assigned to 500 mg tid. During the titration, all patients were to take 2 tablets tid (1 × 250-mg telotristat ethyl tablet and 1 placebo tablet or 2 placebo tablets). After 7 days, patients

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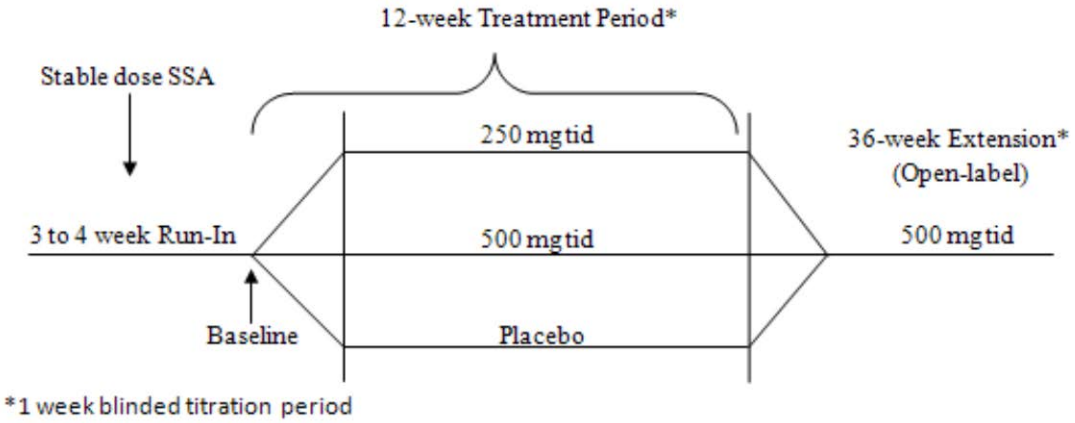
were to receive their assigned treatment and dose level for the remaining 11 weeks of the double-blind treatment (DBT) Period. No changes or initiation of SSA therapy were to be permitted during the DBT Period, with the exception of the use of rescue short-acting SSA.

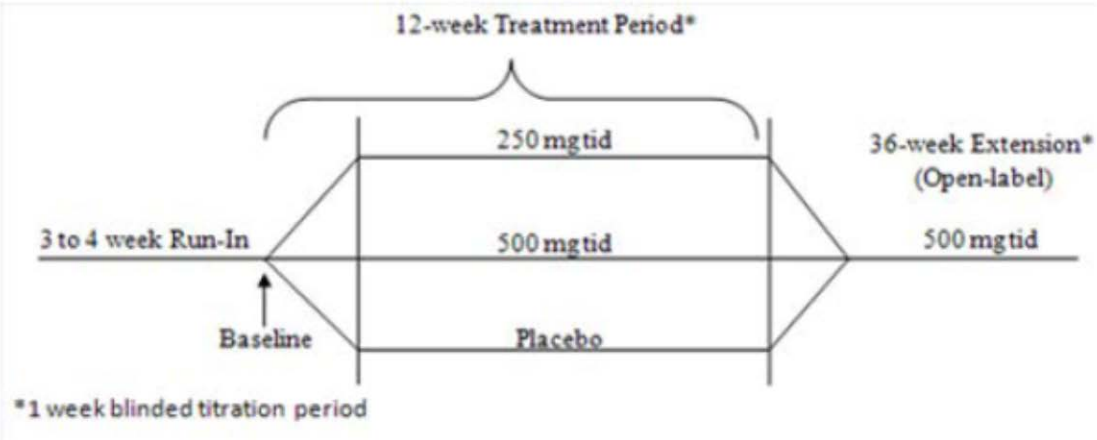
Upon completion of the DBT Period, patients were to continue in an open label extension (OLE) Period in which all patients were to receive active study drug at the 500 mg tid dose level. The treatment schemata for studies LX301 and LX303 are summarized in Figure 1 and Figure 2.

Figure 1.Treatment Schedule for Study LX1606.1-301-CS



[Source: Figure 9.1-1 on page 32 of CSR LX1606.1-301-CS.]

Figure 2.Treatment Schedule for Study LX1606.1-303-CS



[Source: Figure 9.1-1 on page 34 of CSR LX1606.1-303-CS.]

Study LX301

The primary objective of the study was to confirm that at least 1 or more treatment groups of telotristat ethyl compared with placebo was effective in reducing the number of BMs/day.

Primary Efficacy Endpoint: Change from Baseline in the number of daily BMs averaged over the 12-week double-blind treatment period. Patients recorded the number of daily BMs in the daily diary. The observed data was to be used and the average was based on the number of days with valid, non-missing data. The change from Baseline was to be imputed as zero when a patient had more than 6 weeks of missing data (a week of missing data is defined as a patient missing more than or equal to 4 days of diary in that week).

Secondary Efficacy Endpoints (included in the multiple testing procedure):

- Change from Baseline in urinary 5-HIAA levels at Week 12
- Change from Baseline in the daily number of cutaneous flushing episodes averaged across all time points during the Double-blind Treatment Period
- Change from Baseline in abdominal pain averaged across all time points during the Double-blind Treatment Period

Study LX 303

The primary objectives of the study were to evaluate the effect of telotristat ethyl versus Placebo over the DBT Period of the study on:

- The incidence of TEAEs
- Percent (%) change from Baseline in 24-hour u5-HIAA levels at Week 12

Primary Efficacy Endpoint: Percent (%) change from Baseline in 24-hour u5-HIAA levels at Week 12. Urinary 5-Hydroxyindoleacetic Acid (u5-HIAA) Levels (mg/24 hours) was assessed at Screening/Baseline, Week 6 and Week 12.

Secondary Efficacy Endpoints (not included in the multiple testing procedure):

- Change from Baseline in the number of daily BMs averaged over the 12-week Double-blind Treatment Period
- Change from Baseline in stool consistency averaged across all time points during the Double-blind Treatment Period
- Change from Baseline in the number of cutaneous flushing episodes across all time points during the Double-blind Treatment Period
- Change from Baseline in abdominal pain averaged across all time points during the Double-blind Treatment Period
- Change from Baseline in the frequency of rescue short-acting SSA used to treat CS symptoms across all time points during the Double-blind Treatment Period
- Change from Baseline in the number of daily BMs averaged over the 12-week Double-blind Treatment Period and at each study week, among patients who are not on SSA therapy at Baseline.

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3.2.1.2 Statistical Methodologies

Statistical analyses of efficacy endpoints are based on intent-to-treat (ITT) population which includes all randomized patients.

Primary Analysis for Primary Endpoints
The primary efficacy endpoints in studies LX301 and LX303 were analyzed by the blocked 2-sample Wilcoxon rank sum statistic stratified by the baseline urinary 5-HIAA levels (≤ upper limit of normal reference range [ULN], >ULN, and Unknown). Descriptive statistics of the primary endpoints and the Hodges-Lehmann estimator of location shift with its respective CLs were reported for each comparison.

Primary Analysis for Secondary Endpoints
For all secondary endpoints in studies LX301 and LX303, the same analysis method as was pre-specified for the primary endpoints (blocked 2-sample WRS test stratified by the baseline urinary 5-HIAA levels) was used as the primary test for evaluating treatment group differences.

Multiple Testing Approach
In study LX301, two comparisons (250 mg vs. placebo, and 500 mg vs. placebo) were conducted, each at 0.025 significance level. Within each treatment group contrast, fixed-sequence (hierarchical) testing approach was applied to primary and secondary endpoints.

In study LX303, two comparisons in the primary endpoint were conducted sequentially (hierarchically). The first null hypothesis that there is no treatment difference between 500 mg vs. placebo in the percent (%) change from Baseline in 24-hour u5-HIAA levels at Week 12 was to be evaluated at 0.05 significance level. Failing to reject the first null hypothesis would stop the testing of the second null hypothesis that there is no treatment difference between 250 mg versus placebo. No multiplicity adjustment was pre-specified for testing secondary endpoints in study LX303.

Handling of Missing Data
In Study LX301, for the primary analysis that used change from Baseline averaged over the 12-week of DBT Period, the change from Baseline was imputed as zero when a patient had more than 6 weeks of missing data (a week of missing data was defined as a patient missing more than or equal to 4 days of diary in that week). Otherwise the observed data were to be used and the mean response was to be based on the number of days with valid, non-missing data.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Study LX301
Study LX301 enrolled patients at 48 study sites in in the United States, Canada, Germany, United Kingdom, Italy, France, Spain, Sweden, Belgium, Netherlands, Israel, and Australia. A total of 136 patients were randomized in a 1:1:1 ratio among the treatment groups, and 117 patients (86.0%) completed the double-blind treatment period. The most common reason for premature withdrawal in the DBT by treatment group was AE: 4.4% (n=2) in the telotristat ethyl 250 mg group, 4.3% (n=2) in the telotristat ethyl 500 mg group, and 6.7% (n=3) in the placebo group.

Study LX303
Study LX303 enrolled patients at 31 sites in the United States, Canada, Germany, United Kingdom, France, Spain, Sweden, Belgium, Netherlands, Israel, and Australia. A total of 76 patients were randomly assigned to receive study drug in a 1:1:1 ratio, and 68 patients (89.5%) completed the double-blind treatment period. The most common reasons for premature withdrawal were withdrawal of consent and AEs. Three patients withdrew consent in the telotristat ethyl 500 mg group compared with 1 patient in the telotristat ethyl 250 mg group and no patients in the placebo group. Two of these 4 patients experienced AEs that were ongoing at the time of discontinuation.

Subject disposition for both studies is briefly summarized in Table 1. Further details on discontinuation rates by reasons are included in Appendix A of this review.

Table 1. Subject Disposition

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301	**N (%)**	**N (%)**	**N (%)**
Patients Randomized	45	45	46
ITT Patients	45	45	45
Patients Completed	38 (84.4%)	41 (91.1%)	38 (82.6%)
Discontinued	7 (15.6%)	4 (8.9%)	8 (17.5%)
Study LX303			
Patients Randomized	26	25	25
ITT Patients	26	25	25
Patients Completed	24 (92.3%)	22 (88.0%)	22 (88.0%)
Discontinued	2 (7.7%)	3 (12.0%)	3 (12.0%)

Source: CSR LX1606.1-301-CS Table 10.1.1-2 (pg. 90), CSR LX1606.1-303-CS Table 10.1.1-2 (pg. 88)

Reviewer's Remark: Patient 0109-006 in Study LX301was initially randomized to telotristat ethyl 500 mg, but did not meet the eligibility criteria due to on bruising found during the Day 1 physical examination. This patient did not receive study drug and was further excluded from the

ITT population. This patient was rescreened, reenrolled, and subsequently randomized as patient 0109-007 to receive telotristat ethyl 250 mg.

Demographic Characteristics

Study LX301
The majority of patients were white (approximately 90%); 51.8% were males, and over 45% were 65 years or older. The mean age was 63.5 years (range: from 38 to 88 years).

Study LX303
The majority of patients were white (97.4%); 55.3% were males, and 46.1% were 65 years or older. The mean age was 62.8 years (range: from 35 to 84 years).

In both studies, the demographic characteristics for randomized patients were generally comparable between the treatment groups. Summaries of demographic characteristic by treatment arms are included in Appendix B.

Baseline Characteristics
Baseline data for symptoms and conditions associated with CS are summarized in Table 2. Due to differences in the inclusion/exclusion criteria between the two studies, mean baseline BM frequencies per day in study LX 301 were substantially higher than in study LX303 i.e. mean of 5.7 and median of 5.3 in Study LX301 versus mean of 2.5 and median of 2.3 in Study LX303.

Also, in study LX301, 24-hour urinary 5-hydroxyindoleacetic acid levels and the number of bowel movements per day at baseline were not balanced among the treatment groups. Based on the primary efficacy analysis, at 5% nominal significance level, both, u5-HIAA and BM, were significantly lower in the placebo group compared to Telotristat ethyl 250 mg treatment group. Details are included as Reviewer's Exploratory Analyses in Sections 3.2.3.1 and 3.2.3.2. No significant differences among the treatments arms with respect to u5-HIAA and BM measures were detected in Study LX303.

In both studies, the u5-HIAA levels at baseline showed high variability with scores ranging from 0 to 786. Observed score distributions were skewed to the right, and there was a substantial disparity between distribution means and medians.

Table 2. Baseline Characteristics for Symptoms Associated With Carcinoid Syndrome (ITT Population)

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301	**N=45**	**N=45**	**N=45**
BMs (count/day)			
Mean (SD)	5.2 (1.4)	6.1 (2.1)	5.8 (2.0)
Median (Min, Max)	5.1 (3.5, 9.0)	5.5 (3.5, 13.0)	5.4 (3.6, 12.5)
u5-HIAA (mg/24 hours)	N=44	N=42	N=44
Mean (SD)	81.0 (161.0)	92.6 (114.9)	89.5 (144.5)
Median (Min, Max)	26.1 (0, 786.2)	67.0 (2.2, 637.8)	28.3 (0, 608.0)
Study LX303	**N=26**	**N=25**	**N=25**
BMs (count/day)	N=25	N=25	N=25
Mean (SD)	2.2 (0.7)	2.5 (1.2)	2.8 (1.6)
Median (Min, Max)	2.3 (1.0, 3.4)	2.2 (0.8, 6.6)	2.4 (0.8, 6.6)
u5-HIAA (mg/24 hours)			
Mean (SD)	82.0 (113.6)	86.3 (73.5)	66.0 (89.0)
Median (Min, Max)	31.1 (3.2, 439.3)	84.0 (2.3, 279.4)	40 (0.4, 332.3)

Source: CSR LX1606.1-301-CS Table 11.2.1.1-2 (pg. 99), CSR LX1606.1-303-CS Table 11.2.1.1-2 (pg. 96)

3.2.3 Statistical Reviewer's Findings and Conclusions

3.2.3.1 Statistical Analysis of Bowel Movement

Primary Analysis (stratified Wilcoxon Rank Sum test)

The sponsor's primary statistical analyses results for the change from baseline in the number of BMs averaged over the 12-week double-blind treatment period for studies, LX301 and LX303, are shown in Table 3. In study LX301, observed reductions in BMs/day from Baseline for the telotristat ethyl 250 mg and 500 mg groups were statistically significant compared to the reductions in the placebo group. In study LX303, telotristat ethyl 250 mg and 500 mg groups were numerically better than placebo with nominal p-values <0.01 (no multiplicity adjustment was pre-specified). The results were confirmed by the statistical reviewer. Magnitude of treatment differences appeared to be similar between the two doses of telotristat ethyl 250 mg and 500 mg.

Table 3. Sponsor's Analysis for of Change from Baseline in the Number of Bowel Movement (counts/day) Averaged Over the 12 Week Double-Blind Treatment Period (ITT Population)

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301 (Primary Endpoint)	N=45	N=45	N=45
Change from Baseline Mean (SD) Median (Min, Max)	 -0.62 (0.83) -0.61 (-2.7, 0.8)	 -1.43 (1.36) -1.34 (-6.1, 1.6)	 -1.46 (1.31) -1.21 (-6.7, 0.6)
Hodges-Lehmann est. of treatment difference	--	**-0.813**	**-0.689**
97.5% CL		-1.26, -0.29	-1.17, -0.22
p-value	--	<0.001	<0.001
Study LX303 (Secondary Endpoint)	N=26	N=25	N=25
Change from Baseline Mean (SD) Median (Min, Max)	 0.05 (0.33) 0.004 (-0.68, 0.90)	 -0.45 (0.69) -0.42 (-2.0, 1.0)	 -0.60 (0.72) -0.53 (-3.0, 0.5)
Hodges-Lehmann est. of treatment difference	--	**-0.45**	**-0.54**
95% CL		-0.72, -0.17	-0.79, -0.25
p-value	--	0.004	<0.001

SD= Standard Deviation; CL=Confidence Limits
Source: CSR LX1606.1-301-CS Table 11.4.1.1-1 (pg. 114), CSR LX1606.1-303-CS Table 11.4.1.2.1-1 (pg. 118)

Sensitivity Analysis Assigning the Mean Baseline Score to Missing Post Baseline Observations.

In Study LX301, the sponsor pre-specified several sensitivity analyses for the primary endpoint - change from Baseline in the number of BMs averaged over the 12-week DBT period (e.g. repeating primary analysis for PP population, analysis based on actual treatment patients received etc.). Table 4 presents sponsor's sensitivity analysis to missing data using imputation method that assigned a patient's baseline mean value to a missing post-baseline daily value (i.e. assigned a change score of 0 to the missing post-baseline daily value). Conclusions were consistent with those of the primary analysis, which were confirmed by the statistical reviewer.

Table 4. Sponsor's Sensitivity Analysis of Change from Baseline in the Number of Bowel Movement (counts/day) Averaged Over the Double-Blind Treatment Period (ITT Population) –imputing patient's mean baseline values to missing post baseline values.

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301 (Primary Endpoint)	N=45	N=45	N=45
Mean Change from Baseline (SD)	-0.65 (0.81)	-1.53 (1.45)	-1.50 (1.29)
Hodges-Lehmann est. of treatment difference	--	**-0.834**	**-0.707**
97.5% CL		-1.28, -0.29	-1.18, -0.25
p-value	--	<0.001	<0.001

SD= Standard Deviation; CL=Confidence Limits
Source: CSR LX1606.1-301-CS Table 14.2.2.5 (pg. 352)

Reviewer's Exploratory Analyses

As seen from Table 2 in Section 3.2.2, the statistical review team observed a noticeable difference between baseline BM frequencies (counts/day) among the treatment groups. To assess the difference and its potential effect on the primary efficacy outcome, the statistical reviewer conducted additional exploratory analyses by comparing BM frequencies in the treatment groups at baseline and BM frequencies in the treatment groups averaged over the 12-week double-blind treatment period. The differences between treatment arms were evaluated using the primary efficacy analysis, i.e., Wilcoxon rank sum test stratified by the baseline u5-HIAA levels. In order to further investigate the issue of baseline imbalance across arms on patients' daily BMs, the statistical review team sent an information request (IR) to the sponsor (dated November 07, 2016).

Reviewer's results are displayed in Table 5 and Table 6. As seen from Table 5, we found that in study LX301, baseline BM frequency in the placebo arm appeared to be lower than in telotristat ethyl 250mg arm. Although, nominally, based on the sponsor's p-value, the global difference among all three arms is not significant (overall p=0.09), the resulting p-value for the baseline comparison of telotristat ethyl 250 mg versus placebo was 0.04.

We particularly noted that in spite of higher baseline values the observed BM frequencies averaged over 12 week double-blind treatment period in telotristat ethyl arms were generally lower than in the placebo arms (see Table 6). The nominal p-values for differences of telotristat ethyl arms and placebo were >0.2 in study LX301 and >0.1 in study LX303, respectively. Of note, these results were confirmed by the sponsor (see FDA IR dated November 07, 2016).

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Table 5. Reviewer's Analysis of Baseline Bowel Movement (counts/day) (ITT Population)

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301	N=45	N=45	N=45
Baseline Mean (SD) Median (Min, Max)	 5.2 (1.3) 5.1 (3.5, 9.0)	 6.1 (2.1) 5.5 (3.5, 13.0)	 5.8 (2.0) 5.4 (3.6, 12.5)
Hodges-Lehmann est. of treatment group difference	--	**0.61**	**0.39**
95% CL		(0.01, 1.27)	(-0.12, 0.97)
p-value	--	0.043	0.09
Study LX303	N=26	N=25	N=25
Baseline Mean (SD) Median (Min, Max)	N=25 2.2 (0.7) 2.3 (1.0, 3.4)	N=25 2.5 (1.2) 2.2 (0.8, 6.6)	N=25 2.8 (1.6) 2.4 (0.8, 6.6)
Hodges-Lehmann est. of treatment group difference	--	**0.19**	**0.35**
95% CL		(-0.31, 0.82)	(-0.26, 1.05)
p-value	--	0.53	0.26

SD= Standard Deviation; CL=Confidence Limits

Table 6. Reviewer's Analysis of Number of Bowel Movement (counts/day) Averaged Over the Double-Blind Treatment Period (ITT Population)

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301 **(Primary Endpoint)**	N=45	N=45	N=45
Average over DBT Period Mean (SD) Median (Min, Max)	 4.6 (1.6) 4.4 (1.7, 8.7)	 4.7 (2.0) 4.1 (2.0, 10.4)	 4.4 (1.8) 3.9 (1.4, 10.3)
Hodges-Lehmann est. of treatment difference	--	**-0.12**	**-0.35**
95% CL		(-0.8, 0.5)	(-1.0, 0.3)
p-value	--	0.8	0.22
Study LX303 **(Secondary Endpoint)**	N=26	N=25	N=25
Average over DBT Period Mean (SD) Median (Min, Max)	 2.3 (0.8) 2.2 (1.1, 4.3)	 2.1 (1.1) 1.9 (0.9, 6.0)	 2.2 (1.4) 1.5 (0.8, 6.6)
Hodges-Lehmann est. of treatment difference	--	**-0.27**	**-0.31**
95% CL		-0.76, 0.15	-0.87, 0.30
p-value	--	0.13	0.45

SD= Standard Deviation; CL=Confidence Limits
Corresponds to Table 1 and Table 3of Response to FDA Information Request (IR) dated 07 Nov2016.

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3.2.3.2 Statistical Analysis of Urinary 5-Hydroxyindolleacetic Acid Levels

Primary Analysis (stratified Wilcoxon Rank Sum test)

As specified in study protocols, patients' urinary 5-hydroxyindoleacetic acid (u5-HIAA) levels (mg/24 hours) were to be assessed at Screening/Baseline, Week 6 and Week 12. Analyses of absolute change from baseline and percent change from baseline in u5-HIAA levels (mg/24 hours) at Week 12 were only based on the set of patients who had Week 12 assessment (results are presented in Table 7 and Table 8).

As reported by the sponsor and confirmed by the statistical reviewer, in study LX303, telotristat ethyl 250 mg and 500 mg groups were statistically better than placebo in *percent* change from baseline (pre-specified primary endpoint) based on stratified Wilcoxon rank sum test (pre-specified primary analysis).

In study LX301, absolute change from baseline in 24-hour u5-HIAA levels at Week 12 was a pre-specified secondary endpoint. Treatment comparisons of telotristat ethyl 250 mg and 500 mg groups versus placebo were included in the hierarchical multiple testing procedure. Both dose groups (250 mg and 500 mg) were statistically significantly better than placebo group with p-values <0.001.

Table 7. Sponsor's Analysis for Absolute Change from Baseline in Urinary 5-Hydroxyindoleacetic Acid Levels (mg/24 hours) at Week 12 based on Blocked 2-sample Wilcoxon Rank Sum Test

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301 (Secondary Endpoint)	N=29	N=32	N=31
Change from Baseline Mean (SD) Median (Min, Max)	 11.5 (35.6) 1.4 (-35.8, 155.0)	 -40.1 (84.8) -21.7 (-458.6, 77.2)	 -57.7 (82.2) -19.0 (-301.0, 1.0)
Hodges-Lehmann est. of treatment difference	--	-30.1	-33.8
97.5% CL	--	-56.0, -8.1	-66.2, -14.6
p-value	--	<0.001	<0.001
Study LX303 (Exploratory Endpoint)	N=22	N=17	N=19
Change from Baseline Mean (SD) Median (Min, Max)	 35.6 (99.5) 2.1 (-76.5, 393.7)	 -32.2 (43.4) -18.3 (-149.1, 29.3)	 -56.0 (73.5) -35.9 (-319.8, -0.8)
Hodges-Lehmann est. of treatment difference	--	-29.8	-40.6
95% CL		-78.8, -9.2	-96.4, -28.7
p-value	--	0.003	<0.001

SD= Standard Deviation; CL=Confidence Limits
Source: CSR LX1606.1-301-CS Table 11.4.1.3.1-1 (pg.117), CSR LX1606.1-303-CS Table 14.2.1.1 (pg.298)

Reference ID: 4022296

Table 8. Sponsor's Analysis for Percent Change from Baseline in Urinary 5-Hydroxyindoleacetic Acid Levels (mg/24 hours) at Week 12 based on Blocked 2-sample Wilcoxon Rank Sum Test

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301 (Exploratory Endpoint)	N=28	N=32	N=30
Percent Change Mean (SD) Median (Min, Max)	 14.4 (57.8) 4.6 (-100.0, 155.3)	 -42.3 (42.0) -53.6 (-96.1, 133.3)	 -63.5 (21.9) -67.9 (-95.1, -15.9)
Hodges-Lehmann est. of treatment difference	--	-53.4	-70.0
95% CL	--	-69.3, -38.8	-85.4, -54.8
p-value	--	<0.001	<0.001
Study LX303 (Primary Endpoint)	N=22	N=17	N=19
Percent Change Mean (SD) Median (Min, Max)	 97.7 (397.0) 8.0 (-43.6, 1864.5)	 -33.2 (58.5) -39.9 (-94.7, 162.8)	 -76.5 (17.4) -76.1 (-98.0, -28.6)
Hodges-Lehmann est. of treatment difference	--	-54.0	-89.7
95% CL	--	-85.0, -25.2	-113.1, -63.9
p-value	--	<0.001	<0.001

SD= Standard Deviation; CL=Confidence Limits
Source: CSR LX1606.1-301-CS Table 14.2.3.6.ah (pg.540), CSR LX1606.1-303-CS Table 11.4.1.1.1-1 (pg.114)

Sponsor's Supplemental Analysis

As a supplemental analysis for urinary 5-hydroxyindoleacetic acid levels (mg/24 hours), the sponsor performed the pre-specified MMRM analysis with treatment group, urinary 5-HIAA stratification at randomization, time (Week 6 and Week 12) treatment-by-time interaction as fixed effects, and patient as a random effect. An unstructured covariance matrix was used to model the within-subject errors. For both studies, the least squares (LS) mean differences at Week 12 were generally in favor of telotristat ethyl 250 mg and 500 mg in comparison with placebo. Details are given in Appendix C (Table 21 and Table 22).

Reviewer's Remark: The empirical distributions of change and percent change in u5-HIAA levels are severely skewed and appear to be different for the three treatment arms. In such cases, likelihood based methods (such as MMRM) may produce biased estimates.

Reviewer's Exploratory Analyses

As seen from Table 2 in Section 3.2.2, the statistical review team observed a noticeable difference between baseline u5-HIAA levels in the treatment groups. To assess the difference and its potential effect on the primary efficacy outcome, the statistical reviewer conducted additional exploratory analysis by comparing u5-HIAA levels in the treatment groups at baseline and by comparing u5-HIAAlevels at week 12 of the double-blind treatment period. The differences between treatment arms were evaluated using the primary efficacy analysis approach, Wilcoxon rank sum test stratified by the baseline u5-HIAA levels. In information requests (IR) to the sponsor dated October 04 and November 07, 2016, the statistical review team raised a

question regarding baseline imbalance of the urinary (u5-HIAA) data and requested for an exploration of the imbalance.

Reviewer's results are displayed in Table 9 and Table 10. We found that in study LX301, baseline u5-HIAA score in the placebo arm was lower than in telotristat ethyl 250 mg arm (nominal p-value of 0.017). The sponsor's p-value for the test of global difference among all three arms based on stratified Wilcoxon rank sum test was also nominally significant (overall p=0.04). This raises a concern about imbalance between the treatment arms at baseline and potential problem with randomization.

At Week 12 of the double-blind treatment period, observed u5-HIAA levels were lower in the telotristat ethyl groups in both studies (Table 10). In particular, the nominal p-values for the treatment differences of telotristat ethyl 500 mg from placebo in studies LX301 and LX303 were 0.004 and <0.0001 respectively. These results were confirmed by the sponsor (see FDA IR dated November 07, 2016).

Table 9. Reviewer's Analysis of Baseline Urinary 5-Hydroxyindoleacetic Acid Levels (mg/24 hours) based on Blocked 2-sample Wilcoxon Rank Sum Test.

	Placebo	**Telotristat ethyl 250mg**	**Telotristat ethyl 500mg**
Study LX301	N=45	N=45	N=45
Baseline Mean (SD) Median (Min, Max)	N=44 81.0 (161.0) 26.1 (0, 786.2)	N=42 92.6 (114.9) 67.0 (2.2, 637.8)	N=44 89.5 (144.5) 28.3 (0, 608.0)
Hodges-Lehmann est. of treatment group difference	--	**13.0**	**4.0**
95% CL	--	(-0.8, 56.8)	(-7.0, 18.7)
p-value	--	0.017	0.78
Study LX303	N=26	N=25	N=25
Baseline Mean (SD) Median (Min, Max)	 82.0 (113.6) 31.1 (3.2, 439.3)	 86.3 (73.5) 84.0 (2.3, 279.4)	 66.0 (88.9) 40 (0.4, 332.3)
Hodges-Lehmann est. of treatment group difference	--	**10.3**	**-2.4**
95% CL		-13.0, 65.8	-28.7, 26.0
p-value	--	0.79	0.19

SD= Standard Deviation; CL=Confidence Limits

Table 10. Reviewer's Analysis of Urinary 5-Hydroxyindoleacetic Acid Levels (mg/24 hours) at Week 12 based on Blocked 2-sample Wilcoxon Rank Sum Test (ITT Population)

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301 (Secondary Endpoint)	N=29	N=34	N=32
Mean (SD) at Week 12 Median (Min, Max)	50.9 (64.9) 22.0 (0, 310.0)	51.3 (70.1) 21.5 (0, 256.5)	35.7 (68.4) 12.5 (0.8, 307.0)
Hodges-Lehmann est. of treatment difference	--	**-4.3**	**--9.2**
95% CL	--	-17.2, -13.0	-27.0, 0.0
p-value	--	0.46	0.004
Study LX303 (Exploratory Endpoint)	N=22	N=17	N=19
Mean (SD) at Week 12 Median (Min, Max)	120.4 (177.6) 40.1 (5.4, 762.7)	36.9 (42.5) 18.5 (2.3, 166.7)	11.7 (12.2) 7.8 (0.8, 47.5)
Hodges-Lehmann est. of treatment difference	--	**-16.9**	**-30.4**
95% CL	--	-95.5, 3.4	-100.6, -6.2
p-value	--	0.019	<0.0001

SD= Standard Deviation; CL=Confidence Limits
Note that the above results are corresponds to Table 2 and Table 4 of Response to FDA Information Request (IR) dated 07 Nov2016.

In addition, a very high variability of u5-HIAA data (mg/24 hours) was observed for all visits, including baseline. Baseline scores ranged from 0 to 786.2 (mg/24 hours) in study LX301 and from 0.4 to 439.3 (mg/24 hours) in study LX303, respectively. This creates difficulty in assessing clinically meaningful effect and weakens interpretability of the efficacy findings. For instance, baseline u5-HIAA scores near 0 represent the best possible values (which should correspond to a healthy condition), and thus, cannot be further improved. On the other hand, a moderate increase from a low baseline score may result in an extremely high percent change. For example, patients 0705-504 and 2704-502 (study LX303, Telotristat ethyl 500 mg arm) had respective baseline scores of 0.4 and 0.6, and Week 6 scores of 2.9 and 3. This resulted in 625% and 400% changes from baseline to Week 6 respectively. The highest observed percent change at Week 12 occurred in the placebo arm in study LX303 and it was equal to 1864%.

3.2.3.3 Statistical Analysis of Additional Secondary Endpoints

Change from Baseline in the Daily Number of Cutaneous Flushing Episodes

In the analysis of the daily number of cutaneous flushing averaged across all time points during the double-blind treatment period, neither telotristat ethyl versus placebo treatment comparison was statistically significant. Analysis details are included in Table 11.

Table 11. Sponsor's Analysis of Cutaneous Flushing Episodes (counts/day) Averaged Across All Time Points During the Double-Blind Treatment Period (ITT Population)

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301 (Secondary Endpoint)	N=45	N=45	N=45
Mean Change from Baseline (SD)	-0.16 (1.16)	-0.30 (1.31)	-0.53 (1.34)
Hodges-Lehmann est. of treatment difference	--	**0.04**	**0.0**
97.5% CL	--	-0.23, 0.33	-0.35, 0.21
p-value	--	0.39	0.84
Study LX303 (Exploratory Endpoint)	N=26	N=25	N=25
Mean Change from Baseline (SD)	-0.33 (1.22)	-0.06 (0.98)	0.114 (2.10)
Hodges-Lehmann est. of treatment difference	--	**0.11**	**0.02**
95% CL	--	-0.17, 0.61	-0.28, 0.62
p-value	--	0.67	0.58

SD= Standard Deviation; CL=Confidence Limits
Source: CSR LX1606.1-301-CS Table 14.2.4.1.1 (pg. 542), CSR LX1606.1-303-CS Table 12.2.4.1.1 (pg.534)

Change from Baseline in Abdominal Pain During the Double-blind Treatment Period

In the analysis of the abdominal pain (11-point Numeric Rating Scale) averaged across all time points during the double-blind treatment period, neither of the two telotristat ethyl dose groups was statistically significantly different from the placebo group (see Table 12).

Table 12. Sponsor's Analysis of Abdominal Pain Averaged Across All Time Points During the Double-Blind Treatment Period (ITT Population)

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301 (Secondary Endpoint)	N=45	N=45	N=45
Mean Change from Baseline (SD)	-0.23 (1.16)	-0.49 (1.44)	-0.33 (1.18)
Hodges-Lehmann est. of treatment difference	--	**-0.17**	**-0.05**
97.5% CL	--	-0.54, 0.22	-0.46, 0.33
p-value	--	0.28	0.87
Study LX303 (Exploratory Endpoint)	N=26	N=25	N=25
Mean Change from Baseline (SD)	-0.06 (0.78)	-0.23 (0.97)	0.02 (0.77)
Hodges-Lehmann est. of treatment difference	--	**0.06**	**0.14**
95% CL	--	-0.42, 0.33	-0.39, 0.51
p-value	--	0.61	0.66

SD= Standard Deviation; CL=Confidence Limits
Source: CSR LX1606.1-301-CS Table 14.2.5.1.1 (pg. 650), CSR LX1606.1-303-CS Table 14.2.5.1 (pg. 600)

Reference ID: 4022296

3.3 Evaluation of Safety

Safety was not evaluated in this review. Please refer to the clinical review for details on the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The purpose of the following subgroup analyses is to assess the consistency of treatment effects in bowel movement across subgroups.

4.1.1 Gender

Table 13 displays reviewer's subgroup summaries by gender in studies 301 and 303. Overall, in all gender subgroups, both telotristat ethyl treatment arms (250 mg and 500 mg) were numerically better than placebo.

Table 13. Reviewer's Subgroup Analysis by Gender: Change in Bowel Movement (counts/day) Averaged Over the Double-Blind Treatment Period

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301			
Male	N=24	N=21	N=25
Mean Change from Baseline (SD)	-0.47 (0.83)	-1.21 (1.07)	-1.36 (1.06)
Hodges-Lehmann est. of treatment difference	--	**-0.84**	**-0.85**
Female	N=21	N=24	N=20
Mean Change from Baseline (SD)	-0.80 (0.81)	-1.63 (1.57)	-1.57 (1.59)
Hodges-Lehmann est. of treatment difference	--	**-0.73**	**-0.43**
Study LX303			
Male	N=13	N=14	N=15
Mean Change from Baseline (SD)	0.10 (0.43)	-0.10 (0.49)	-0.49 (0.60)
Hodges-Lehmann est. of treatment difference	--	**-0.24**	**-0.58**
Female	N=12	N=11	N=10
Mean Change from Baseline (SD)	-0.01 (0.15)	-0.90 (0.67)	-0.75 (0.89)
Hodges-Lehmann est. of treatment difference	--	**-0.87**	**-0.47**

SD= Standard Deviation;

4.1.2 Race

Racial Subgroups were not investigated by this reviewer since in both studies overwhelming majority of patients were White (over 90%).

4.1.3 Age

Table 14 presents reviewer's analysis by age subgroup (<65 years, ≥65 years) in studies 301 and 303. Overall, in all subgroups, both telotristat ethyl treatment arms (250 mg and 500 mg) were numerically better than placebo.

Table 14. Reviewer's Subgroup Analysis by Age: Change in Bowel Movement (counts/day) Averaged Over the Double-Blind Treatment Period

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301			
Age < 65 years	N=25	N=26	N=22
Mean Change from Baseline (SD)	-0.75 (0.79)	-1.32 (1.32)	-1.48 (1.23)
Hodges-Lehmann est. of treatment difference	--	**-0.58**	**-0.60**
Age ≥ 65	N=20	N=19	N=23
Mean Change from Baseline (SD)	-0.46 (0.86)	-1.58 (1.44)	-1.43 (1.41)
Hodges-Lehmann est. of treatment difference	--	**-1.04**	**-0.82**
Study LX303			
Age < 65 years	N=12	N=14	N=15
Mean Change from Baseline (SD)	0.15 (0.25)	-0.38 (0.78)	-0.66 (0.87)
Hodges-Lehmann est. of treatment difference	--	**-0.50**	**-0.60**
Age ≥ 65 years	N=13	N=11	N=10
Mean Change from Baseline (SD)	-0.04 (0.37)	-0.55 (0.58)	-0.49 (0.46)
Hodges-Lehmann est. of treatment difference	--	**-0.38**	**-0.48**

SD= Standard Deviation;

4.1.4 Regional

Table 15 displays reviewer's subgroup analysis by region (North America, Rest of the World) in studies 301 and 303. In all considered subgroups, both telotristat ethyl treatment arms (250 mg and 500 mg) were numerically better than placebo.

Table 15. Reviewer's Subgroup Analysis by Region Change in Bowel Movement (counts/day) Averaged Over the Double-Blind Treatment Period

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301			
North America	N=15	N=15	N=14
Mean Change from Baseline (SD)	-0.46 (0.77)	-1.52 (1.72)	-0.77 (0.80)
Hodges-Lehmann est. of treatment difference	--	**-0.98**	**-0.30**
Rest of the World	N=30	N=30	N=31
Mean Change from Baseline (SD)	-0.70 (0.86)	-1.39 (1.18)	-1.77 (1.38)
Hodges-Lehmann est. of treatment difference	--	**-0.72**	**-0.92**
Study LX303			
North America	N=4	N=6	N=8
Mean Change from Baseline (SD)	-0.03 (0.07)	-0.36 (0.55)	-0.64 (1.04)
Hodges-Lehmann est. of treatment difference	--	**-0.27**	**-0.45**
Rest of the World	N=21	N=19	N=17
Mean Change from Baseline (SD)	0.06 (0.35)	-0.58 (0.56)	-0.48 (0.74)
Hodges-Lehmann est. of treatment difference	--	**-0.47**	**-0.58**

SD= Standard Deviation;

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Randomization

There is a concern regarding baseline imbalance in study LX301 (Table 5 and Table 9). In particular, baseline BM frequency and baseline u5-HIAA levels in the placebo arm were lower than in telotristat ethyl 250 mg arm (p-values of 0.043 and 0.017 if compared using the primary analysis method).

Reference ID: 4022296

Variability of U5HIAA Levels

In both studies, urinary 5-hydroxyindoleacetic acid levels (mg/24 hours) exhibited very high variability at all visits including baseline (see Table 2 for baseline scores and Table 16 for Week 12 scores). In particular, baseline scores ranged from 0 to 786.2 in study LX301 and from 0.4 to 439.3 in study LX303. This creates difficulty in assessing clinically meaningful effect and weakens interpretability of the efficacy findings. For instance, baseline u5-HIAA scores near 0 represent the best possible values (which should correspond to a healthy condition), and thus, cannot be further improved. On the other hand, a moderate increase from a low baseline score may result in an extremely high percent change. For example, patients 0705-504 and 2704-502 (study LX303, telotristat ethyl 500 mg arm) had respective baseline scores of 0.4 and 0.6, and Week 6 scores of 2.9 and 3. This represents 625% and 400% changes from baseline to Week 6 respectively. The highest observed percent change at Week 12 occurred in the placebo arm in study LX303 and it was equal to 1864%.

Table 16. Urinary 5-Hydroxyindoleacetic Acid Levels (mg/24 hours) (ITT Population)

	Placebo	**Telotristat ethyl 250mg**	**Telotristat ethyl 500mg**
Study LX301	N=29	N=34	N=32
Actual Value Mean (SD) at Week 12 Median (Min, Max)	 50.9 (64.9) 22.0 (0, 310.0)	 51.3 (70.1) 21.5 (0, 256.5)	 35.7 (68.4) 12.5 (0.8, 307.0)
Percent Change at Week 12 Mean (SD) Median (Min, Max)	 14.4 (57.8) 4.6 (-100.0, 155.3)	 -42.3 (42.0) -53.6 (-96.1, 133.3)	 -63.5 (21.9) -67.9 (-95.1, -15.9)
Study LX303	N=22	N=17	N=19
Actual Value Mean (SD) at Week 12 Median (Min, Max)	 120.4 (177.6) 40.1 (5.4, 762.7)	 36.9 (42.5) 18.5 (2.3, 166.7)	 11.7 (12.2) 7.8 (0.8, 47.5)
Percent Change at Week 12 Mean (SD) Median (Min, Max)	 97.7 (397.0) 8.0 (-43.6, 1864.5)	 -33.2 (58.5) -39.9 (-94.7, 162.8)	 -76.5 (17.4) -76.1 (-98.0, -28.6)

SD= Standard Deviation; CL=Confidence Limits

Source: CSR LX1606.1-301-CS Table 14.2.3.3.1 (pg.527), CSR LX1606.1-303-CS Table 14.2.1.3.1 (pg.305), CSR LX1606.1-301-CS Table 14.2.3.6.ah (pg.540), CSR LX1606.1-303-CS Table 11.4.1.1.1-1 (pg.114)

Multiplicity and Lack of Replication

Due to lack of multiplicity adjustment for secondary endpoints in study LX303, efficacy results pertaining to BM frequency in study LX303 cannot be used to formally replicate primary efficacy findings for change in BM frequency averaged over 12 weeks in study LX301.

Collective Evidence

The efficacy of telotristat ethyl in the treatment of Carcinoid Syndrom was evaluated in two 12-week, placebo-controlled Phase 3 studies, study LX301 and study LX303. Based on the pre-specified primary analysis method, the Wilcoxon rank sum statistic stratified by the baseline urinary 5-HIAA levels, we have the following findings:

- in study LX301 telotristat ethyl 250mg and 500mg treatment groups had statistically significant changes from baseline in the number of daily BMs (counts/day) averaged of 12 week double-blind treatment period and in the u5-HIAA levels (mg/24 hours) at Week 12 in comparison with placebo treatment group.
- in study LX303, telotristat ethyl 250mg and 500mg had statistically significantly higher percent reductions than placebo in u5-HIAA levels (mg/24 hours) at Week 12. Both doses were also numerically better than placebo in changes from baseline in the number of daily BMs (counts/day) averaged of 12 week double-blind treatment period.

Observed magnitude of treatment differences for change in BM frequency endpoint appeared to be similar between the two doses of telotristat ethyl 250 mg and 500 mg. In study LX303 efficacy results pertaining to change in BM frequency cannot be considered statistically significant because treatment comparisons were not adjusted for multiplicity.

For both studies, the urinary 5-hydroxyindoleacetic acid levels exhibited very high variability at baseline and post-baseline visits, and significant imbalance at baseline in study LX301. This creates difficulty in assessing clinically meaningful effect and weakens interpretability of the efficacy findings.

5.3 Conclusions and Recommendations

Compared with placebo, telotristat ethyl showed statistically significant reductions in the number of daily bowel movements (counts/day) and the urinary 5-hydroxyindoleacetic acid (u5-HIAA) levels (mg/24 hours), based on pre-specified primary analysis. However, treatment effect in u5-HIAA is difficult to interpret due to concerns indicated above.

APPENDIX A

Table 17. Study LX301 Patient Disposition for the Double-Blind Treatment Period (All Enrolled Patients)

Patient Status	Placebo n (%)	LX1606 250 mg n (%)	LX1606 500 mg n (%)
Randomized[a]	45	45	46
Completed the DBT Period[a]	38 (84.4)	41 (91.1)	38 (82.6)
Discontinued the DBT Period[a]	7 (15.6)	4 (8.9)	8 (17.4)
Adverse event	3 (6.7)	2 (4.4)	2 (4.3)
Death[b]	2 (4.4)	0	1 (2.2)
Lack of efficacy	0	0	0
Lost to follow-up	0	0	0
Noncompliance with study drug	0	0	0
Physician decision	1 (2.2)	0	1 (2.2)
Pregnancy	0	0	0
Disease progression	0	0	0
Protocol violation	0	0	0
Study terminated by Sponsor	0	0	0
Withdrawal of consent	1 (2.2)	1 (2.2)	3 (6.5)
Other	0	1 (2.2)	1 (2.2)

Source: Table 14.1.1, Listing 16.2.1, and Listing 16.2.3.1

[a] Percentages are based on the number of patients randomized.

[b] Details regarding deaths are provided in Section 12.3.1.1.

Abbreviations: DBT = Double-blind Treatment; tid = 3 times daily

Source: CSR LX1606.1-301-CS Table 10.1.1-2 (pg. 90)

Table 18. Study LX303 Patient Disposition for the Double-Blind Treatment Period (All Enrolled Patients)

Patient Status	Placebo N (%)	LX1606 250 mg N (%)	LX1606 500 mg N (%)	Total N (%)
Enrolled				76
Randomized[a]	26	25	25	76
Completed the Double-blind Treatment Period[a]	24 (92.3)	22 (88.0)	22 (88.0)	68 (89.5)
Discontinued the Double-blind Treatment Period[a]	2 (7.7)	3 (12.0)	3 (12.0)	8 (10.5)
Primary reason for discontinuation[a]				
Adverse event	1 (3.8)	2 (8.0)	0	3 (3.9)
Death	0	0	0	0
Lack of efficacy	0	0	0	0
Physician decision	1 (3.8)	0	0	1 (1.3)
Withdrawal of consent	0	1 (4.0)	3 (12.0)	4 (5.3)
Other	0	0	0	0

Source: Table 14.1.1, Listing 16.2.1, and Listing 16.2.3.1

[a] Percentages are based on the number of patients randomized.

Source: CSR LX1606.1-303-CS Table 10.1.1-2 (pg. 88)

APPENDIX B

Table 19. Study LX301 Demographic and Baseline Characteristics Prior to the Double-blind Treatment Period (Safety Population)

Patient Characteristic	Statistic	Placebo N=45	LX1606 250 mg N=45	LX1606 500 mg N=45
Age (years) at the time of consent	n	45	45	45
	Mean (SD)	63.3 (8.67)	62.4 (9.12)	64.9 (9.04)
	Median	64.0	64.0	65.0
	Min, Max	42, 80	37, 83	44, 88
Age group				
<65 years	n (%)	25 (55.6)	26 (57.8)	22 (48.9)
≥65 years	n (%)	20 (44.4)	19 (42.2)	23 (51.1)
Sex				
Male	n (%)	24 (53.3)	21 (46.7)	25 (55.6)
Female	n (%)	21 (46.7)	24 (53.3)	20 (44.4)
Ethnicity[a]				
Hispanic or Latino	n (%)	0	0	1 (2.2)
Not Hispanic or Latino	n (%)	45 (100)	44 (97.8)	44 (97.8)
Race[a]				
White	n (%)	40 (88.9)	41 (91.1)	40 (88.9)
Black or African American	n (%)	1 (2.2)	0	0
Asian	n (%)	0	0	0
American Indian or Alaska Native	n (%)	1 (2.2)	0	0
Native Hawaiian or other Pacific Islander	n (%)	0	0	0
Other	n (%)	0	0	1 (2.2)
Weight (kg)	n	43	44	44
	Mean (SD)	70.87 (13.940)	70.05 (14.832)	73.44 (19.971)
	Median	71.40	70.70	70.75
	Min, Max	42.6, 103.7	40.0, 102.0	43.5, 112.0
Height (cm)	n	39	41	40
	Mean (SD)	168.80 (10.707)	169.32 (9.607)	169.93 (10.436)
	Median	170.00	170.00	170.20
	Min, Max	123.2, 190.0	149.0, 186.0	148.8, 192.0
Baseline BMI (kg/m^2)[b]	n	38	41	39
	Mean (SD)	25.13 (4.790)	24.26 (4.702)	25.24 (5.352)
	Median	26.19	23.25	23.60
	Min, Max	15.2, 36.0	17.0, 37.0	15.9, 37.2

Reference ID: 4022296

Patient Characteristic	Statistic	Placebo N=45	LX1606 250 mg N=45	LX1606 500 mg N=45
SSA therapy schedule at study entry[c]				
3-week	n (%)	11 (24.4)	11 (24.4)	17 (37.8)
4-week	n (%)	34 (75.6)	34 (75.6)	28 (62.2)
SSA therapy name at study entry				
Octreotide	n (%)	30 (66.7)	40 (88.9)	33 (73.3)
Lanreotide	n (%)	15 (33.3)	5 (11.1)	12 (26.7)
Childbearing potential				
Yes	n (%)	3 (6.7)	0	0
No	n (%)	18 (40.0)	24 (53.3)	20 (44.4)
Not applicable	n (%)	24 (53.3)	21 (46.7)	25 (55.6)
Urinary 5-HIAA at randomization				
≤ULN	n (%)	12 (26.7)	12 (26.7)	12 (26.7)
>ULN	n (%)	26 (57.8)	26 (57.8)	26 (57.8)
Unknown	n (%)	7 (15.6)	7 (15.6)	7 (15.6)

Source: Table 14.1.2.1, Listing 16.2.4.1, and Listing 16.2.4.2

[a] Race information was not provided for all 11 patients in France, and ethnicity information was not provided for 1 of these patients.

[b] BMI was calculated by weight (kg) / (height [cm] *0.01)^2.

[c] Patients who were on a 2-week SSA therapy or receiving SSA therapy via a subcutaneous continuous infusion pump are included in the "4-week" category.

Abbreviations: BMI = body mass index; LX1606 = telotristat etiprate; Max = maximum; Min = minimum; SD = standard deviations; SSA = somatostatin analog; ULN = upper limit of normal; 5-HIAA = hydroxyindoleacetic acid

Source: CSR LX1606.1-301-CS Table 11.2.1.1-1(pg. 97-98)

Table 20. Study LX303 Demographic and Baseline Characteristics (Safety Population)

Characteristic	Statistic	Placebo N=26	LX1606 250 mg N=25	LX1606 500 mg N=25	Total N=76
Age (years) at the time of consent	n	26	25	25	76
	Mean (SD)	62.2 (10.32)	63.6 (12.62)	62.7 (11.97)	62.8 (11.52)
	Median	65.0	62.0	63.0	64.0
	Min, Max	41, 78	38, 84	35, 83	35, 84
Age groups					
<65 years	n (%)	12 (46.2)	14 (56.0)	15 (60.0)	41 (53.9)
≥65 years	n (%)	14 (53.8)	11 (44.0)	10 (40.0)	35 (46.1)
Sex					
Male	n (%)	13 (50.0)	14 (56.0)	15 (60.0)	42 (55.3)
Female	n (%)	13 (50.0)	11 (44.0)	10 (40.0)	34 (44.7)
Ethnicity[a]					
Not Hispanic or Latino	n (%)	25 (96.2)	25 (100)	25 (100)	75 (98.7)
Race[a]					
White	n (%)	25 (96.2)	25 (100)	24 (96.0)	74 (97.4)
Black or African American	n (%)	0	0	1 (4.0)	1 (1.3)
Weight (kg)	n	26	25	25	76
	Mean (SD)	76.38 (16.959)	74.74 (17.839)	76.69 (26.188)	75.94 (20.442)
	Median	77.00	72.00	69.20	72.90
	Min, Max	50.5, 110.2	44.0, 109.9	45.8, 166.7	44.0, 166.7
Height (cm)	n	25	23	24	72
	Mean (SD)	169.48 (9.765)	169.74 (10.025)	170.08 (8.525)	169.76 (9.327)
	Median	168.50	170.00	169.00	168.55
	Min, Max	149.0, 184.0	146.0, 185.0	157.0, 190.5	146.0, 190.5
Baseline BMI (kg/m^2)[b]	n	25	23	24	72
	Mean (SD)	26.28 (4.364)	25.96 (5.258)	26.21 (9.213)	26.16 (6.521)
	Median	26.51	27.10	23.11	25.76
	Min, Max	19.0, 35.6	16.0, 36.5	17.0, 62.0	16.0, 62.0
SSA therapy schedule at study entry[c]					
3-Week	n (%)	6 (23.1)	7 (28.0)	9 (36.0)	22 (28.9)
4-Week	n (%)	20 (76.9)	16 (64.0)	12 (48.0)	48 (63.2)
Not on SSA[d]	n (%)	0	2 (8.0)	4 (16.0)	6 (7.9)

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Characteristic	Statistic	Placebo N=26	LX1606 250 mg N=25	LX1606 500 mg N=25	Total N=76
SSA therapy name at study entry					
Octreotide	n (%)	12 (46.2)	17 (68.0)	16 (64.0)	45 (59.2)
Lanreotide	n (%)	14 (53.8)	5 (20.0)	3 (12.0)	22 (28.9)
Unknown[e]	n (%)	0	1 (4.0)	2 (8.0)	3 (3.9)
Not applicable	n (%)	0	2 (8.0)	4 (16.0)	6 (7.9)
Childbearing potential					
Yes	n (%)	2 (7.7)	4 (16.0)	1 (4.0)	7 (9.2)
No	n (%)	11 (42.3)	7 (28.0)	9 (36.0)	27 (35.5)
Not applicable	n (%)	13 (50.0)	14 (56.0)	15 (60.0)	42 (55.3)
Baseline u5-HIAA level[f]					
≤ULN	n (%)	9 (34.6)	5 (20.0)	8 (32.0)	22 (28.9)
>ULN	n (%)	17 (65.4)	18 (72.0)	17 (68.0)	52 (68.4)
Unknown	n (%)	0	2 (8.0)	0	2 (2.6)

Source: Table 14.1.2.1, Listing 16.2.4.1, and Listing 16.2.4.2

Abbreviations: BMI = body mass index; eCRF = electronic case report form; Max = maximum; Min = minimum; SD = standard deviation; SSA = somatostatin analog; u5-HIAA = urinary 5-hydroxyindoleacetic acid; ULN = upper limit of normal

Note: Percentages are based on the number of patients in each treatment group.

[a] Race and ethnicity information was not provided for 1 patient in France.

[b] BMI was calculated by weight (kg) / (height [cm] × 0.01)^2.

[c] Patients who were on a 2-week SSA therapy or receiving SSA therapy via a subcutaneous continuous infusion pump were included in the "4-week" category.

[d] Patients counted in the "Unknown" category for SSA therapy at study entry were not included in the count of patients "not on SSA therapy" for SSA therapy schedule at study entry. See footnote "e" for further details.

[e] In the original eCRF, Investigators did not have the choice of "not applicable" for those patients not receiving SSA therapy at Baseline. Therefore, SSA therapy was classified as "Unknown" for 3 patients because there was no corresponding SSA listed as a concomitant medication. The eCRF was later updated to provide the choice of "not applicable."

[f] Although referred to as "Baseline u5-HIAA level," this category actually presents the stratification categories used for randomization. For the 2 patients included in the "Unknown" category, the u5-HIAA levels were not available to the Investigator before randomization, but the Baseline levels are included in the analyses of the absolute and percent changes from Baseline in u5-HIAA levels.

Source: CSR LX1606.1-303-CS Table 11.2.1.1-1(pg. 94-95)

APPENDIX C

The Supplemental Analyses of Absolute and Percent Change from Baseline in U5-HIAA l Levels using MMRM

Table 21. Absolute Change from Baseline in Urinary 5-Hydroxyindoleacetic Acid Levels (mg/24 hours) at Week 12 based on MMRM analysis

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301 (Secondary Endpoint)			
Week 6 LS Mean Change	N=35 13.2	N=38 -35.1	N=35 -50.0
Week 12 LS Mean Change	N=29 **4.1**	N=32 **-33.8**	N=31 **-47.1**
p-values at Week 12	--	0.04	0.006
Study LX303 (Exploratory Endpoint)			
Week 6 LS Mean Change	N=23 -38.9	N=21 -26.1	N=22 -71.8
Week 12 LS Mean Change	N=22 **17.4**	N=17 **-42.9**	N=19 **-71.5**
p-values at Week 12		0.023	<0.001

SD= Standard Deviation; CL=Confidence Limits
Source: CSR LX1606.1-301-CS Table 14.2.3.1 (pg.523-524), CSR LX1606.1-303-CS Table 14.2.1.1 (pg.298, 300)

Table 22. Percent Change from Baseline in Urinary 5-Hydroxyindoleacetic Acid Levels (mg/24 hours) at Week 12 based on MMRM analysis

	Placebo	Telotristat ethyl 250mg	Telotristat ethyl 500mg
Study LX301 (Exploratory Endpoint)			
Week 6 LS Mean Change	N=35 51.7	N=38 -42.0	N=35 -63.2
Week 12 LS Mean Change	N=28 **12.3**	N=32 **-43.3**	N=30 **-63.4**
p-value at Week 12	--	<0.001	<0.001
Study LX303 (Primary Endpoint)			
Week 6 LS Mean Change	N=23 -9.9	N=21 136.0	N=22 -19.2
Week 12 LS Mean Change	N=22 **88.6**	N=17 **-33.7**	N=19 **-72.4**
p-value at Week 12	--	0.14	0.043

SD= Standard Deviation; CL=Confidence Limits
Source: CSR LX1606.1-301-CS Table 14.2.3.6.ah (pg.540-541), CSR LX1606.1-303-CS Table 14.2.1.1 (pg.297, 299)

Reference ID: 4022296

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/s/

GEORGE KORDZAKHIA
12/02/2016

YEH FONG CHEN
12/03/2016

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL OUTCOME ASSESSMENT

NDA/BLA #:	NDA 208794
Supplement #:	1
Drug Name:	Xermelo (telotristat etiprate) Oral Tablets
Indication(s):	Carcinoid Syndrome
Applicant:	Lexicon Pharmaceuticals, Inc.
Measure(s):	Daily Bowel Movement Frequency
Clinical Outcome Assessment (COA) Type:	Patient-reported Outcome (PRO)
Date(s):	Date Submitted: March 29, 2016
	PDUFA Due Date: February 28, 2017
	Review Completion Date: November 29, 2016
Review Priority:	Priority
Biometrics Division:	DBIII
COA Statistical Reviewer:	Lili Garrard, PhD
Concurring Reviewers:	Scott Komo, DrPH (DBIV), Laura Lee Johnson, PhD
Medical Division:	DGIEP
Primary Statistical Reviewer:	George Kordzakhia, PhD
COA Staff Reviewer:	Wen-Hung Chen, PhD
Clinical Team:	Wen-Yi Gao, MD
	Stephanie Omokaro, MD (Medical Team Leader)
Project Manager(s):	Benjamin Vali, Brian Strongin

Keywords: NDA Review, patient-reported outcome (PRO), meaningful change

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1 EXECUTIVE SUMMARY

The applicant has developed Xermelo (telotristat etiprate) oral tablets for the treatment of Carcinoid Syndrome (CS) in patients that are not adequately controlled by somatostatin analog (SSA) therapy. The applicant submitted data from two randomized, placebo-controlled, parallel-group, multicenter, double-blind, Phase 3 trials (LX1606.301 and LX1606.303; hereafter Studies 301 and 303). Study 301 served as the single pivotal trial with Study 303 as the companion trial. Both studies included a 12-week treatment period and a 36-week treatment extension period. 135 patients in Study 301 and 76 patients in Study 303 were randomized in an approximately 1:1:1 ratio to three treatment arms: placebo, 250 mg three times daily, and 500 mg three times daily. The primary endpoint of Study 301 was the change from baseline in the number of daily bowel movements (BMs) averaged over the 12-week treatment period. The primary endpoint for Study 303 was the percent change from baseline in the 24-hour urinary 5-hydroxyindoleacetic acid (u5-HIAA) levels at Week 12. The primary endpoint of Study 301 was one of the Study 303 secondary endpoints that had no pre-specified multiplicity adjustment. This review focuses on the psychometric evaluation of the applicant's proposed meaningful change threshold for Study 301, with this statistical reviewer's post-hoc evaluation of the potential generalizability of the Study 301 results to the Study 303 patient population. For the statistical evaluation of efficacy and safety for Xermelo (telotristat etiprate), please refer to the review of Dr. George Kordzakhia, the primary statistical reviewer for this NDA submission.

A notable statistical review issue is that the same Study 301 data were used both to demonstrate treatment efficacy and evaluate a meaningful change threshold. Although the Agency does not recommend this practice due to generalizability concerns (i.e., the threshold may only be relevant to the current set of patients), the Statistical and Clinical review teams felt that a certain degree of flexibility should be exercised due to the rare disease nature of CS.

Although this statistical reviewer replicated the applicant's analyses results, this reviewer came to a different conclusion from what the applicant proposed as a meaningful change threshold, based on the totality of information. Using both anchor-based and distribution-based approaches, findings from the Study 301 psychometric evaluation of the meaningful change threshold suggest that a reduction of at least 2 BMs/day in overall average BM frequency from baseline may be potentially meaningful to patients. The applicant stated in their Study 301 psychometric report that a reduction of at least 0.87 BM/day from baseline may be potentially meaningful to patients. In addition, based on this statistical reviewer's post-hoc evaluation, the overall average reduction of at least 2 daily BMs threshold from Study 301 cannot be generalized to Study 303 patients due to differences in the study populations.

Using this reviewer's suggested Study 301 meaningful change threshold, an absolute reduction of at least 2 BMs/day was shown in 33% of patients in the 250 mg group, 24% of patients in the 500 mg group, and 4% of patients in the placebo group. Although this reviewer came to a different conclusion from the applicant for the meaningful change threshold, the cumulative distribution function (CDF) plot of absolute change in overall average BM frequency from baseline (refer to Figure 14 in review) shows a clear separation between the treatment arms and the placebo arm for both the reviewer and applicant proposed meaningful change thresholds.

Reference ID: 4019904

2 INTRODUCTION

2.1 Overview

The applicant, Lexicon Pharmaceuticals, is developing Xermelo (telotristat etiprate) oral tablets for the treatment of Carcinoid Syndrome (CS) in patients that are not adequately controlled by somatostatin analog (SSA) therapy. CS is a chronic condition caused by secretions of certain chemicals from rare cancerous carcinoid tumors into the bloodstream. The most common occurrences of carcinoid tumors are found in the small intestine and the bronchial system of the lungs. CS often is characterized by severe diarrhea and flushing.

This NDA submission serves two purposes: (1) to assess the efficacy and safety of Xermelo (telotristat etiprate), and (2) to evaluate the definition of meaningful change in daily bowel movement (BM) frequency for Study 301 patients. This review focuses on the psychometric evaluation of the applicant's proposed meaningful change threshold. For the statistical evaluation of efficacy and safety for Xermelo (telotristat etiprate), please refer to the review of Dr. George Kordzakhia, the primary statistical reviewer for this NDA submission.

2.1.1 Regulatory History

The applicant's development program for Xermelo (telotristat etiprate) was designated as a Fast Track development program on May 19, 2008. Xermelo (telotristat etiprate) was designated as an orphan drug on March 9, 2012.

On April 11, 2012, the Agency and the applicant met for an End-of-Phase 2 (EOP2) meeting to discuss the development plan for Xermelo (telotristat etiprate). The applicant proposed to conduct a single pivotal Phase 3 trial (Study 301) to evaluate the efficacy and safety of Xermelo (telotristat etiprate) in patients with refractory carcinoid syndrome. The protocol synopsis of Study 301 was submitted in the meeting package. The proposed primary efficacy endpoint of Study 301 was the reduction of the number of BMs over the 12 week double-blind portion of the study. The Agency commented that two adequate and well-controlled studies generally were recommended to demonstrate efficacy. However, the Agency recognized the limited number of patients that might be available to enroll in Phase 3 trials. Therefore if only one Phase 3 trial was conducted, it would have to demonstrate statistically robust evidence of important clinical benefit. The Agency agreed with the applicant that it was acceptable to have a 12-week duration of dosing for the double-blind portion of the trial and to use short-acting octreotide as a rescue therapy, under the notion that the patients given octreotide would be considered as treatment failures in the primary efficacy analysis. The Agency also agreed that the global assessment of adequate relief might be useful in designing Phase 3 trials; however, as a proposed secondary endpoint, adequate relief (b) (4) in a patient population to be studied in the Phase 3 trial. The Agency did not agree with the applicant's plan of including patients who are on lanreotide in the trial; however, the Agency would further consider the implications of potential lanreotide use in patients outside of the United States. The Agency also did not agree with the dose selection of 500 mg three times a day for Study 301 and asked the applicant to justify the

dose selection. The Agency commented that the applicant "*should provide data to justify the use of your proposed primary endpoint, 'reducing the number of bowel movements over the 12-week double blind portion of the study' and your durability definition of proportion of responders with ≥25% reduction in daily number of BMs for ≥50% of time over the double-blind portion of the study.*" The Agency also commented that both consistency and frequency were likely to be important endpoints, and the Agency recommended using urgency as an exploratory endpoint.

On July 9, 2013, the Agency and the applicant met to have further discussions based on comments from the EOP2 meeting. In the meeting package, the applicant submitted consensus statements from an applicant-sponsored external Advisory Board Meeting (March 20, 2013) with an expert panel consisting of four CS physician experts, one gastrointestinal (GI) physician expert, and one nurse practitioner who had close interactions with CS patients. The applicant proposed that "an overall reduction in bowel movements per day (BMs/d) of approximately 30% is clinically important to patients, and is anticipated to improve their quality of life." The Agency stated:

> *"In general, it appears that your use of reduction in BM frequency would be acceptable, and a 30% reduction may be acceptable for defining a meaningful response; however, we need to have the SEALD team review your data to determine if your instrument is appropriate. We may send additional recommendations based on the SEALD evaluation. Furthermore, you need to justify the adequacy of the proposed 50% rule (a patient daily response occurs at least 50% of the time over the double-blind portion of the study) to determine durability of the primary efficacy endpoint. Provide rationale and data to support that this is clinically meaningful."*

The durability endpoint was proposed as one of the secondary endpoints in the applicant's background package for the July 9, 2013 meeting.

On October 9, 2013, the Agency and the applicant held a teleconference specifically to discuss assessment of durability of treatment effect and analyses planned for Study 301. In the submitted meeting package the durability response endpoint was proposed as an exploratory endpoint for Study 301; this was a change from the July 9, 2013 submitted meeting package which listed durability response as a proposed secondary endpoint. The Agency agreed with "*using the 50% rule as a measure of durability for the primary endpoint of reduction in the number of daily bowel movement compared to baseline over the 12-week Treatment Period of the trial.*" The Agency recommended further analysis of results from the Phase 2 study LX1606.1-202-CS (hereafter Study 202) to evaluate the proposed 30% response threshold for stool counts. The Agency warned the applicant that an insufficiently specific threshold for the self-report measure might compromise the ability to detect difference should there be unexpected placebo response in the planned Phase 3 trial. The Agency recommended exploratory calculations of specificity and sensitivity using different responder thresholds. The applicant also notified the Agency regarding plans for an additional Phase 3 trial (Study 303) that would be a companion study with telotristat etiprate in patients with CS intended to evaluate the incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). The proposed protocol for Study 303 was not submitted for review at the time of the meeting.

On February 14, 2014, the applicant submitted an original protocol for Study 303.

On February 24, 2015, the Agency and the applicant met for a Pre-NDA meeting. The Agency provided general comments on the NDA package submission (i.e., study tagging files, case report forms, integrated summary of efficacy and integrated summary of safety). No further discussions regarding the 30% response threshold occurred at the meeting for either Studies 301 or 303.

2.1.2 Clinical Studies Overview

Prior to the NDA submission, the applicant submitted data on 23 patients in Study 202 for the evaluation of the safety and tolerability of orally administered LX1606 Hippurate (telotristat etiprate) in patients with symptomatic carcinoid syndrome. As mentioned in Section 2.1.1, the Agency recommended further analysis of Study 202 results to evaluate the proposed 30% response threshold for stool counts (proposed as an exploratory endpoint); however, this recommendation was not implemented by the applicant. In this NDA submission, the applicant submitted data from the single pivotal trial Study 301 and the companion trial Study 303. The purpose of Study 301 was to evaluate the efficacy and safety of Xermelo (telotristat etiprate) at two treatment dose levels versus placebo in patients whose diarrhea associated with carcinoid syndrome was not well-controlled by the stable dose of SSA therapy. Study 303 was designed as a companion study to the pivotal Study 301 to provide confirmation of the pharmacodynamics (PD) effect, safety, and efficacy of Xermelo (telotristat etiprate) in a broader patient population. An overview of the relevant trials is presented in Table 1. It should be noted that all randomized patients were included in the intent-to-treat (ITT) analysis population for both Studies 301 and 303, and the ITT population was used for the primary efficacy analyses. The psychometric evaluation of the meaningful change threshold was based solely on the ITT population in Study 301. The applicant did not conduct a psychometric study for Study 303. In addition, the applicant did not submit any data to support the proposed 30% response threshold for Study 303.

Table 1: List of Relevant Clinical Studies

Study ID	Phase and Design	Study Population	Treatment Arms	Number of Subjects	Duration
LX1606.1-202-CS	Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Ascending, Multidose	Age ≥18 years, males and females of childbearing potential agreed to the use of an adequate contraception method during the study and for 30 days after the last follow-up visit, biopsy-proven metastatic carcinoid tumor with confirmed disease extent, refractory to octreotide therapy, and ability and willingness to provide written informed consent	Three times daily: • Placebo • 150 mg • 250 mg • 350 mg • 500 mg	Placebo: 5 150 mg: 3 250 mg: 3 350 mg: 3 500 mg: 9	Treatment period: 28 days Optional open-label extension period: 8 weeks Addition optional open-label extension period: 172 weeks
LX1606.301	Phase 3, Randomized, Placebo-controlled, Parallel-group, Multicenter, Double-blind	Age ≥18 years, well-differentiated metastatic neuroendocrine tumor, diarrhea associated with carcinoid syndrome, on stable dose of SSA therapy for at least 3 months, and ≥4 daily BMs	Three times daily: • Placebo • 250 mg • 500 mg	Placebo: 45 250 mg: 45 500 mg: 45	Treatment period: 12 weeks Open-label extension period: 36 weeks
LX1606.303		Age ≥18 years, well-differentiated metastatic neuroendocrine tumor, carcinoid syndrome, if on SSA therapy • <4 daily BMs, **AND** • At least one of: poor stool consistency, abdominal pain, nausea, flushing, or elevated u5-HIAA If not on SSA therapy • ≥4 daily BMs, **OR** • At least one of: poor stool consistency, abdominal pain, nausea, flushing, or elevated u5-HIAA		Placebo: 26 250 mg: 25 500 mg: 25	

Source: Reviewer's table

Reference ID: 4019904

2.2 Data Sources

This reviewer evaluated the applicant's Study 301 psychometric report, datasets, and proposed labeling. This submission was submitted in eCTD format and entirely electronic. The applicant's original NDA submission including the datasets is stored at the following location: \\CDSESUB1\evsprod\NDA208794\0001\m5. During the review, the FDA requested the applicant to submit additional correlation analyses, scatter plots, empirical probability density function (EPDF) plots, empirical cumulative distribution function (ECDF) plots, exact copies of all study instruments, and the Patient Exit Interview Sub-study dataset. The applicant's subsequent submissions are stored at the following locations: \\CDSESUB1\evsprod\NDA208794\0017\m5, \\CDSESUB1\evsprod\NDA208794\0031\m5, \\CDSESUB1\evsprod\NDA208794\0035\m5, and \\CDSESUB1\evsprod\NDA208794\0038\m1.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This reviewer replicated the applicant's analyses for the psychometric evaluation of a response threshold for Study 301. During the review, additional analyses and patient exit interview dataset were requested through information requests. Overall, the data and the analysis quality of this NDA submission were determined to be acceptable for the psychometric study review. For the data and analysis quality related to the statistical evaluation of efficacy and safety, please refer to the review of Dr. George Kordzakhia, the primary statistical reviewer for this NDA submission. For the analysis quality related to the Patient Exit Interview Sub-study in Study 301, please refer to the review of Dr. Wen-Hung Chen, the Clinical Outcome Assessments (COA) Staff reviewer for this NDA submission.

3.2 Psychometric Evaluation of PRO Measure

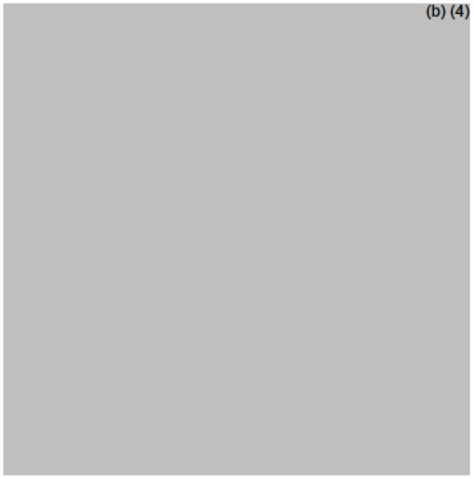
Study 301 (n = 135) and Study 303 (n = 76) were designed to enroll and randomize patients in an approximately 1:1:1 ratio to 250 mg three times daily, 500 mg three times daily, or placebo three times daily study arm. Patients administered the study drug orally three times daily for 12 weeks. The primary endpoint of Study 301 was the change from baseline in the number of daily BMs averaged over the 12-week treatment period. The primary endpoint for Study 303 was the percent (%) change from baseline in the 24-hour u5-HIAA levels (a biomarker) at Week 12. The primary endpoint of Study 301 was one of the six secondary endpoints of Study 303; however, Study 303 did not have a pre-specified multiplicity adjustment for testing the secondary endpoints. This review focuses on the psychometric evaluation of the applicant's proposed meaningful change threshold for Study 301, with this reviewer's post-hoc evaluation of the potential generalizability of the Study 301 results to the Study 303 patient population.

Reference ID: 4019904

3.2.1 Daily Bowel Movement Frequency

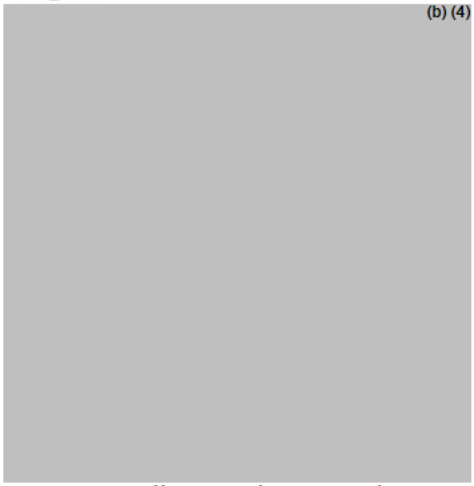
The applicant's PRO measure was a single item with a recall period of 24 hours that asked patients to report the number of BMs they had via an electronic diary. Figure 1 below provides a screen shot of the electronic PRO (ePRO) measure—Daily Bowel Movement Frequency, from the Study 301 clinical study report (CSR). Patients were asked to confirm their responses before moving onto the next item in the diary. Figure 2 shows the confirmation screen from the electronic diary after a response has been entered for the BM frequency item.

Figure 1: Daily Bowel Movement Frequency



Source: Applicant's DiaryPro Patient Screen Shots.pdf of the Study 301 CSR

Figure 2: Confirmation Screen of BM Frequency



Source: Applicant's DiaryPro Patient Screen Shots.pdf of the the Study 301 CSR

3.2.2 Patient Exit Interview Subpopulation

A double-blind (interviewer and patients), semi-structured telephone exit interview was conducted for a subset of Study 301 patients at the end of the treatment period. Patients included in the exit interview had either completed or withdrawn from the 12-week treatment period.

Table 2 below provides a comparison of the baseline characteristics between the exit interview subpopulation and the Study 301 overall patient population. Although the patient exit interview subpopulation only consisted of 35 (26%) patients, the baseline characteristics of the participants were comparable to the baseline characteristics of the overall Study 301 population. Despite the small sample size in the exit interview subpopulation, the comparability between the two populations provides some confidence for this reviewer on including information from the patient exit interview in the later psychometric evaluation of a meaningful change for the primary efficacy endpoint of Study 301. However, any inferences based on the patient exit interview results should be taken with caution due to the small sample size.

Table 2: Baseline Characteristics: Exit Interview Subpopulation vs. Overall Population

Patient Characteristics	Exit Interview Subpopulation (n = 35)	Study 301 Overall Population (n = 135)
Age (mean)	62	64
Female (%)	51	48
White (%)	97	90[a]
Baseline Body Mass Index (BMI)[b]	26	25
Baseline BM Frequency (BM/day)	5.76	5.70
Average BM Frequency Reduction Over 12 Weeks (BM/day)	-1.11	-1.17

Source: Reviewer's table (modified based on applicant's Table D-1 of Patient Reported Outcome Substudy.pdf of the Study 301 CSR)

[a] Race data were missing for 11 out of 135 overall patients.

[b] Baseline BMI data were missing for 4 out of 35 exit interview patients and 17 out of 135 overall patients.

3.2.3 Other Study Instruments

In Study 301 three PROs (in addition to the Daily Bowel Movement Frequency ePRO described in Section 3.2.1) were administered to the overall study population. Data from three additional COAs (two PROs and a version of a clinician-reported outcome) were collected as part of the Study 301 Patient Exit Interview Sub-study mentioned in Section 3.2.2. These six additional measures served as potential anchors for the psychometric evaluation of the applicant's proposed meaningful change threshold for Study 301. An anchor is an external tool or instrument that measures similar concepts; to be useful an anchor should be easier to interpret than the primary COA measure. Anchors can be used to facilitate the interpretation of change in the primary COA measure score. For Study 303, patient exit interviews were not conducted. The three PROs (in addition to the Daily Bowel Movement Frequency ePRO described in Section 3.2.1) administered to the overall population in Study 301 also were administered in Study 303.

EORTC QLQ-C30 Version 3.0

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire (EORTC QLQ-C30) Version 3.0 is a PRO measure that contains 30 items that measure health-related quality of life in patients with cancer. Fifteen domains from three general categories are covered by the EORTC QLQ-C30: global quality of life, physical functioning, role functioning, emotional functioning, social functioning, cognitive functioning, pain, fatigue, nausea and vomiting, appetite loss, constipation, diarrhea, dyspnea,

Reference ID: 4019904

insomnia, and financial difficulties. The EORTC QLQ-C30 instrument has a transformed score ranging from 0 to 100 for each of the 15 domains. All 30 items from the EORTC QLQ-C30 instrument were administered to all study patients at Day 1, Week 6, and Week 12 study visits during the treatment period in both Study 301 and Study 303.

The recall period and possible response options vary among the EORTC QLQ-C30 items.
Global health status

- Global quality of life (2 items): during the past week; seven response options ranging from "very poor" to "excellent"

Functional scales

- Physical functioning (5 items): no specified recall period; response options are "not at all," "a little," "quite a bit," and "very much."

The following domains all have a recall period of "during the past week" and response options of "not at all," "a little," "quite a bit," and "very much."

- Role functioning (2 items)
- Emotional functioning (4 items)
- Social functioning (2 items)
- Cognitive functioning (2 items)

Symptom scales
The following domains all have a recall period of "during the past week" and response options of "not at all," "a little," "quite a bit," and "very much."

- Pain (2 items)
- Fatigue (3 items)
- Nausea and vomiting (2 items)
- Appetite loss (1 item)
- Constipation (1 item)
- Diarrhea (1 item)
- Dyspnea (1 item)
- Insomnia (1 item)
- Financial difficulties (1 item)

<u>EORTC GI.NET21</u>
The EORTC gastrointestinal neuroendocrine tumors (EORTC GI.NET21) questionnaire is a disease-specific module (out of 20 available modules) of the EORTC QLQ-C30 instrument. It should be noted that all 20 disease-specific modules are developed to be used in conjunction with the QLQ-C30 and not to be used alone. The EORTC GI.NET21 is a PRO measure that contains 21 items measuring health-related quality of life in cancer patients with GI-related neuroendocrine tumors. Nine domains are covered by the EORTC GI.NET21: endocrine symptoms, GI symptoms, treatment-related symptoms, social function, disease-related worries, muscle and/or bone pain, sexual function, information, and body image. The EORTC GI.NET21 instrument also has a transformed score ranging from 0 to 100 for each of the nine domains. All 21 items from the EORTC GI.NET21 instrument were administered to all study patients at Day

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1, Week 6, and Week 12 study visits during the treatment period in both Study 301 and Study 303.

The recall period and possible response options vary among the EORTC GI.NET21 items. The following domains all have a recall period of "during the past week" and response options of "not at all," "a little," "quite a bit," and "very much."

- Endocrine symptoms (3 items)
- GI symptoms (5 items)
- Treatment-related symptoms (3 items): the side-effects and problem from repeated injections items have an extra response option of "N/A."
- Social function (3 items)
- Disease-related worries (3 items): the results of tests item has an extra response option of "N/A."
- Muscle and/or bone pain (1 item)
- Body image (1 item)

The following two domains all have a recall period of "during the past four weeks" and response options of "not at all," "a little," "quite a bit," and "very much."

- Information (1 item)
- Sexual function (1 item): this item has an extra response option of "N/A."

Adequate Relief of CS Symptoms Associated with GI Symptoms

The applicant's subjective global assessment of adequate relief of CS symptoms associated with GI symptoms PRO measure was a single item with a recall period of seven days that asked patients to report whether they had adequate relief of CS symptoms via the same electronic diary used to collect the primary PRO measure (i.e., Daily BM Frequency). The binary response options were "yes" and "no." Figure 3 below provides a screen shot of the adequate relief of CS symptoms associated with GI symptoms ePRO measure. The adequate relief item was administered to all study patients on a weekly basis during the treatment period in both Study 301 and Study 303. The applicant's Study 301 psychometric report stated that "*for adequate relief, patients were categorized by change from 'no' to 'yes' from baseline to Week 12*."

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Figure 3: Subjective Global Assessment of Adequate Relief

Source: Applicant's DiaryPro Patient Screen Shots.pdf of the Study 301 CSR

Patient Perception of Change in BMs

The patient perception of change in BMs was a single PRO measure from the patient exit interview. This item asked the patients to report their perception of the number of BMs since they started the study medication at the time of the exit interview. The possible response options were "a great deal better," "much better," "a little better," "the same," "a little worse," "much worse," and "a great deal worse," with higher scores indicating greater improvements in patient perception of change in BMs. The patient perception of change in BMs item was administered to the subset of patients enrolled in the Patient Exit Interview Sub-study, which was conducted at the end of the treatment period in Study 301.

Patient Satisfaction with Study Medication—Relief of CS Symptoms

The patient overall satisfaction with study medication—relief of CS symptoms was a single PRO measure from the patient exit interview. This item asked the patients to report their overall satisfaction with how the study medication relieved their CS symptoms. The possible response options were "very satisfied," "somewhat satisfied," "neither satisfied nor dissatisfied," "somewhat dissatisfied," and "very dissatisfied," with higher scores indicating greater satisfaction with how the study medication relieved patients' CS symptoms. The patient satisfaction with study medication—relief of CS symptoms item was administered to the subset of patients enrolled in the Patient Exit Interview Sub-study, which was conducted at the end of the treatment period in Study 301.

Clinician-Rated Patient Reported Meaningful Change in BMs

The patient reported meaningful change in BMs was a version of clinician-reported outcome (ClinRO) measure. During the double-blind, semi-structured interview, patients were asked about symptom changes in a general manner, including patients' perception of the clinical relevance of a reduction in BM frequency. The interview was conducted in an open-ended format without pre-specified response options; therefore, the patients were allowed to speak freely using their own words. Based on the patient' response, the clinical interviewer made an interpretation and provided a score of either "yes" or "no." The clinician-rated patient reported

meaningful change in BMs item was administered to the subset of patients enrolled in the Patient Exit Interview Sub-study, which was conducted at the end of the treatment period in Study 301.

Although the applicant used six additional measures as anchors for the psychometric evaluation of the meaningful change in Study 301, this reviewer deemed that only four measures may be considered as potential anchors; ultimately only one of these four measures was considered a reasonable standalone anchor.

The two EORTC instruments are not considered in this review due to concerns over score interpretability and the broad concepts measured by the instruments. In the 2009 *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, it is clearly stated that "to be useful, the anchors chosen should be easier to interpret than the PRO measure itself" (p. 25). With the exception of the diarrhea domain in EORTC QLQ-C30, all the rest of the domains in both the QLQ-C30 and GI.NET21 instruments are harder to interpret than the applicant's primary PRO measure (i.e., Daily BM Frequency). The majority of the domains measure much broader concepts in comparison to the primary PRO measure (e.g., global health status in QLQ-C30 or GI symptoms in GI.NET21). The QLQ-C30 diarrhea domain consists of a single item, "during the past week, have you had diarrhea?"

The appropriateness of the clinician-rated patient reported meaningful change in BMs item also needs to be further evaluated, as patients' responses were coded (i.e., yes/no) based on the clinical interviewer's interpretation and not directly captured from the patients. For a more detailed review of the Study 301 Patient Exit Interview Sub-study, please refer to the review of Dr. Wen-Hung Chen, the COA Staff reviewer for this NDA submission.

3.2.4 Statistical Methodologies

As previously mentioned in Section 2.1.2, the psychometric evaluation of the applicant's proposed meaningful change threshold was based on the ITT population in Study 301. The psychometric study statistical analysis plan (SAP) specified that analyses were to be conducted for the absolute (raw) change from baseline in overall BMs (averaged over 12 weeks). The SAP specified that correlation analyses were used to examine the strength and magnitude of relationship between the primary PRO measure and potential anchors. The applicant used both Pearson's product-moment correlation coefficients and Spearman's rho for interval or multi-item ordinal subscales to evaluate the relationship between daily BM frequency and the domains from the two EORTC instruments. The SAP specified that the threshold for consideration as an anchor was a correlation coefficient > 0.30 at baseline, Week 12, or change from baseline. The review of the correlation analyses focuses on the primary endpoint, which was the change from baseline in overall BMs averaged over 12 weeks. As mentioned in Section 3.2.3, this reviewer does not consider the two EORTC instruments as acceptable anchors. Thus, the Agency requested additional biserial correlation analyses for daily BM frequency vs. subjective global assessment of adequate relief of CS symptoms associated with GI symptoms, and daily BM frequency vs. clinician-rated patient reported meaningful change in BMs; polyserial correlation analyses for daily BM frequency vs. patient perception of change in BMs, and daily BM frequency vs. patient overall satisfaction with study medication—relief of CS symptoms. It should be noted that

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correlation analyses are helpful in examining the appropriateness of selected anchors; however, correlations should not be used as the sole criterion for anchor selection.

An anchor-based approach was used to evaluate meaningful change in daily BMs frequency for patients on Xermelo (telotristat etiprate). The SAP specified that anchor-based thresholds were determined using the mean change and the associated effect size (ES) for each anchor-based group of patients. The ES was specified to be calculated as the change from baseline in the number of BMs averaged over the 12 week of treatment period divided by the standard deviation of the average baseline BM frequency. The SAP specified cutoffs for ES where small, moderate, and large changes were indicated by 0.2, 0.5, and 0.8, respectively. During the review, the Agency requested the applicant to provide empirical probability density function (EPDF) plots and empirical cumulative distribution function (ECDF) plots by anchor category for the four potential anchors (i.e., adequate relief, perception of change in BMs, satisfaction with study medication, and clinician-rated patient reported meaningful change in BMs). A potential range for the meaningful change can be derived from ECDF plots (e.g., using median change, 25th percentile change, 75th percentile change). The EPDF plots were requested as they are useful in aiding the interpretation of ECDF plots. EPDF plots provide an overview of the center, spread, and shape (e.g., dispersion and/or skewness) of the distribution of the primary PRO measure across various anchor categories.

The SAP also specified that a distribution-based threshold was determined using the ½ standard deviation (SD) rule, which was ½ the SD of the change from baseline in overall BMs. According to the 2009 *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, distribution-based approach should be considered as supportive to anchor-based estimates to provide confidence in the responder definition.

3.2.5 Patient Compliance and Baseline Characteristics

The ITT population in Study 301 included a total of 135 patients at baseline and the overall 12-week treatment period. All 135 (100%) patients had available change from baseline in overall BMs data. Among the 135 patients, 35 (26%) patients were recruited for the Patient Exit Interview Sub-study.

Because a psychometric study was not conducted for Study 303, this reviewer explored a post-hoc evaluation of the potential generalizability of the Study 301 results to the Study 303 patient population. For Study 301, all patients were required to meet the following entry criteria:

- Age ≥18 years
- Well-differentiated metastatic neuroendocrine tumor
- Diarrhea associated with carcinoid syndrome
- On stable dose of SSA therapy for at least 3 months
- An average of ≥4 daily BMs at baseline

For Study 303, all patients were required to meet the following entry criteria. In addition, patients who previously were screened for Study 301 and did not meet the entry criteria also might be eligible for Study 303.

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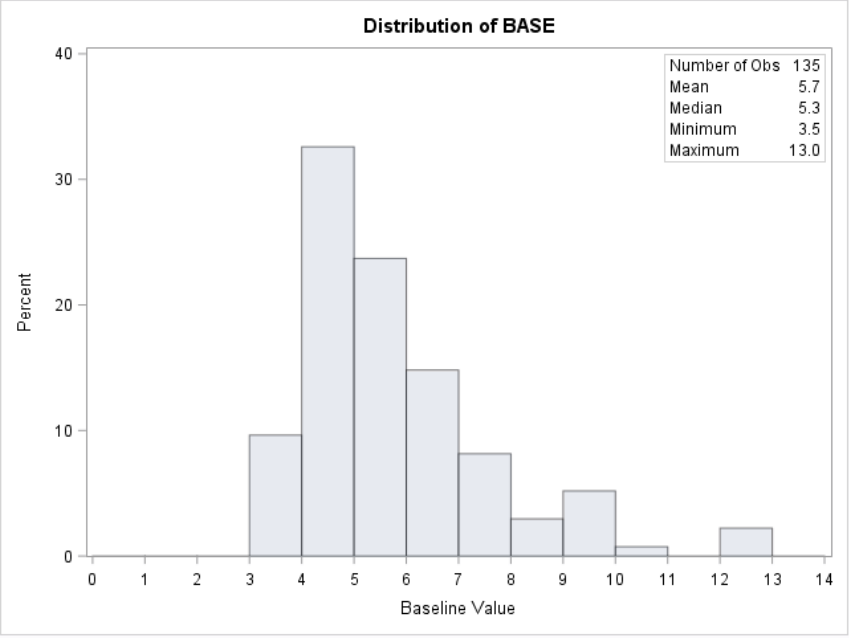
- Age ≥18 years
- Well-differentiated metastatic neuroendocrine tumor
- Carcinoid syndrome
- If on stable dose of SSA therapy for at least 3 months
    - An average of <4 daily BMs at baseline, **AND**
    - At least one of the following: poor stool consistency, abdominal pain, nausea, flushing, or elevated u5-HIAA
- If not on SSA therapy
    - An average of ≥4 daily BMs at baseline, **OR**
    - At least one of the following: poor stool consistency, abdominal pain, nausea, flushing, or elevated u5-HIAA

Figure 4 and Figure 5 below show the distribution of the baseline BMs for all patients in Study 301 and Study 303, respectively. The histograms indicate that Study 301 patients had much more diarrhea at baseline than Study 303 patients had. The majority (93%) of the Study 303 patients had <4 BMs at baseline (without considering at least 1 of the signs/symptoms of CS). The patient populations of Studies 301 and 303 differ from each other based on the above mentioned entry criteria and baseline BMs; therefore, this reviewer does not recommend generalizing the meaningful change results from Study 301 to the Study 303 patient population.

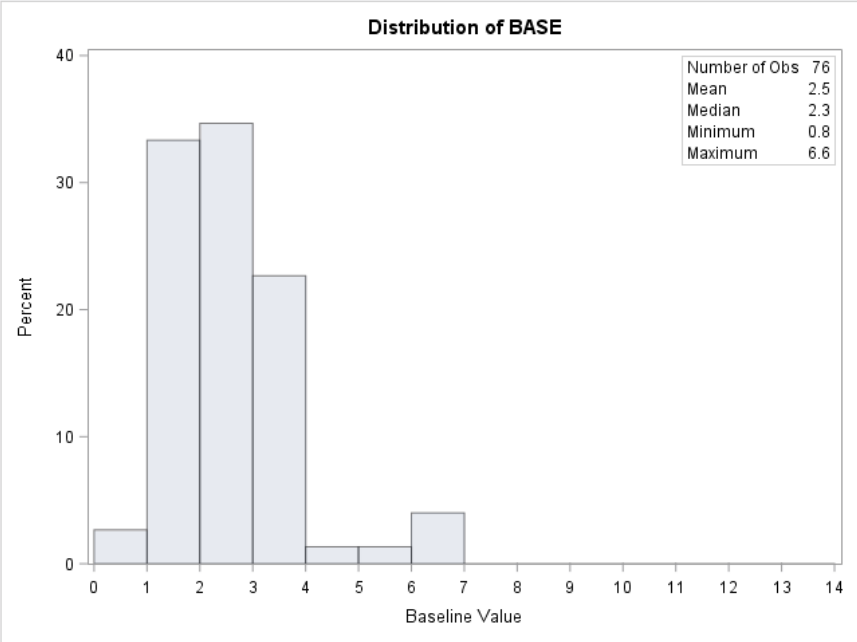
For overall patient disposition, demographics, and other baseline characteristics in Study 301 and Study 303, please refer to the review of Dr. George Kordzakhia, the primary statistical reviewer for this NDA submission.

Figure 4: Study 301 Patient Baseline Bowel Movements



Source: Reviewer's figure

Figure 5: Study 303 Patient Baseline Bowel Movements



Source: Reviewer's figure

3.2.6 Results and Conclusions

Sample sizes varied among the different anchors due to missing data and exclusion of patients for specific analyses (described below); however, the psychometric SAP did not pre-specify the inclusion/exclusion criteria for analyses. As previously mentioned in Section 3.2.3, the applicant's Study 301 psychometric report stated that "*for adequate relief, patients were categorized by change from 'no' to 'yes' from baseline to Week 12*." Among the 113 patients (out of a total of 135 patients) that had available adequate relief data at both baseline and Week 12, 19 patients had a score change from "no" at baseline to "yes" at Week 12 (i.e., responder); 75 patients had a score of "no" at baseline and remained as "no" at Week 12 (i.e., non-responder); 16 patients had a score of "yes" at baseline and remained as "yes" at Week 12 (excluded from meaningful change analyses); and 3 patients had a score change from "yes" at baseline to "no" at Week 12 (excluded from meaningful change analyses). In addition, one patient was excluded from related analyses due to missing the patient perception of change in BMs item. Two patients were excluded from related analyses for missing the satisfaction with study medication—relief of CS symptoms item.

The results for the clinician-rated patient reported meaningful change in BMs item were further filtered based on the results of the perception of change in BMs item, where the applicant included only patients who reported their perception of change in BMs as either "a great deal better," "much better," "a little better," or "the same." The inclusion criteria were clarified through an information request to the applicant during the review. As a result, in order to replicate the applicant's analyses, three patients were excluded, one for missing a response to the meaningful change in BMs item, one for missing a response to the patient perception of change in BMs item, and one for reporting "a little worse" to the patient perception of change in BMs

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item. All patients who reported "the same" for their perception of change in BMs were coded as "no" for meaningful change in BMs by the clinical interviewer.

Table 3 provides a summary of correlations for the absolute change from baseline in overall BM frequency with the four anchors. As expected, negative correlations are observed as smaller negative values of the absolute change indicate greater reduction in overall BM frequency from baseline. Results indicate that three of the four potential anchors exceeded the psychometric SAP specified acceptability threshold of > 0.30 for the absolute change from baseline in overall BM frequency. The clinician-rated patient reported meaningful change in BMs has a slightly lower correlation with the primary endpoint of Study 301. It should be noted that the overall relatively modest correlation results were expected as the assessment time frame for the four anchors differed from the assessment time frame of the primary efficacy endpoint (i.e., averaged over the 12-week treatment period). As mentioned in Section 3.2.3, a responder for subjective global assessment of adequate relief was defined as a patient who reported adequate relief at Week 12; and all three anchors from the patient exit interview were administered at the end of the treatment period in Study 301.

Table 3: Summary of Correlations for Absolute Change from Baseline in Overall BM Frequency with Other Study Anchors

		Absolute Change from Baseline in Overall BM Frequency	
Anchors	**n**	**Biserial Correlation**	**Polyserial Correlation**
Subjective Global Assessment of Adequate Relief	94	-0.31	n/a
Patient Perception of Change in BMs	34	n/a	-0.57
Satisfaction with Study Medication—Relief of CS Symptoms	33	n/a	-0.48
Clinician-rated Patient Reported Meaningful Change in BMs	32	-0.23	n/a

Source: Reviewer's table

Table 4 provides a summary of the meaningful change thresholds for the absolute change using different criteria such as the mean change, effect size, median change, 25th percentile change, and the 75th percentile change. The median change refers to the location where the median line (corresponding to a cumulative 50% of patients) intersects with the ECDF curve of a particular anchor category. The 25th percentile and the 75th percentile can provide a sense of variability in the distribution of each anchor category. Figures 6 to 13 show the associated EPDF plots and ECDF plots of the absolute change in overall average BM frequency from baseline, stratified by various anchors. All figures are presented in the order of subjective global assessment of adequate relief, patient perception of change in BMs, satisfaction with study medication—relief of CS symptoms, and clinician-rated patient reported meaningful change in BMs. It should be noted that all results presented in Table 4 and Figures 6 to 13 were based on pooled data from all treatment arms.

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The EPDF plots show that the distribution of the absolute change in overall average BM frequency across the various anchor categories are shifted to the left, indicating a reduction of BMs (with some placebo effects observed). Among the four anchors, subjective global assessment of adequate relief has a more visible separation between the two EPDF curves. This reviewer recommends that the subjective global assessment of adequate relief anchor should carry more weight in making a determining range for the meaningful change thresholds. A large amount of overlapping among the EPDF curves is observed for the three anchors from the patient exit interview. As mentioned in Section 3.2.2, only 35 patients were included in the exit interview subpopulation. The pattern observed in these EPDF plots may indicate that patients could not well distinguish among the various anchor categories, or the overlapping pattern is due to the small sample size. Although the anchors chosen from the patient exit interview may not be the optimal anchors, they still can provide useful information.

In Table 4, for the subjective global assessment of adequate relief anchor, the median change suggests a reduction of approximately at least 2 BMs/day as meaningful to patients who reported adequate relief at Week 12. For patient perception of change in BMs, a median change of a reduction of at least 2 BMs/day is meaningful to patients who reported "a great deal better." There are some ambiguities among the responses of "much better," "a little better," and "the same." Only four patients reported "much better"; therefore, the small sample size hinders the extent of inference that can be made based on the data. The "a little better" and "the same" categories each had 10 patients reporting; however, what patients consider as a meaningful change for these two anchor categories contradicts each other. Patients who reported "a little better" consider a reduction of 0.5 BM/day as meaningful, whereas a reduction close to 1 BM/day is considered to be meaningful to patients who reported "the same." Similar ambiguities also are presented with the satisfaction with study medication—relief of CS symptoms anchor. The median change for patients who reported "neither satisfied nor dissatisfied" is close to -1 BM/day, which is higher than the median change for patients who reported "somewhat satisfied." For patients who reported "very satisfied," the median change suggests a reduction of at least 2 BMs/day as meaningful to patients. Finally, the clinician-rated patient reported meaningful change in BMs anchor provides contradictory information as the numerical difference between the median changes for the "Yes" and "No" categories is negligible with both suggesting a reduction of at least 1 BM/day.

Based on the totality of information from four potential anchors and using both anchor-based and distribution-based approaches, a suggested range for meaningful change threshold is a reduction of at least 2 BMs/day in overall average BM frequency. The suggested absolute change differs from the applicant's proposed threshold of -0.87 BM/day (≈ -0.9 BM/day),which was selected based on effect size and also corresponded to the "much better" category for patient perception of change in BMs. As mentioned previously, there were only four patients in this anchor category upon whom to base a conclusion.

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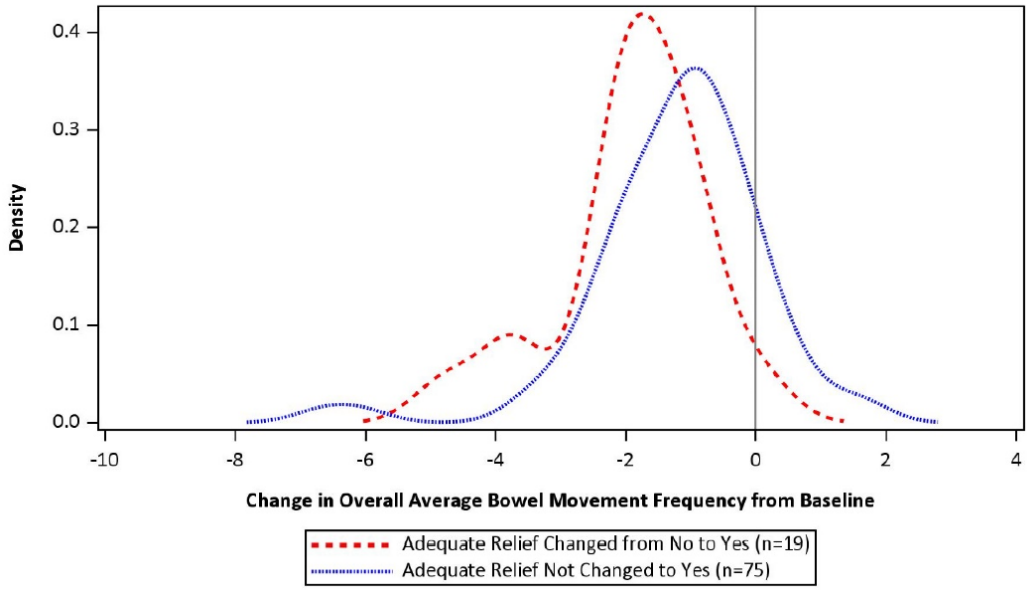
Table 4: Summary of Meaningful Change Thresholds (Absolute Change)

	Overall Average BM Frequency				
	n	**Mean Change**	**Effect Size**	**Median Change**	**25th, 75th Percentile**
Anchor-based Threshold					
Subjective Global Assessment of Adequate Relief					
Changed to Yes at Week 12	19	-1.9	-1.2	-1.8	-2.2, -1.1
Not Changed to Yes at Week 12	75	-1.2	-0.6	-1.0	-1.9, -0.5
Patient Perception of Change in BMs					
A great deal better	9	-2.5	-1.6	-2.0	-3.2, -1.2
Much better	4	-0.9	-1.5	-0.7	-1.3, -0.4
A little better	10	-0.4	-0.2	-0.5	-0.8, -0.2
The same	10	-1.0	-0.5	-0.9	-1.6, -0.5
A little worse	1	0.6	n/a	0.6	0.6, 0.6
Much worse	0	n/a	n/a	n/a	n/a
A great deal worse	0	n/a	n/a	n/a	n/a
Satisfaction with Study Medication—Relief of CS Symptoms					
Very satisfied	12	-2.1	-1.3	-1.9	-2.7, -0.9
Somewhat satisfied	7	-0.3	-0.2	-0.5	-0.6, -0.2
Neither satisfied nor dissatisfied	8	-0.8	-0.4	-0.9	-1.2, -0.6
Somewhat dissatisfied	3	-0.4	-1.2	-0.8	-1.2, 0.8
Very dissatisfied	3	-0.9	-0.4	-0.9	-2.5, 0.6
Clinician-rated Patient Reported Meaningful Change in BMs					
Yes	20	-1.4	-1.0	-1.0	-2.0, -0.5
No	12	-0.9	-0.4	-0.9	-1.4, -0.5
Distribution-based Threshold					
½ Change from Baseline SD	135	-0.62	n/a	n/a	n/a

Source: Reviewer's table

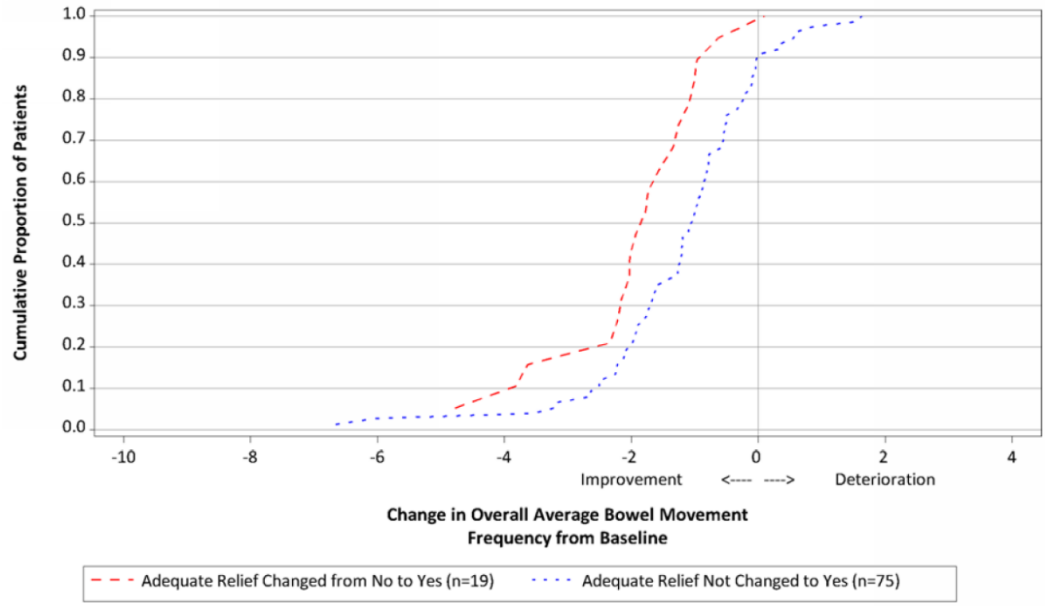
Reference ID: 4019904

Figure 6: EPDF of Absolute Change in Overall Average BM Frequency from Baseline Stratified by Subjective Global Assessment of Adequate Relief



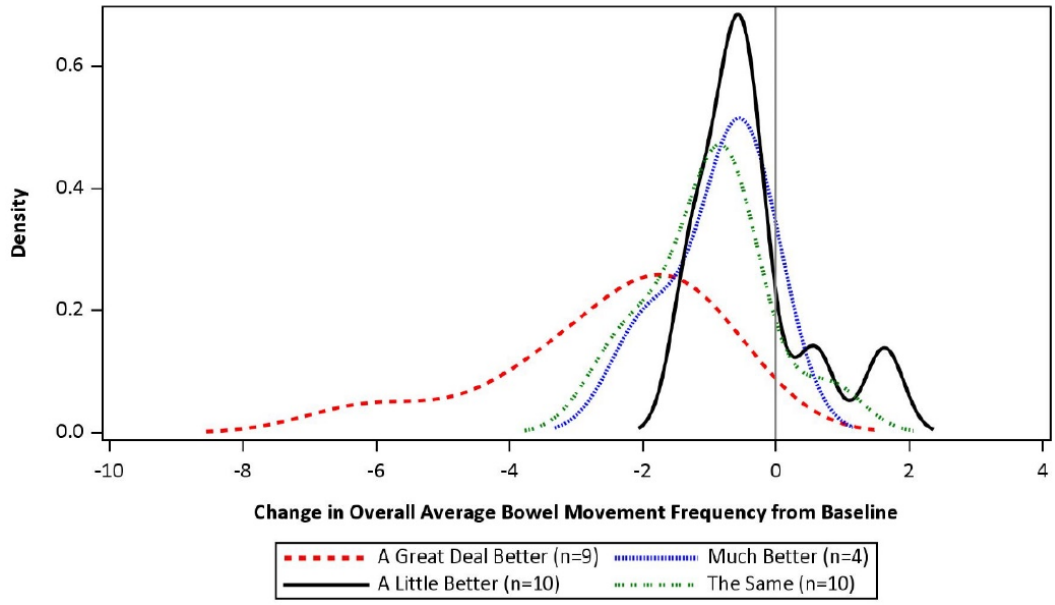
Source: Figure 4.2.3 from applicant's response to 06/28/2016 information request (IR)

Figure 7: ECDF of Absolute Change in Overall Average BM Frequency from Baseline Stratified by Subjective Global Assessment of Adequate Relief



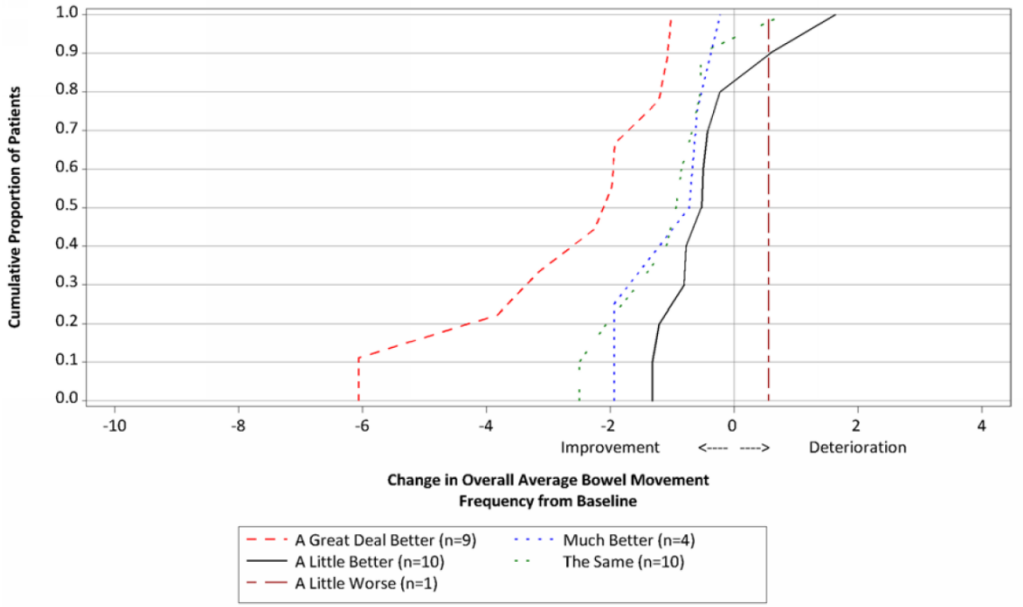
Source: Figure 5.2.3 from applicant's response to 06/28/2016 IR

Figure 8: EPDF of Absolute Change in Overall Average BM Frequency from Baseline Stratified by Patient Perception of Change in BMs



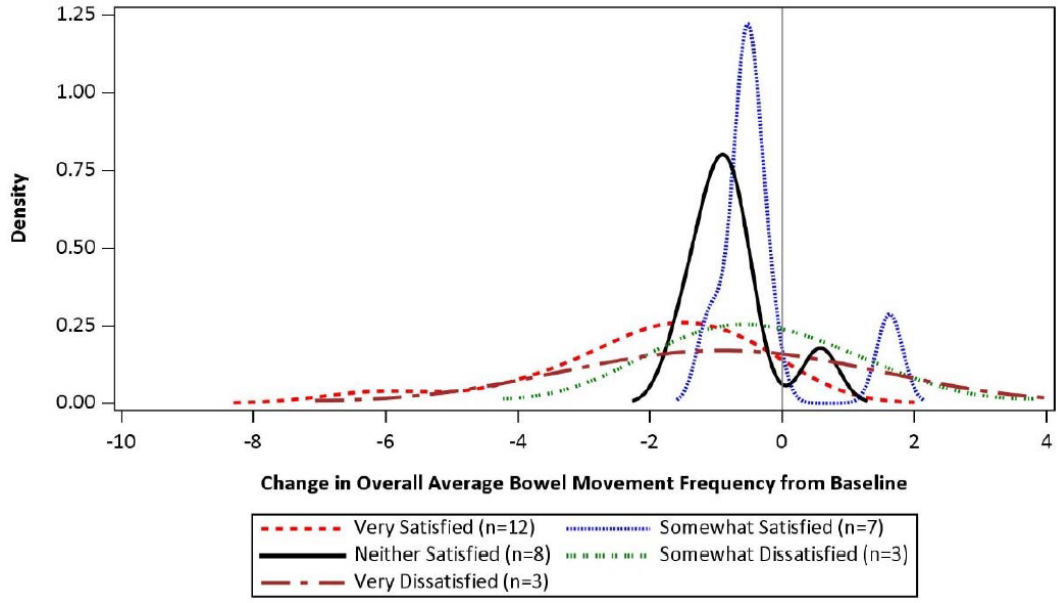
Source: Figure 4.2.4 from applicant's response to 06/28/2016 IR

Figure 9: ECDF of Absolute Change in Overall Average BM Frequency from Baseline Stratified by Patient Perception of Change in BMs



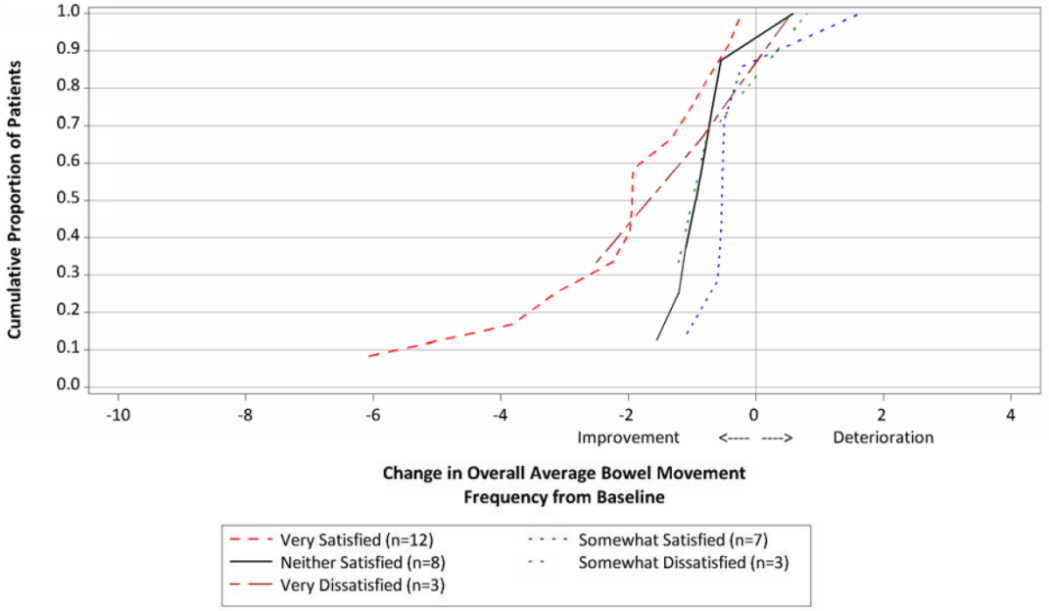
Source: Figure 5.2.4 from applicant's response to 06/28/2016 IR

Figure 10: EPDF of Absolute Change in Overall Average BM Frequency from Baseline Stratified by Patient Satisfaction with Study Medication—Relief of CS Symptoms



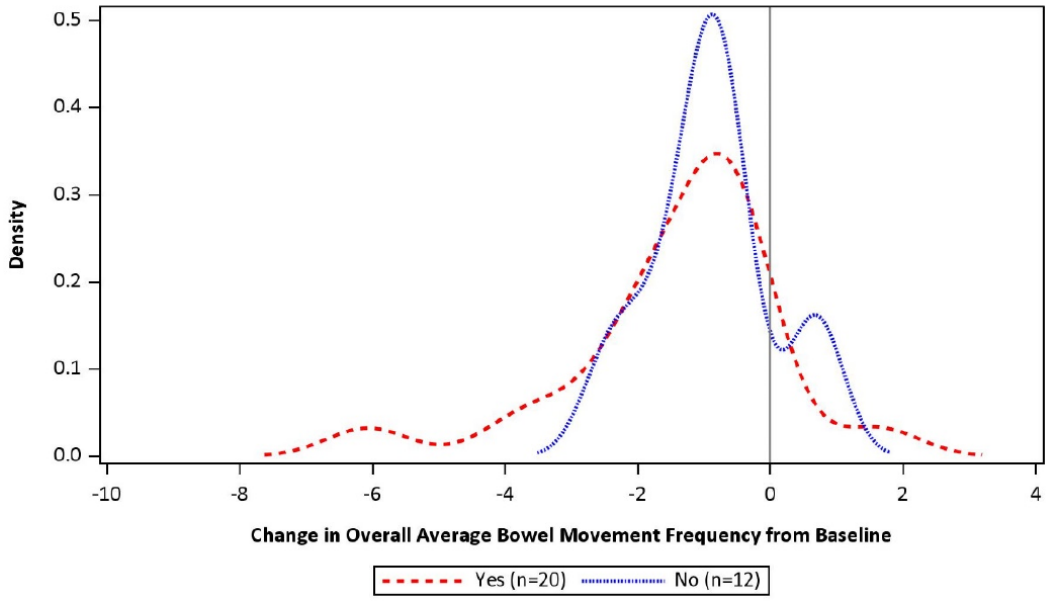
Source: Figure 4.2.6 from applicant's response to 06/28/2016 IR

Figure 11: ECDF of Absolute Change in Overall Average BM Frequency from Baseline Stratified by Patient Satisfaction with Study Medication—Relief of CS Symptoms



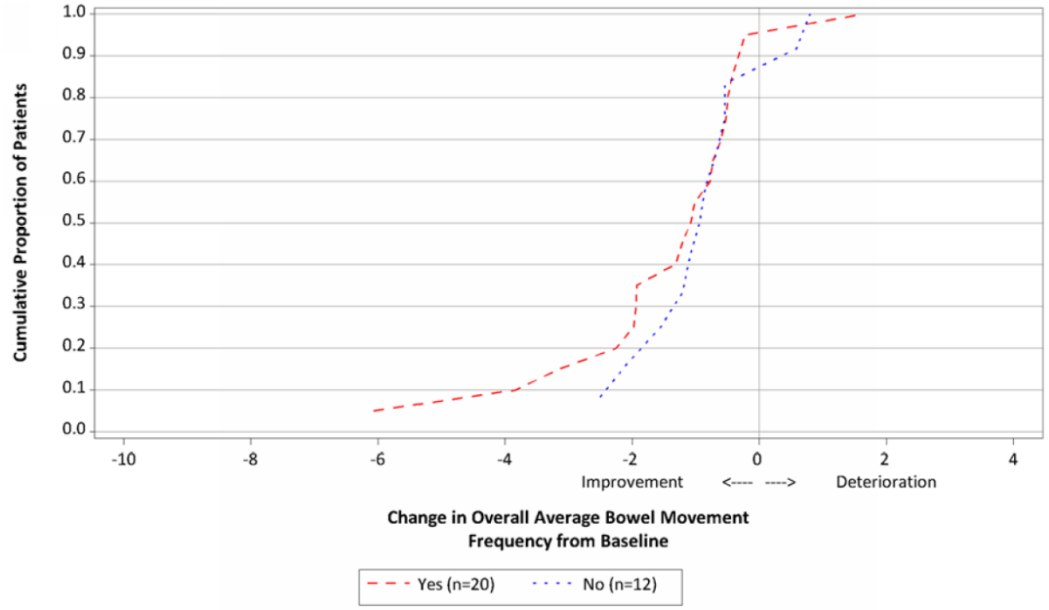
Source: Figure 5.2.6 from applicant's response to 06/28/2016 IR

Figure 12: EPDF of Absolute Change in Overall Average BM Frequency from Baseline Stratified by Clinician-rated Patient Reported Meaningful Change in BMs



Source: Figure 4.2.5 from applicant's response to 06/28/2016 IR

Figure 13: ECDF of Absolute Change in Overall Average BM Frequency from Baseline Stratified by Clinician-rated Patient Reported Meaningful Change in BMs

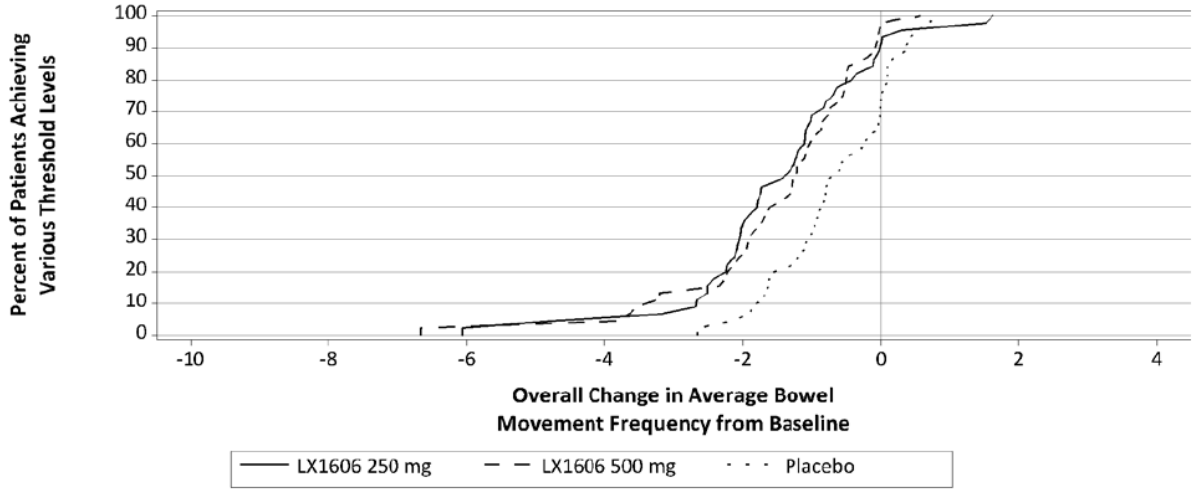


Source: Figure 5.2.5 from applicant's response to 06/28/2016 IR

3.3 Evaluation of Efficacy

For detailed statistical evaluation of efficacy for Xermelo (telotristat etiprate), please refer to the review of Dr. George Kordzakhia. Based on this reviewer's recommendation of a reduction of at least 2 BMs/day, 33% of patients randomized to the 250 mg three times daily arm, 24% of patients randomized to the 500 mg three times daily arm, and 4% of patients randomized to placebo achieved the recommended range of meaningful change thresholds. Figure 14 depicts the ECDF plot of the absolute change in overall average BM frequency from baseline stratified by treatment groups. Although the two treatment arms cross each other, one can still see that there is consistent separation between the treatment arms and the placebo arm along the x-axis. In addition, separation can be observed between the treatment arms and the placebo for both reviewer recommended and applicant proposed meaningful change thresholds.

Figure 14: ECDF of Absolute Change in Overall Average BM Frequency from Baseline Stratified by Treatment (Study 301)



Source: Figure 6 of applicant's LX1606-1-301 COS Psychometric Report.pdf

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

The applicant submitted data from two randomized, placebo-controlled, parallel-group, multicenter, double-blind, Phase 3 trials (Studies 301 and 303). Study 301 served as the single pivotal trial with Study 303 as the companion trial. The primary endpoint of Study 301 was the change from baseline in the number of daily BMs averaged over the 12-week treatment period. The primary endpoint for Study 303 was the percent change from baseline in the 24-hour u5-HIAA levels at Week 12. The primary endpoint of Study 301 was one of the Study 303 secondary endpoints that had no pre-specified multiplicity adjustment. This review focuses on the psychometric evaluation of the applicant's proposed meaningful change threshold for patients in Study 301.

Reference ID: 4019904

In general, it is preferable to finalize the development of a new outcome measure before the initiation of Phase 3 trials. This NDA submission used the same Study 301 data both to demonstrate treatment efficacy and evaluate a meaningful change threshold. This practice is not recommended by the Agency due to concerns related to over-fitting, where the threshold may only be relevant to the current set of patients; and uncertainty remains as to whether the study results can be generalized to other patients with the disease. However, for rare diseases, such as Carcinoid Syndrome in this NDA, a certain degree of flexibility should be exercised based on discussions between the Statistical and Clinical review teams. The issue of generalizability is less of a concern depending on how "rare" a rare disease is.

Other concerns arise from the assessment of the psychometric properties of the primary PRO measure in Study 301. The reliability of the Daily BM Frequency measure was not assessed prior to the implementation of the Phase 3 trials. The selected EORTC anchors were limited by score interpretability and the broad concepts measured by the instruments. The anchors chosen from the patient exit interview were relevant as the items were captured directly from the patients' perspective; however, the small sample size reduced confidence on the amount of statistical inference that can be made from the patient exit interview results.

4.2 Conclusions and Recommendations

Although this statistical reviewer replicated the applicant's analyses results, this reviewer and the applicant came to different conclusions for the meaningful change threshold based on the totality of information. Findings from the Study 301 psychometric evaluation of the meaningful change threshold suggest that a reduction of at least 2 BMs/day in overall average BM frequency from baseline may be potentially meaningful to patients. The applicant stated in their Study 301 psychometric report that a reduction of at least 0.87 BM/day from baseline may be potentially meaningful to patients. A clear separation between the treatment arms and the placebo arm can be observed for both the reviewer and applicant proposed meaningful change thresholds. There is a higher proportion of Xermelo (telotristat etiprate) treated patients compared to placebo patients in the range around this reviewer's recommended meaningful change threshold. However, due to differences in the study populations the meaningful change threshold from Study 301 cannot be generalized to Study 303 patients.

4.3 Labeling Recommendations

The inclusion of (b) (4) the proposed labeling. For additional labeling recommendations for Xermelo (telotristat etiprate), please refer to the review of Dr. George Kordzakhia, the primary statistical reviewer for this NDA submission.

5 APPENDIX

5.1 Post-hoc Exploratory Evaluation of Relative Change in Overall BMs

As mentioned in Section 2.1.1, the applicant proposed a ≥30% reduction of daily BMs as part of the durable response definition (i.e., the proportion of responders with at least 30% daily BM reduction for at least 50% of the time over the double-blind portion of the study) in both Study 301 and Study 303. The durable response endpoint was included in the NDA submission as an exploratory endpoint to support further interpretation of the primary endpoint of Study 301 (i.e., absolute change from baseline in daily BMs averaged over the 12-week treatment period); however, the durable response endpoint was not adjusted for multiplicity. Given that the applicant proposed a ≥30% reduction of daily BMs threshold, this reviewer conducted post-hoc exploratory analyses to evaluate the meaningful change threshold for the relative (percent) change from baseline in daily BMs. During the review, the Agency requested the applicant to repeat all pre-specified analyses for the relative change from baseline in overall BMs. Thus, the statistical methodologies discussed in Section 3.2.4 also apply to the relative change in overall BMs.

Prior to discussing the post-hoc analyses of relative change in overall BMs, it is important to re-iterate that meaningful change threshold results from Study 301 cannot be generalized to Study 303 patient population due to the differences in the two study populations, as discussed in Section 3.2.5. This conclusion can be supported further using the applicant's proposed ≥30% reduction in daily BMs threshold that results in a reduction of approximately ≥ 1.6 BMs from the baseline median of 5.3 BMs in Study 301 as compared to ≥ 0.7 BM from the baseline median of 2.3 BMs in Study 303 (refer to Figures 4 and 5 in Section 3.2.5).

Table 5 below provides a summary of correlations for the relative change from baseline in overall BM frequency with the four anchors. Overall results are similar to those obtained from the absolute change from baseline. However, all four potential anchors exceeded the psychometric SAP specified acceptability threshold of > 0.30, with the clinician-rated patient reported meaningful change in BMs being only slightly larger than the threshold of 0.30.

Table 5: Summary of Correlations for Relative Change from Baseline in Overall BM Frequency with Other Study Anchors

		Relative Change from Baseline in Overall BM Frequency	
Anchors	**n**	**Biserial Correlation**	**Polyserial Correlation**
Subjective Global Assessment of Adequate Relief	94	-0.43	n/a
Patient Perception of Change in BMs	34	n/a	-0.61
Satisfaction with Study Medication—Relief of CS Symptoms	33	n/a	-0.56
Clinician-rated Patient Reported Meaningful Change in BMs	32	-0.33	n/a

Source: Reviewer's table

Table 6 provides a summary of the meaningful change thresholds for the relative change of overall average BM frequency from baseline using different criteria. Note that effect sizes could not be computed due to unavailable baseline standard deviation for the overall percent change from baseline. The corresponding EPDF plots and ECDF plots are displayed in Figures 16 to 23. All figures are presented in the order of subjective global assessment of adequate relief, patient perception of change in BMs, satisfaction with study medication—relief of CS symptoms, and clinician-rated patient reported meaningful change in BMs. It should be noted that all results presented in Table 6 and Figures 16 to 23 were based on pooled data from all treatment arms. The results presented in Table 6 exhibit very similar patterns to the results in Table 4 of Section 3.2.6 for the absolute change of overall average BM frequency from baseline, including similar ambiguities presented with both the perception of change in BMs and satisfaction with study medication anchors. For the subjective global assessment of adequate relief anchor, the median change suggests a reduction of at least 33% of daily BMs as meaningful to patients who reported adequate relief at Week 12. Patients who reported "a great deal better" consider a reduction close to 40% of daily BMs as meaningful. For patients who reported "very satisfied" with how the study medication relieved their CS symptoms, the median change suggests a reduction of 35% of daily BMs as meaningful to patients. There is a larger numerical difference between the median changes for both categories of the clinician-rated patient reported meaningful change in BMs; and patients in the "yes" group consider a reduction of at least 22% of daily BMs to be meaningful.

Using the median changes and the 25th and 75th percentile results, a suggested range for meaningful change threshold is at least 25% to 40% reduction in daily BMs. The suggested range is tighter than the applicant's post-hoc proposed range of 15% to 40% reduction in daily BMs. Based on this reviewer's recommendation, the applicant's proposed ≥30% reduction in daily BMs as a meaningful change threshold appears to be reasonable for the Study 301 patient population. The results also reasonably can be extrapolated to the exploratory endpoint of durable response. However, as was discussed previously, there were no multiplicity strategies to control the Type I error for the exploratory endpoints and the sample sizes were small for most the anchors.

Reference ID: 4019904

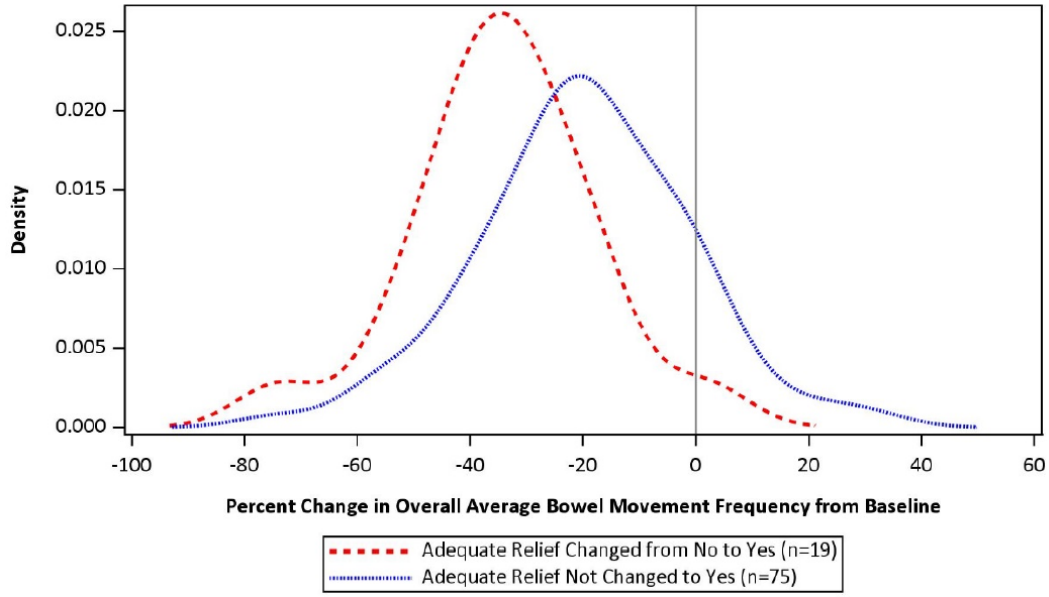
Table 6: Summary of Meaningful Change Thresholds (Relative Change)

	Overall Average BM Frequency			
	n	**Mean % Change**	**Median % Change**	**25th, 75th Percentile**
Anchor-based Threshold				
Subjective Global Assessment of Adequate Relief				
Changed to Yes at Week 12	19	-34.2	-33.3	-42.6, -25.1
Not Changed to Yes at Week 12	75	-19.9	-20.4	-29.5, -7.5
Patient Perception of Change in BMs				
A great deal better	9	-41.2	-39.1	-42.7, -28.7
Much better	4	-20.1	-17.5	-30.2, -9.9
A little better	10	-9.0	-10.2	-19.3, -3.9
The same	10	-15.9	-16.2	-26.4, -12.8
A little worse	1	6.8	6.8	6.8, 6.8
Much worse	0	n/a	n/a	n/a
A great deal worse	0	n/a	n/a	n/a
Satisfaction with Study Medication—Relief of CS Symptoms				
Very satisfied	12	-36.4	-35.0	-42.2, -24.3
Somewhat satisfied	7	-6.2	-8.9	-15.0, -4.7
Neither satisfied nor dissatisfied	8	-14.7	-15.4	-19.7, -11.6
Somewhat dissatisfied	3	-8.7	-16.7	-24.5, 15.1
Very dissatisfied	3	-12.5	-17.9	-26.4, 6.8
Clinician-rated Patient Reported Meaningful Change in BMs				
Yes	20	-25.4	-22.2	-39.8, -10.2
No	12	-14.3	-16.2	-22.9, -11.6
Distribution-based Threshold				
½ Change from Baseline SD	135	-9.40	n/a	n/a

Source: Reviewer's table

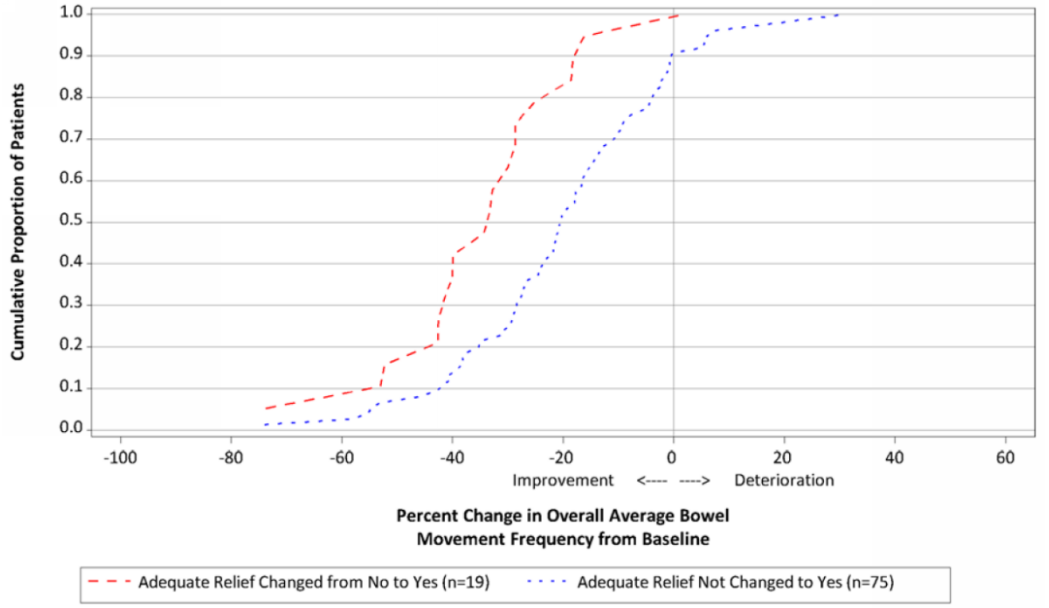
Reference ID: 4019904

Figure 16: EPDF of Relative Change in Overall Average BM Frequency from Baseline Stratified by Subjective Global Assessment of Adequate Relief



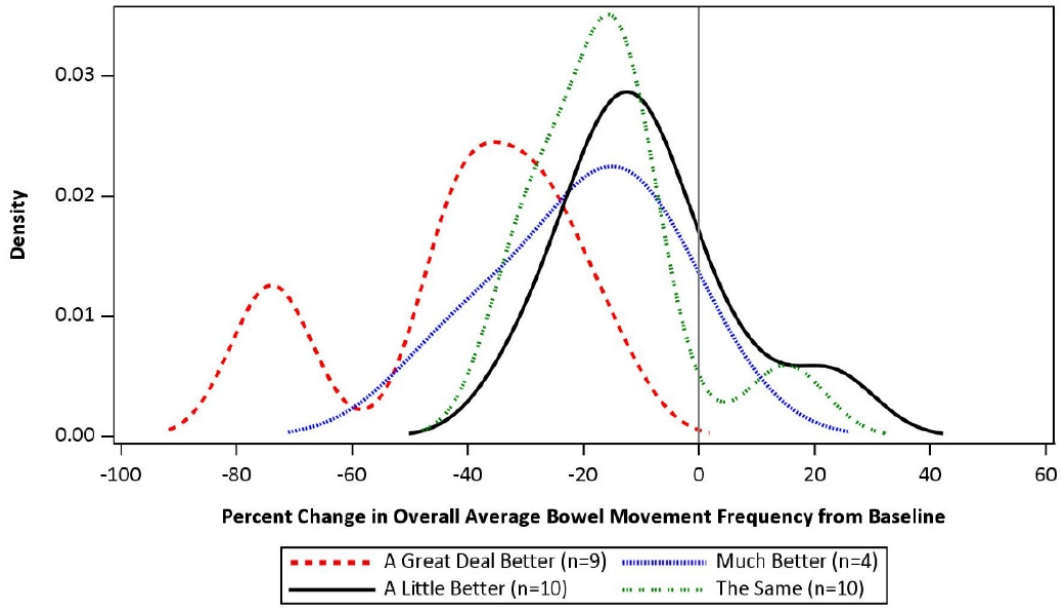
Source: Figure 4.2.3a from applicant's response to 06/28/2016 IR

Figure 17: ECDF of Relative Change in Overall Average BM Frequency from Baseline Stratified by Subjective Global Assessment of Adequate Relief



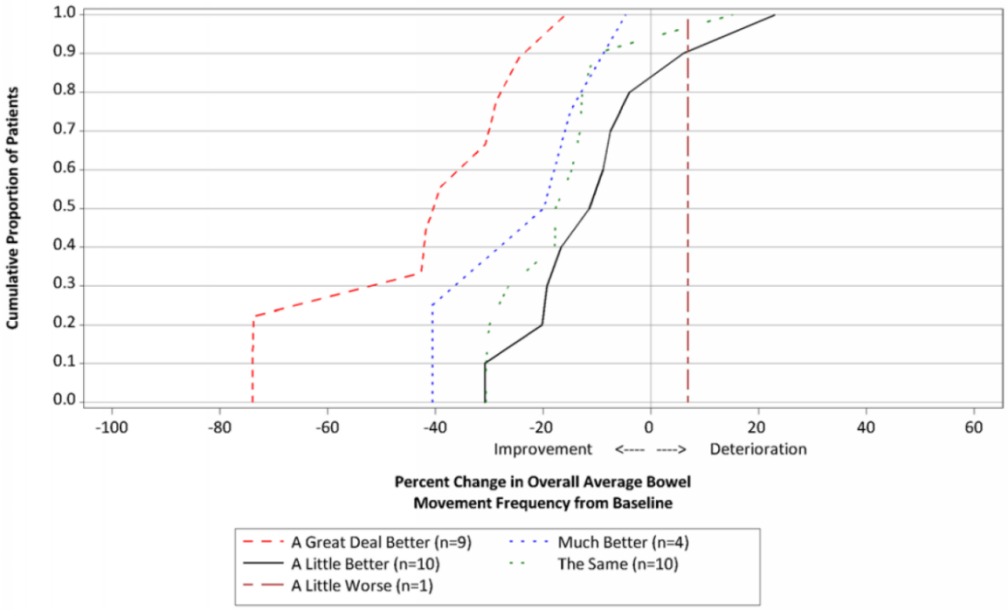
Source: Figure 5.2.3a from applicant's response to 06/28/2016 IR

Figure 18: EPDF of Relative Change in Overall Average BM Frequency from Baseline Stratified by Patient Perception of Change in BMs



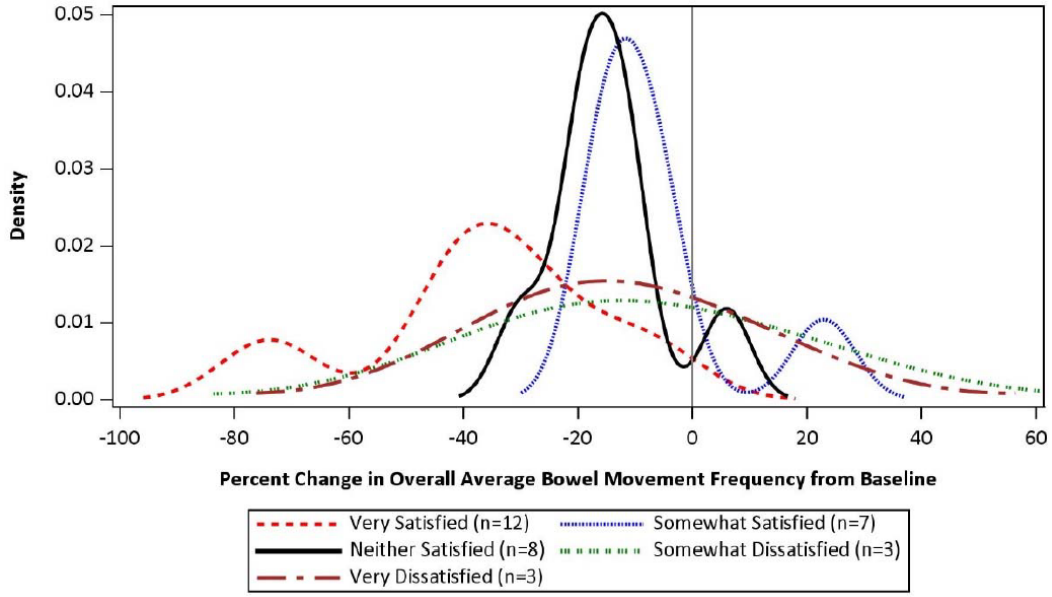
Source: Figure 4.2.4a from applicant's response to 06/28/2016 IR

Figure 19: ECDF of Relative Change in Overall Average BM Frequency from Baseline Stratified by Patient Perception of Change in BMs



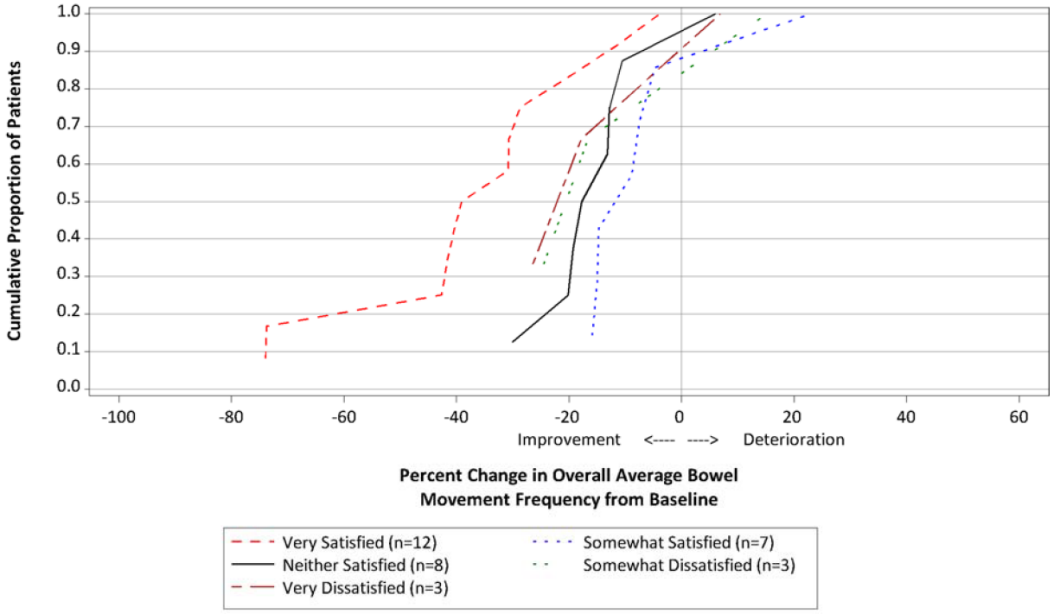
Source: Figure 5.2.4a from applicant's response to 06/28/2016 IR

Figure 20: EPDF of Relative Change in Overall Average BM Frequency from Baseline Stratified by Patient Satisfaction with Study Medication—Relief of CS Symptoms



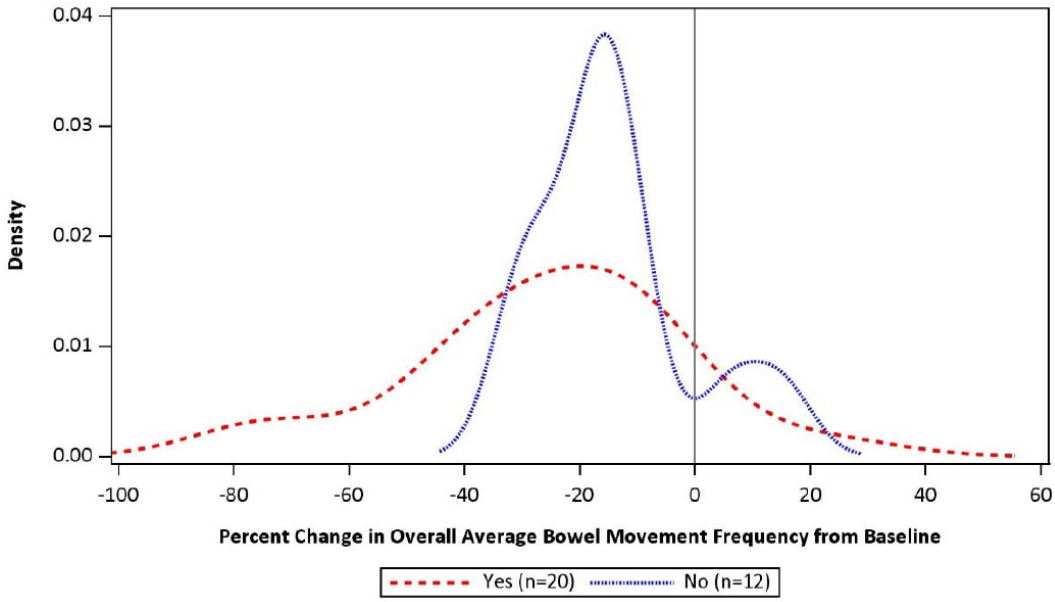
Source: Figure 4.2.6a from applicant's response to 06/28/2016 IR

Figure 21: ECDF of Relative Change in Overall Average BM Frequency from Baseline Stratified by Patient Satisfaction with Study Medication—Relief of CS Symptoms



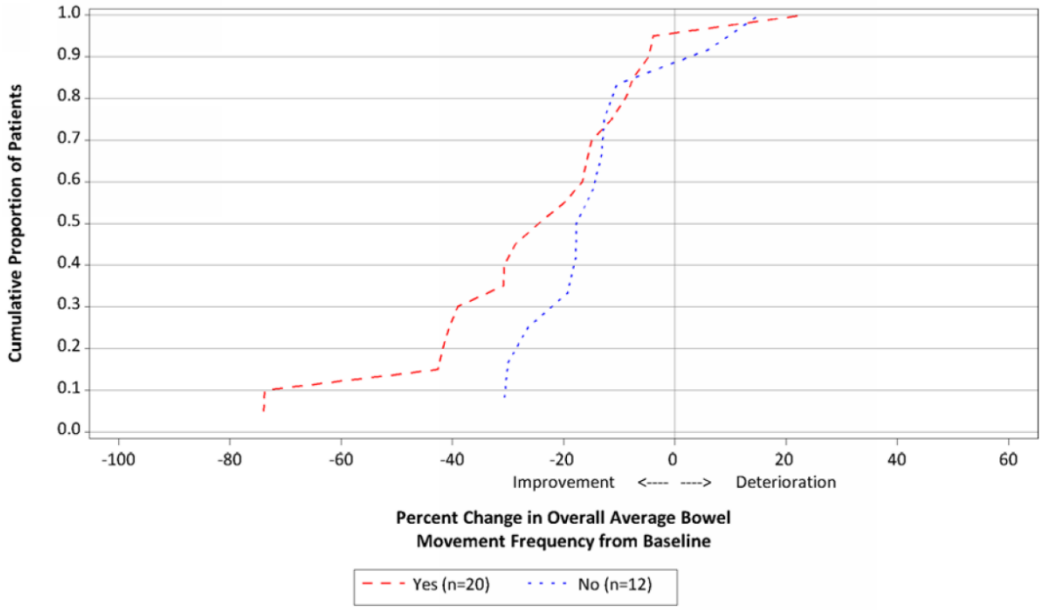
Source: Figure 5.2.6a from applicant's response to 06/28/2016 IR

Figure 22: EPDF of Relative Change in Overall Average BM Frequency from Baseline Stratified by Clinician-rated Patient Reported Meaningful Change in BMs



Source: Figure 4.2.5a from applicant's response to 06/28/2016 IR

Figure 23: ECDF of Relative Change in Overall Average BM Frequency from Baseline Stratified by Clinician-rated Patient Reported Meaningful Change in BMs



Source: Figure 5.2.5a from applicant's response to 06/28/2016 IR

5.2 Post-hoc Evaluation of Efficacy for Relative Change in Overall BMs

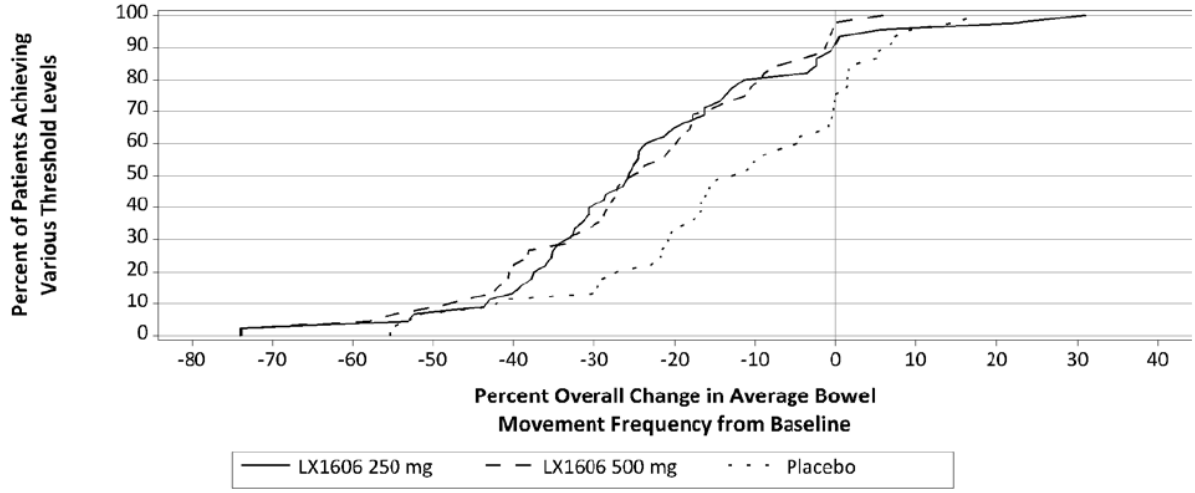
Table 7 summarizes the efficacy results by treatment arms and various meaningful change thresholds, based on this reviewer's recommendation and the applicant's proposal (≥30% reduction). Figure 24 depicts the ECDF plot of the relative change in overall average BM frequency from baseline stratified by treatment groups. Separation can be observed between the treatment arms and the placebo arm for the applicant proposed >=30% reduction in daily BMs.

Table 7: Summary of Efficacy Results by Treatment and Clinically Meaningful Change Thresholds (Relative Change)

	Reviewer Recommendation	Applicant Proposal
Treatment Arm	**25% to 40% Reduction in Daily BMs**	**≥30% Reduction in Daily BMs**
250 mg	53% to 13%	40%
500 mg	49% to 20%	33%
Placebo	20% to 11%	13%

Source: Reviewer's table

Figure 24: ECDF of Relative Change in Overall Average BM Frequency from Baseline Stratified by Treatment (Study 301)



Source: Figure 7 of applicant's LX1606-1-301 COS Psychometric Report.pdf

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/s/

LILI GARRARD
11/29/2016

SCOTT S KOMO
11/29/2016
I concur

LAURA L JOHNSON
11/29/2016

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA/BLA #:	NDA208794/S-0001 (IND 078749)
Drug Name:	Xermelo™ (Telotristat Etiprate Oral Tablets)
Indication(s):	The (b) (4) treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy
Applicant:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place, The Woodlands, TX 77381, USA Laboratory: (b) (4) (b) (4)
Date(s):	Received 3/30/2016
Documents Reviewed:	Study LX1606-N52 (Tg.rasH2 mice) reports and electronic datasets in SEND format submitted with the electronic submission on 3/30/2016 (via S-0001). The electronic tumor.xpt file submitted on 6/20/2016 (via S0012).
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Feng Zhou, M.S.
Concurring Reviewers:	Karl Lin, Ph.D. Team Leader
Medical Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Pharmacology Team:	Ke Zhang, Ph.D; David Joseph, Ph.D
Project Manager:	Brian Strongin, CPMS
Keywords:	Carcinogenicity, Dose response

Table of Contents

Reference ID: 3970322

1 Summary

This review evaluates statistically the tumorigenicity data of carcinogenicity studies of telotristat etiprate (LX1606) (NDA 208794). The studies included a 26 week study in the Tg.rasH2 mice. The review analyzes the dose-response relationship of tumor incidence and mortality (including tumor-related mortality). The analyses of tumor data consisted of trend analyses for dose-response relationship in tumor incidence and pairwise comparisons in tumor incidence between individual treated groups and the vehicle control. The pairwise comparisons were also carried out between the positive control and the vehicle control groups.

From the statistical point of view, the review concludes that LX1606 had a negative effect on survival. The tumor analysis showed no statistically significant dose-response relationship in tumor incidence for either sex in mice.

Mouse Study: Mice (25/sex/dose) were dosed by the oral gavage with LX1606 daily for up to 26 weeks. The respective LX1606 dose in the low (LD), mid (MD), and high-dose (HD) groups was 30, 100, or 300 mg/kg in males and females. The study had two control groups: vehicle (VC), and positive control (PC). The PC mice (10/sex) were dosed with 1000 mg/kg of urethane formulated in saline.

The survival analysis showed no statistically significant effects on mortality in either trend analysis or pairwise comparison in LX1606 treatment groups in either sex. The pairwise comparisons showed a statistically significant increase in mortality between vehicle control and positive control ($p<0.0001$). The respective survival rates in the VC, LD, MD, HD, PC groups at the termination (Week 26) were 96%, 96%, 96%, 96%, and 30% in male mice; 88%, 92%, 88%, 92%, and 20% in female mice.

The tumor analysis did not show any statistically significant dose-response relationship in incidence in any tumors in males or females. The PC group showed statistically significant increases in the incidence of a number of tumors in both males and females ($p<0.05$), when compared to the vehicle control. Those tumor types included alveolar-bronchiolar adenoma in lungs with bronchi and lymphosarcoma in spleen in both male and female mice.

2 Background

The sponsor conducted one 26-week carcinogenicity study to assess the carcinogenic potential of telotristat etiprate (LX1606) in hemizygous Tg.rasH2 mice.

The sponsor stated that "*The strain of mouse, design of the study, and the doses used were determined in consultation with the FDA, and in accordance with the Executive Carcinogenicity Assessment Committee (ECAC). Treatment of hemizygous Tg.rasH2 mice with telotristat etiprate at daily oral doses up to 300 mg/kg/day for 26 consecutive weeks did not increase the incidence of neoplastic lesions (LX1606-N52, Table 2.6.7.10.1). At 300 mg/kg/day dosage, the exposures to LP-778902 were 15x (males) and 23x (females) the exposure at the MRHD. As agreed to with the FDA during the April 11, 20112, a 2 year rat carcinogenicity study will be submitted post-marketing approval and Lexicon will provide a safety update from the ongoing 2 year rat carcinogenicity study during the NDA review cycle.*"

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The sponsor submitted the electronic data in SEND format on 3/30/2016 via submission NDA 208794/S0001. The submitted SEND format data did not include the two variables (tumorcod and organcod) which were included in the tumor.xpt file. The reviewer requested the tumor.xpt file from the sponsor while worked on extracting the tumor.xpt file from submitted SEND format data. The sponsor submitted the tumor.xpt file on 6/20/2016 via submission NDA 208794/S0012 as the response to an information request (IR) which sent out on 6/15/2016. This reviewer's analyses were based on the tumor.xpt file submitted by the sponsor. The statistical evaluation of survival data and tumor incidence included in the sponsor's report was performed by (b) (4).

The phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases. The mg/kg/day will be referred to as mkd. Results of this review have been discussed with the reviewing pharmacologist Dr. Ke Zhang.

3 Mouse Study

Study Report: Statistical Analysis Report (page 593 in LX1606-N52.pdf); SAS data: Tumor.xpt

This study assessed the carcinogenic potential of LX1606 in male and female hemizygous Tg.rasH2 mice. The test material was administered by oral gavage at doses of 30, 100, or 300 mkd of LX1606 once daily for at least 26 weeks. This review refers these dose groups as the low (LD), mid (MD), and high (HD) dose groups, respectively. There was a vehicle control (VC) [0.25% (w/v) methylcellulose in de-ionized (DI) water]. There was a positive control (PC) which was dosed with three total intraperitoneal (i.p.) injections, once each on Days 1, 3 and 5 only, with 1000 mg/kg of urethane formulated in saline. All treatments were administered at a dose volume of 10 mL/kg. There were 25 mice for each sex and dose group except positive control group which included 10 mice for each sex.

Data evaluated included mortality, clinical signs, body weights and body weight changes, food consumption, organ weights, macroscopic (gross necropsy) and microscopic (histology) findings. During Week 27, surviving animals were sacrificed by Carbon dioxide (CO_2) overdose and necropsied. Positive control animals were sacrificed by CO_2 overdose and necropsied during Week 12.

For all the sponsor's analyses, the data from the positive control group were excluded and actual dose levels were used in the statistical analysis.

3.1 Sponsor's Analyses

The sponsor stated that *"All calculations and statistical analyses in this report are based on the SAS® transport file (Tumour Data.stc) received from the Testing Facility on November 4, 2014 and corresponding documentation."* . The submitted data was in SEND format and submitted the Tumor.xpt file per request.

3.1.1 Survival Analysis

Kaplan-Meier estimates of group survival rates were calculated, by sex, and shown graphically. The generalized Wilcoxon test for survival was used to compare the homogeneity of survival rates across the vehicle control and test article groups, by sex, at the 0.05 significance level. If the survival rates were significantly different, the generalized Wilcoxon test was used to make pairwise comparisons of each test article group with the vehicle control group. Additionally, the positive control group was compared to the vehicle control group using the generalized Wilcoxon test.

File Name: outputfile-558213214.pdf

Survival times in which the status of the animal's death was classified as an accidental death, planned interim sacrifice or terminal sacrifice were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings: There were no statistically significant findings among males or females for survival rates.

3.1.2 Tumor Data Analysis

The incidence of tumors was analyzed by Peto's mortality-prevalence method, without continuity correction, incorporating the context (incidental, fatal, or mortalityindependent) in which tumors were observed. The following fixed intervals were used for incidental tumor analyses: weeks 1 – end of study (up to, but not including, scheduled terminal sacrifices), and scheduled terminal sacrifice. All tumors in the scheduled terminal sacrifice interval were considered incidental for the purpose of statistical analysis.

Tumors classified as mortality-independent were analyzed with Peto's mortality independent method incorporating the day of detection. Each diagnosed tumor type was analyzed separately and, at the discretion of the study director, analysis of combined tumor types and/or organs was performed. All metastases and invasive tumors were considered secondary and not statistically analyzed.

A 1-sided comparison of each test article group with the vehicle control was performed. An exact permutation test was conducted for all analyses. Findings were evaluated for statistical significance at both the 0.01 and 0.05 levels and all p values were reported.

Because the positive control group was scheduled for early terminal sacrifice, tumor incidence in the positive control group was compared to the vehicle control group with a 1-sided Fisher's exact test at both the 0.01 and 0.05 significance levels and all p values were reported.

The sponsor analyzed all tumor finding as well as the following tumor combinations:

Tumor Combinations

Sex	Organ	Tumor	Tumor Presented as:
M/F	Lung	alveolar-bronchiolar adenoma; alveolar-bronchiolar carcinoma	carcinoma/adenoma
M/F	Multiple Organs*	hemangiosarcoma	hemangiosarcoma
M/F	Multiple Organs*	hemangiosarcoma hemangioma	hemangiosarcoma/hemangioma
M/F	Multiple Organs*	lymphoma	lymphoma

Sponsor's findings: For both males and females, there were no statistically significant tumor findings in the test article groups when compared to the vehicle control group.

There was a statistically significant increase in following tumors: alveolar bronchiolar adenoma, alveolar-bronchiolar carcinoma in lungs with bronchi, and hemangiosarcoma in the spleen when comparing the positive control with the vehicle control group.

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3.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer performed survival and tumor data analyses using the TUMOR.xpt file which submitted on 6/20/2016 via submission NDA 208794/S0012 as the response to an information request (IR) which sent out on 6/15/2016.

3.2.1 Survival Analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 1A and 1B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 1A and 1B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose groups are given in Tables 2A and 2B in the appendix for male and female mice, respectively.

Reviewer's findings: The studies were terminated on week 27 for treated groups and vehicle control. The mice in the PC group were terminated at week 12 as planned. This reviewer's analysis showed the numbers (percent) of deaths were 0, 2 (8%), 1 (4%), 2 (8%), and 0 for VC, LD, MD, HD, PC groups in male mice and 4 (16%), 2 (8%), 0, 1(4%), and 1 (4%) for VC, LD, MD, HD, PC groups in female mice, respectively. The tests did not show any statistically significant dose response relationship in mortality across control and treated groups in either sex mice. The pairwise comparisons did not show any statistically significant increase in mortality in the treated groups compared to the vehicle control in either male or female mice. The pairwise comparisons did show a statistically significant mortality difference between vehicle control and positive control ($p<0.0001$).

3.2.2 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal in a treatment group that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal in the treatment group that dies at week w_h without developing the tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as Σs_h . As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops the given tumor type being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female mice, respectively. The tumor rates and

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the p-values of the comparisons between the vehicle control and positive control are listed in Tables 4A and 4B in the appendix for male and female mice, respectively.

Multiple testing adjustment: For the adjustment of multiple testing of dose response relationship, the FDA guidance for the 26 weeks transgenic mouse study design and data analysis suggests the use of test levels α=0.05 for both the trend tests and the pairwise comparisons regardless a tumor type is common or rate.

Reviewer's findings: Because of the small group size and short study duration used in transgenic mouse studies, based on the statistical guideline for transgenic mouse studies, the significance level of 0.05 was used in the tests for dose response and pairwise comparisons in tumor incidences of both rare and common tumors. Based on this recommendation of adjustment for multiple testing discussed above, the tumor analysis did not show any statistically significant dose-response relationship in incidence in all tumor types tested in male and female mice. The PC group showed statistically significant increases in the incidence of a number of tumors in both males and females ($p<0.05$), when compared to the vehicle control. Those tumor types included alveolar-bronchiolar adenoma in lungs with bronchi and lymphosarcoma in spleen in both male and female mice.

Tumor Types with P-Values ≤ 0.05 for Pairwise Comparisons between VC and PC in Male Mice

Organ Name	Tumor Name	0 mg/kg/day VC (N=25)	1000 mg/kg of urethane PC (N=10)	P-Value VC vs. PC
lungs with bronchi	alveolar-bronchiolar adenoma	1	10	<0 001*
	C alveolar carci+adenoma	**2**	**10**	**<0.001***
spleen	hemangiosarcoma	0	10	<0 001*
Multiple Organs	**C hemangiosarcoma**	**1**	**10**	**<0.001***

*Indicted the significant at 0.001 alpha levels. PC=1000 mg/kg of urethane.

Tumor Types with P-Values ≤ 0.05 for Pairwise Comparisons between VC and PC in Female Mice

Organ Name	Tumor Name	0 mg/kg/day VC (N=25)	1000 mg/kg of urethane PC (N=10)	P-Value VC vs. PC
lungs with bronchi	alveolar-bronchiolar adenoma	1	10	<0.001*
	C alveolar carci+adenoma	**3**	**10**	**<0.001***
spleen	hemangiosarcoma	2	9	<0.001*
Multiple Organs	**C hemangiosarcoma**	**4**	**9**	**<0.001***

*Indicted the significant at 0.001 alpha levels. PC=1000 mg/kg of urethane.

4 Conclusion

This review evaluates statistically the tumorigenicity data of carcinogenicity studies of telotristat etiprate (LX1606) (NDA 208794). The studies included a 26 week study in the Tg.rasH2 mice. The review analyzes the dose-response relationship of tumor incidence and mortality (including tumor-related mortality). The analyses of tumor data consisted of trend analyses for dose-response relationship in tumor incidence and pairwise comparisons in tumor incidence between individual treated groups and the vehicle control. The pairwise comparisons were also carried out between the positive control and the vehicle control groups.

From the statistical point of view, the review concludes that LX1606 had a negative effect on survival. The tumor analysis showed no statistically significant dose-response relationship in tumor incidence for either sex in mice.

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5 Appendix

Table 1A: Intercurrent Mortality Rate in Male Mice

	0 mg/kg/day VC (n=25)		30 mg/kg/day LD (n=25)		100 mg/kg/day MD (n=25)		300 mg/kg/day HD (n=25)		1000 mg/kg of Urethane PC (n=10)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 – 13	.	.	.	.	.	.	.	.	.	.
14 – 26	0	0	2	8.00	1	4.00	2	8 00	.	.
Planned intermittent sacrifice at week 12									10	100.00
Terminal Sacrifice at week 27	25	100.00	23	92 00	24	96 00	23	92.00	.	.

Test	**VC, LD, MD, HD**	**VC vs. LD**	**VC vs. MD**	**VC vs. HD**	**VC vs. PC**
Dose-Response (Likelihood Ratio)	0.4006	0 0935	0.2390	0.0959	<0 0001
Homogeneity (Log-Rank)	0.5103	0.1531	0.3173	0.1530	<0 0001

All Cum. %Cumulative Percentage except for Terminal sacrifice
**=Significant at 1% level

Table 1B: Intercurrent Mortality Rate in Female Mice

	0 mg/kg/day VC (n=25)		30 mg/kg/day LD (n=25)		100 mg/kg/day MD (n=25)		300 mg/kg/day HD (n=25)		1000 mg/kg of Urethane PC (n=10)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 – 13	1	4.00	.	.	.	.	.	.	1	4.00
14 – 26	3	16 00	2	8.00	.	.	1	4.00	.	.
Planned intermittent sacrifice at week 12									9	96.00
Terminal Sacrifice at week 27	21	84 00	23	92.00	25	100.00	24	96 00	.	.

Test	**VC, LD, MD, HD**	**VC vs. LD**	**VC vs. MD**	**VC vs. HD**	**VC vs. PC**
Dose-Response (Likelihood Ratio)	0.1530	0 3899	0.0173	0.1624	0 5014
Homogeneity (Log-Rank)	0.1513	0 3889	0.0391	0.1712	0.4765

All Cum. %Cumulative Percentage except for Terminal sacrifices.
**=Significant at 1% level

Table 2A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Vehicle Control – Male Mice

Organ Name	**Tumor Name**	**0 mkd VC N=25**	**30 mkd LD N=25**	**100 mkd MD N=25**	**300 mkd HD N=25**	**P-Value**			
						Dos Response	**VC vs. LD**	**VC vs. MD**	**VC vs. HD**
bone, sternum	hemangiosarcoma	0	0	0	1	0 2371	.	.	0.4792
cavity, nasal	adenocarcinoma	0	0	0	2	0 0543	.	.	0.2243
	ameloblastoma	0	0	0	1	0 2371	.	.	0.4792
	osteosarcoma	1	0	0	0	1 0000	1.0000	1.0000	1.0000
ear	hemangiosarcoma	1	0	0	0	1 0000	1.0000	1.0000	1.0000
harderian glands	adenoma	0	1	0	0	0.7423	0.4898	.	.
heart	sarcoma	1	0	0	0	1 0000	1.0000	1.0000	1.0000
hindlimb	hemangiosarcoma	0	1	0	0	0.7423	0.4898	.	.
kidneys	cystadenoma	0	0	0	1	0 2371	.	.	0.4792
liver	hepatocellular adeno	0	0	0	1	0 2371	.	.	0.4792

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Organ Name	Tumor Name	0 mkd VC N=25	30 mkd LD N=25	100 mkd MD N=25	300 mkd HD N=25	P-Value			
						Dos Response	VC vs. LD	VC vs. MD	VC vs. HD
lungs with bronchi	alveolar-bronchiolar carcinoma	1	0	1	0	0.7474	1.0000	0.7551	1.0000
	alveolar-bronchiolar adenoma	1	2	1	1	0 5905	0.4844	0.7551	0.7340
	C alveolar carcinoma+adenoma	**2**	**2**	**2**	**1**	**0.7149**	**0.6798**	**0.6954**	**0.8670**
multicentric	Hemangiosarcoma	0	1	0	0	0.7423	0.4898	.	.
	Lymphoma	0	0	1	0	0.4948	.	0.5000	.
	Mesothelioma	0	0	0	2	0 0618	.	.	0.2449
thymus	Lymphoma	0	0	0	1	0 2371	.	.	0.4792
Multiple Organs	**C hemangiosarcoma**	**1**	**2**	**0**	**1**	**0.6085**	**0.4844**	**1.0000**	**0.7340**
	C lymphoma	**0**	**0**	**1**	**1**	**0.1778**	**.**	**0.5000**	**0.4792**

Table 2B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Vehicle Control – Female Mice

Organ Name	Tumor Name	0 mkd VC N=25	30 mkd LD N=25	100 mkd MD N=25	300 mkd HD N=25	P-Value			
						Dos Response	VC vs. LD	VC vs. MD	VC vs. HD
cavity, nasal	adenocarcinoma	0	0	1	1	0.1921	.	0.5208	0 5106
ear	papilloma	0	0	0	1	0.2577	.	.	0 5208
forelimb	papilloma	0	1	0	0	0.7604	0 5106	.	.
	C papilloma	**0**	**1**	**0**	**1**	**0.3275**	**0.5106**	**.**	**0.5208**
harderian glands	adenoma	0	1	1	0	0.6368	0 5106	0.5208	.
lungs with bronchi	alveolar-bronchiolar adenoma	1	2	1	1	0.6249	0 5163	0.7757	0.7660
	alveolar-bronchiolar carcinoma	2	1	2	0	0.8933	0 8908	0.7270	1 0000
	C alveolar carcinoma+adenoma	**3**	**3**	**3**	**1**	**0.8774**	**0.6878**	**0.7067**	**0.9504**
multicentric	basal cell carcinoma	0	1	0	0	0.7604	0 5106	.	.
	hemangiosarcoma	1	1	0	0	0.9445	0.7660	1.0000	1 0000
	histiocytic sarcoma	0	0	1	0	0.5104	.	0.5208	.
salivary glands	adenocarcinoma	0	1	0	0	0.7604	0 5106	.	.
	sarcoma	0	0	1	0	0.5104	.	0.5208	.
skin (mammary area)	hemangiosarcoma	1	0	0	0	1.0000	1 0000	1.0000	1 0000
spleen	hemangiosarcoma	2	1	1	2	0.4031	0 8830	0.8901	0 6957
uterus	hemangioma	0	1	0	0	0.7604	0 5106	.	.
	hemangiosarcoma	0	0	1	0	0.5104	.	0.5208	.
	C hemangiosarcoma/hemangioma	**0**	**1**	**1**	**0**	**0.6368**	**0.5106**	**0.5208**	**.**
Multiple Organs	**C hemangiosarcoma**	**4**	**2**	**2**	**2**	**0.7211**	**0.8961**	**0.9053**	**0.8961**
	C hemangiosarcoma/hemangioma	**4**	**3**	**2**	**2**	**0.7829**	**0.7742**	**0.9053**	**0.8961**

Table 3A: Tumor Rates and P-Values for Comparisons between Vehicle and Positive Controls– Male Mice

Organ Name	Tumor Name	0 mg/kg/day VC (N=25)	1000 mg/kg PC (N=10)	P-Value VC vs. PC
cavity, nasal	osteosarcoma	1	0	1.0000
ear	hemangiosarcoma	1	0	1.0000
heart	sarcoma	1	0	1.0000
liver	hepatocellular adeno	0	0	.
lungs with bronchi	alveolar-bronchiolar carcinoma	1	0	1.0000
	alveolar-bronchiolar adenoma	1	10	<0 001*
	C alveolar carci+ade	**2**	**10**	**<0.001***

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Organ Name	Tumor Name	0 mg/kg/day VC (N=25)	1000 mg/kg PC (N=10)	P-Value VC vs. PC
Spleen	hemangiosarcoma	0	10	<0 001*
Multiple Organs	**C hemangiosarcoma**	**0**	**10**	**<0.001***
	C lymphoma	**0**	**0**	.

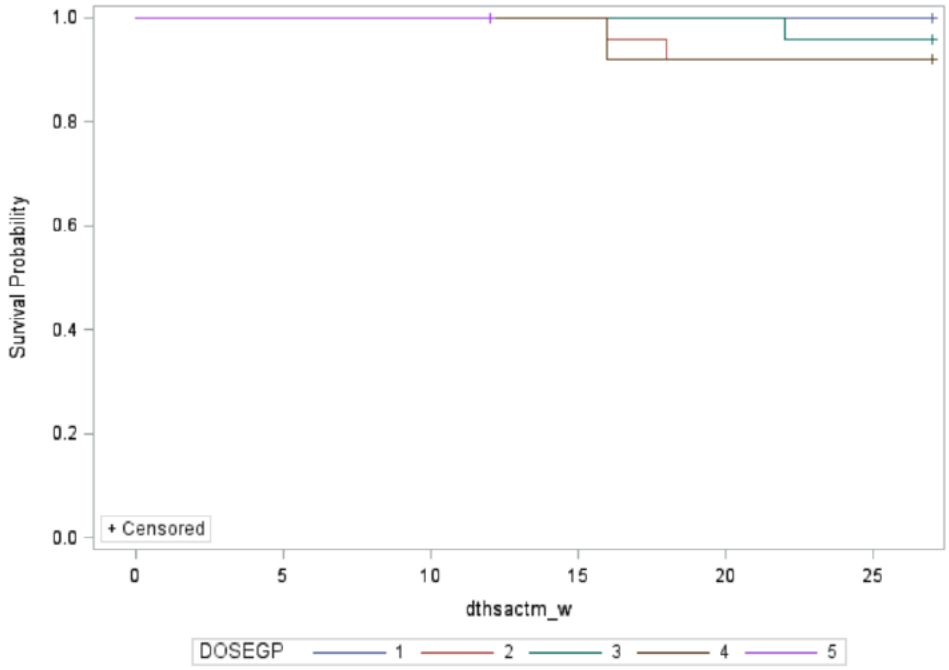
*Indicted the significant at 0.001 alpha levels. PC=1000 mg/kg of urethane.

Table 3B: Tumor Rates and P-Values for Comparisons between Vehicle and Positive Controls– Female Mice

Organ Name	Tumor Name	0 mg/kg/day VC (N=25)	1000 mg/kg PC (N=10)	P-Value VC vs. PC
lungs with bronchi	alveolar-bronchiolar adenoma	1	10	<0 001*
	alveolar-bronchiolar carcinoma	2	0	1.0000
	C alveolar carci+ade	**3**	**10**	**<0.001***
Multicentric	hemangiosarcoma	1	0	1.0000
skin (mammary area)	hemangiosarcoma	1	0	1.0000
Spleen	hemangiosarcoma	2	9	<0 001*
Multiple Organs	**C hemangiosarcoma**	**4**	**9**	**<0.001***

*Indicted the significant at 0.001 alpha levels. PC=1000 mg/kg of urethane.

Figure 1A: Kaplan-Meier Survival Functions for Male Mice



Note: dose group should be 1=VC, 2=30 mkd, 3=100 mkd, 4=300 mkd of LX1606, or 5=1000 mg/kg of urethane formulated in saline (PC)

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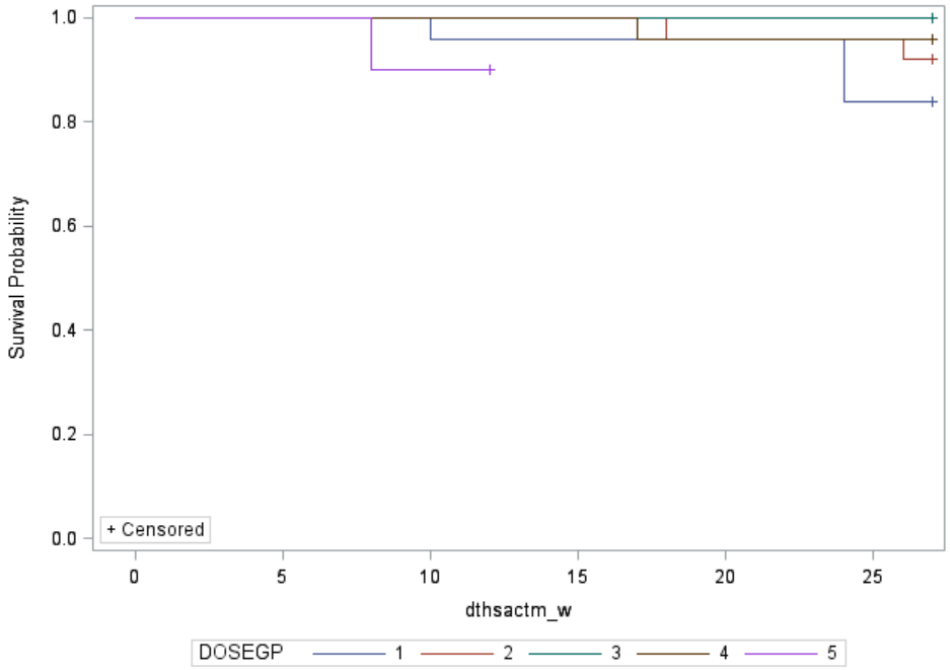
Figure 1B: Kaplan-Meier Survival Functions for Female Mice



Note: dose group should be 1=VC, 2=30 mkd, 3=100 mkd, 4=300 mkd of LX1606, or 5=1000 mg/kg of urethane formulated in saline (PC)

6 References

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