20 July 2017
EMA/508026/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xermelo

International non-proprietary name: telotristat ethyl

Procedure No. EMEA/H/C/003937/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin (5-hydroxytryptamine [5-HT])
ADR	adverse drug reactions
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
BBB	blood-brain barrier
BCS	Biopharmaceutics Classification System
BM	bowel movement
BMI	body mass index
CDF	cumulative distribution function
CL	confidence limit
CNS	central nervous system
CPP	Critical process parameter
CQA	Critical Quality Attribute
CS	carcinoid syndrome
CSR	clinical study report
DBT	Double-blind Treatment (Period)
DSC	Differential Scanning Calorimetry
DSMB	Data Safety Monitoring Board
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic Diary
Emax	maximum reduction
EORTC	European Organisation for Research and Treatment of Cancer
ERC	Ethics Review Committee
FT-IR	Fourier Transform Infrared Spectroscopy

GC	Gas Chromatography
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GI	Gastrointestinal
GI.NET21	Gastrointestinal Symptoms of Carcinoid Neuroendocrine Tumours
GLM	generalised linear model
H-L	Hodges-Lehmann
HDPE	High Density Polyethylene
HPLC	High Performance Liquid Chromatography
HR	Hazard ratio
ICF	informed consent form
ICH	International Conference on Harmonisation (Revised as of 23 October 2015 to: International Council for Harmonisation)
IEC	Independent Ethics Committee
INR	international normalised ratio
IPC	In-process control
IRB	Institutional Review Board
ITT	intent-to-treat
IMP	investigational medicinal product
IR	Infrared
IU	International Units
IWRS	interactive web response system
KF	Karl Fischer titration
LAR	long-acting release
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LDPE	Low Density Polyethylene
LP-778902	active metabolite of telotristat etiprate
LP-951757	Minor metabolite of telotristat
LT	liver test
LX1033	active metabolite of telotristat etiprate
LX1606	Hippurate telotristat etiprate
LX101	LX1606.101-NRM (shortened form of study identifier)

LX102	LX1606.102-NRM (shortened form of study identifier)
LX103	LX1606.103-NRM (shortened form of study identifier)
LX104	LX1606.104-NRM (shortened form of study identifier)
LX105	LX1606.105-NRM (shortened form of study identifier)
LX106	LX1606.106-NRM (shortened form of study identifier)
LX107	LX1606.107-NRM (shortened form of study identifier)
LX108	LX1606.108-NRM (shortened form of study identifier)
LX109	LX1606.109-NRM (shortened form of study identifier)
LX202	LX1606.202-CS (shortened form of study identifier)
LX203	LX1606.203-CS (shortened form of study identifier)
LX204	LX1606.204-UC (shortened form of study identifier)
LX301	LX1606.301-CS (shortened form of study identifier)
LX302	LX1606.302-CS (shortened form of study identifier)
LX303	LX1606.303-CS (shortened form of study identifier)
MCP	multiple comparison procedure
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model with repeated measurements
MS	Mass Spectrometry
NB	negative binomial
NET	neuroendocrine tumour
NMR	Nuclear Magnetic Resonance
OLE	Open-label Extension (Period)
OOS	Out of Specifications
PCTFE	Polychlorotrifluoroethylene
PD	pharmacodynamic(s)
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PP	Per-protocol
PT	prothrombin time
PVC	Poly vinyl chloride

QbD	Quality by design
QOL	quality of life
QTcF	corrected QT interval using Fridericia's formula
QTPP	Quality target product profile
RH	Relative Humidity
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
SSA	somatostatin analogue
TEAE	treatment-emergent adverse event
telotristat ethyl	ethyl ester prodrug of the active metabolite LP-778902
tid	3 times daily
tmax	time to maximum concentration
TPH	tryptophan hydroxylase
TSE	Transmissible Spongiform Encephalopathy
u5-HIAA	urinary 5-hydroxyindoleacetic acid
ULN	upper limit of the normal (reference range)
UV	Ultraviolet
WRS	Wilcoxon rank sum
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Ipsen Pharma submitted on 22 June 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Xermelo, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 January 2014.

Xermelo, was designated as an orphan medicinal product EU/3/09/661 on 08 October 2009 in the following condition: treatment of carcinoid tumours. The orphan drug designation was amended on 30 May 2016 to the following condition: treatment of carcinoid syndrome.

The applicant applied for the following indication:

Xermelo is indicated as an adjunct to somatostatin analogue therapy for the long-term treatment of carcinoid syndrome to improve symptom control in adult patients with metastatic neuroendocrine tumours.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Xermelo as an orphan medicinal product in its approved indications. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0318/2015 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance telotristat contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal

product previously authorised within the European Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 21 June 2012, 19 December 2013 and 21 February 2014. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Harald Enzmann Co-Rapporteur: Ondřej Slanař

- The application was received by the EMA on 22 June 2016.
- The procedure started on 14 July 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 October 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 3 October 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 13 October 2016.
- During the meeting on 10 November 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 February 2017.
- The following GCP inspection was requested by the CHMP and its outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection at two clinical investigator sites in Canada and the United States and the Sponsor site in the United States took place between December 2016 and February 2017 in connection with the conduct of trials with protocol number LX1606.1-301-CS. The final outcome of the inspection carried out was issued on 14 March 2017. Overall, the trial has been conducted according to the ethical principles for clinical trials in human and the data was regarded of acceptable quality. The detected GCP deficiencies did not impact data reliability/validity and could be accepted for the submitted application assessment.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 March 2017.
- During the PRAC meeting on 6 April 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 21 April 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 June 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 July 2017.
- During the meeting on 20 July 2017, the CHMP, in the light of the overall data submitted and the

scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Xermelo on 20 July 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Well-differentiated neuroendocrine tumours (NETs), formerly known as carcinoid tumours, are a relatively rare tumour type that arises from cells of the neuroendocrine system.

2.1.2. Epidemiology and risk factors

In 2013, a pan-European project investigated the prevalence of NETs and concluded that approximately 100,000 people were diagnosed with NETs and still alive in the EU27 at the beginning of 2008[1] which would correspond to approximately 103,000 prevalent cases when extrapolated to the population of the EU28 plus 3 other countries (Liechtenstein, Norway and Iceland) in 2015 (ie, 2 cases per 10,000 inhabitants). This value represents the most recent and accurate estimate based on EU-specific studies. Taking into account the highest occurrence estimate, the prevalence of CS would therefore be 1 cases per 10,000 , which represent around -52.000 patients in the EU (EU28 population = 515,865,302 people in 2016 according to Eurostat).

Neuroendocrine tumours can appear at any age, but they are more common in individuals over 40 years of age, with an incidence being highest in patients aged 65 years and older. They are slightly more frequent in male patients as well as in white patients. [1, 2]

2.1.3. Biologic features

NETs can synthesise, store, and release a variety of polypeptides, biogenic amines, and prostaglandins, which are responsible for the Carcinoid syndrome (CS). CS results from various bioactive amides and peptides produced by some NETs, such as neuron-specific enolase (NSE), 5-hydroxytryptamine (5-HT), 5-hydroxytryptophan (5-HTP), synaptophysin and chromagranins A and C and other peptides such as insulin , growth hormone, neurotensin, adrenocorticotropic hormone (ACTH), beta-melanocyte-stimulating hormone, gastrin, pancreatic polypeptide, calcitonin and various other growth factors (eg TGF-beta , platelet derived growth factor and fibroblast growth factor). The relative contributions of each and specificity of any of these molecules for particular components of the syndrome are uncertain. As the liver inactivates bioactive products secreted into the portal circulation patients with NETs only acquire the CS if they develop hepatic metastases. Altered metabolism of tryptophan occurs in almost all patients with CS. Physiologically approximately 1% of dietary tryptophan is converted to serotonin. This value may increase to 70% or more in patients with CS. Serotonin is metabolised to 5-hydroxyindoleacetic acid (5-HIAA). Tumour production of serotonin is the most likely cause of the diarrhoea in CS, as serotonin stimulates intestinal secretion and motility and inhibits intestinal absorption.

[1] van der Zwan JM, Trama A, Otter R et al. Rare neuroendocrine tumours: results of the surveillance of rare cancers in Europe project. Eur J Cancer. 2013 Jul;49(11):2565-78.
[2] Öberg K, Akerström G, Rindi G, et al. Neuroendocrine gastroenteropancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010 May;21 Suppl 5:v223-7.

Furthermore, serotonin may also stimulate fibroblast growth and fibrogenesis. These effects can lead to peritoneal and cardiac valvular fibrosis associated with CS. [3]

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Carcinoid syndrome (CS) occurs when well-differentiated NETs secrete large amounts of serotonin and other vasoactive products into the systemic circulation. Classically, symptoms associated with CS include cutaneous flushing, diarrhoea, wheezing, abdominal pain, and valvular heart disease.[4]

Predictors of poor prognosis at the time of diagnosis of NETs include older age, sex, histological type, location of origin, tumour stage[5], [6] and the presence of elevated urinary 5-hydroxyindoleacetic acid (u5-HIAA) levels.[7]

From the time of diagnosis of metastatic NETs, median survival has been estimated to be approximately 31-75 months. The most frequent cause of death in patients with NETs is liver failure due to hepatic replacement by tumour.

Roughly 3 quarters of CS patients experience diarrhoea[8], which results in an estimated prevalence figure of 26,693 cases of CS associated with diarrhoea. Uncontrolled diarrhoea may contribute to deterioration in overall health and affect the ability of patients to endure complications of their cancer and its treatment. Uncontrolled diarrhoea can lead to weight loss, malnutrition, dehydration, and electrolyte imbalance; when severe, malabsorption may occur and may even cause death.[9, 10, 11] Valvular heart disease has been associated with high serotonin levels as measured by its metabolite, u5-HIAA. Due to the slow-growing nature of NETs and the prolonged course of disease, about 50% of patients with CS will eventually develop heart disease, which can lead to significant morbidity and mortality. , [12], [13]

5-hydroxyindolacetic acid (5-HIAA) is a major metabolite of serotonin and it is excreted in the urine and can be monitored as a surrogate of 5-HT levels. Levels of 5-HIAA have no clear correlation with symptoms, but they do fluctuate with symptomatology. However, some patients with carcinoid tumour have symptoms of flushing with low or normal levels of 5-HIAA. Additionally, 5-HIAA levels reflect the actions of somatostatin analogues, with a 50% reduction from pretreatment levels being indicative of a biochemical response. In epidemiological studies, high levels of u5-HIAA in patients with NETs have been associated with poor survival. van der Horst-Schrivers et al prospectively studied 76 patients with midgut well-differentiated NETs. Urine collected over a 24-hour period every 3 months was tested for u5-HIAA levels. Patients with high u5-HIAA level (>20 mmol/mol creatinine) had a median survival of 33 months

[3] Feldman JM: Carcinoid tumors and syndrome. Semin Oncol. 1987; 14(3): 237
[4] Kulke MH, Siu LL, Tepper JE et al. Future Directions in the Treatment of Neuroendocrine Tumors: Consensus Report of the National Cancer Institute Neuroendocrine Tumor Clinical Trials Planning Meeting. J Clin Oncol 2011; 29:934- 43.
[5] Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008:26:3063-72.
[6] Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum. Pancreas. 2010 Aug;39(6):753-766.
[7] van der Horst-Schrivers AN, Post WJ, Kema IP, et al. Persistent low urinary excretion of 5-HIAA is a marker for favourable survival during follow-up in patients with disseminated midgut carcinoid tumors. Eur J Cancer 2007; 43(18):2651-7.
[8] Vinik 2015. http://www.ncbi.nlm.nih.gov/pubmed/25905385 (accessed 01 June 2016)
[9] Liu EH, Solorzano CC, Katznelson L, et al. AACE/ACE Disease State Clinical Review: Diagnosis and Management of Midgut Carcinoids. Endo Prac. 2015;21(5):534-545.
[10] Kvols LK. Therapeutic Considerations for the Malignant Carcinoid Syndrome. Acta Oncologica. 1989; 28:3, 433-438.
[11] Santacroce, L Medscape; Malignant Carcinoid Syndrome http://emedicine.medscape.com/article/282515-overview; Updated Feb 10, 2016
[12] Fox DJ, Khattar RS. Carcinoid heart disease: presentation, diagnosis and management. Heart 2004;90: 1224–28.
[13] Gustafsson BI, Hauso O, Drozdov I, Kidd M, Modlin IM. Carcinoid heart disease. International Journal of Cardiology. 2008; 129:318–324.

compared with 90 months for patients with a moderately high level (hazard ratio=3.33; 95% CI 1.66-6.66; p=0.001).[14],[15]

2.1.5. Management

Somatostatin analogues (SSAs), such as lanreotide and octreotide are the standard therapy for the relief of CS and tumor stasis. Somatostatin analogs inhibit the release of serotonin by NETs and have become first-line therapy for CS providing the most efficient treatment for the control of flushing, diarrhea, and other symptoms.[16] Results from the PROMID and CLARINET studies demonstrated the antiproliferative effects of octreotide and lanreotide Autogel. [17, 18] Therefore, use of SSAs to reduce tumour proliferation has become increasingly common in the treatment paradigm for many patients with NET with or without symptoms.

There is also some use of supplemental doses of short-acting SSA therapy for those who do not have sufficient control with a long-acting release (LAR) Depot formulation. Surgical debulking of tumours, radiation, various liver-directed therapies, and chemotherapy may be attempted as a way of addressing overall tumour burden and reducing associated serotonin production.[19, 20] There are no approved treatment options for patients not adequately controlled on SSAs, who continue to experience debilitating symptoms. Since there are limited treatment options available in refractory CS, pasireotide injections might be considered in highly selected patients when other treatments failed or are not feasible. However, pasireotide is not approved for the treatment of CS.

The effect of SSA therapy may diminish with time after 3 months up to more than 2 years of treatment. [21, 22, 23] Based on the evidence reported[24] , it appears that tachyphylaxis may occur in 10.0% to 63.6% patients, or hepatic tumour load can increase. When a patient's response to SSA therapy declines, it is an accepted practice to continue SSA therapy while initiating additional treatments, including additional prescribed and over-the counter medications.[25]

[14] Turaga KK, Kvols LK. Recent progress in the understanding, diagnosis, and treatment of gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin. 2011;61(2):113-132.
[15] van der Horst-Schrivers AN, Post WJ, Kema IP, et al. Persistent low urinary excretion of 5-HIAA is a marker for favourable survival during follow-up in patients with disseminated midgut carcinoid tumours. Eur J Cancer. 2007;43(18):2651-2657.
[16] Modlin IM, Pavel M, Kidd M, Gustafsson BI. Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. Aliment Pharmacol Ther 2010;31(2):169-188.
[17] Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 2014;371(3):224-33.
[18] Rinke A, Müller D. Profile of lanreotide autogel and its potential in the treatment of gastroenteropancreatic neuroendocrine tumors. Gastrointestinal Cancer: Targets and Therapy 2015:5 123–130.
[19] Kulke MH, Siu LL, Tepper JE et al. Future Directions in the Treatment of Neuroendocrine Tumors: Consensus Report of the National Cancer Institute Neuroendocrine Tumor Clinical Trials Planning Meeting. J Clin Oncol 2011; 29:934- 43.
[20] 34 Öberg K et al. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii124-30.
[21] Toumpanakis C, Garland J, Marelli L, et al. Long-term results of patients with malignant carcinoid syndrome receiving octreotide LAR. Aliment Pharmacol Ther. 2009;30:733–40.
[22] Khan MS, El-Khouly F, Davies P, et al. Long-term results of treatment of malignant carcinoid syndrome with prolonged release Lanreotide (Somatuline Autogel). Aliment Pharmacol Ther. 2011;34: 235–42.
[23] Janson ET, Oberg K. Long-term management of the carcinoid syndrome. Treatment with octreotide alone and in combination with alpha-interferon. Acta Oncol.1993;32:225–9.
[24] Wolin EM, Jarzab B, Eriksson B et al. Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues. Drug Des Devel Ther. 2015 Sep 3;9:5075-86.
[25] Strosberg, J., Clinical Benefits of Above-Standard Dose of Octreotide LAR in Patients With Neuroendocrine Tumors for Control of Carcinoid Syndrome Symptoms: A Multicenter Retrospective Chart Review Study. Oncologist, 2014; 19(9):930-936.

About the product

Telotristat etiprate is an orally administered small molecule inhibitor of tryptophan hydroxylase (TPH). In the blood telotristat etiprate appears as telotristat ethyl and its active metabolite telotristat (LX1033 or LP-778902).

LX1033 or LP-778902, the active metabolite of telotristat etiprate, was designed not to cross the blood-brain barrier (BBB). A previously studied TPH inhibitor, parachlorophenylalanine, failed in clinical development because it crossed the BBB and resulted in serious central nervous system (CNS) side effects (Engelman 1967, Turaga et al., 2011). A peripherally acting TPH inhibitor such as telotristat etiprate should alleviate CS with a better CNS profile allowing for long-term treatment.

Both the prodrug (telotristat ethyl) and its active metabolite (telotristat) are inhibitors of L-tryptophan hydroxylases (TPH1 and TPH2, the rate limiting steps in serotonin biosynthesis). Serotonin plays a critical role in regulating several major physiological processes, including secretion, motility, inflammation, and sensation of the gastrointestinal tract, and is over-secreted in patients with carcinoid syndrome. Through inhibition of peripheral TPH1, telotristat reduces the production of serotonin, thus alleviating symptoms associated with carcinoid syndrome.

Type of Application and aspects on development

The applicant applied for the following indication:

- Xermelo is indicated as an adjunct to somatostatin analogue therapy for the long-term treatment of carcinoid syndrome to improve symptom control in adult patients with metastatic neuroendocrine tumours.

The final agreed indication is as following:

- Xermelo is indicated for the treatment of carcinoid syndrome diarrhoea in combination with somatostatin analogue (SSA) therapy in adults inadequately controlled by SSA therapy.

Posology

The recommended dose is 250 mg three times daily (tid).

Available data suggest that clinical response is usually achieved within 12 weeks of treatment.
It is recommended to reassess the benefit of continued therapy in a patient not responding within this time period.

Based on the high inter-subject variability observed, accumulation in a subset of patients with carcinoid syndrome cannot be excluded. Therefore, intake of higher doses is not recommended (see section 5.2).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing telotristat etiprate equivalent to 250 mg telotristat ethyl (free base).

Other ingredients are:

For the tablet core: anhydrous lactose, hydroxypropylcellulose, croscarmellose sodium, magnesium stearate and colloidal anhydrous silica.

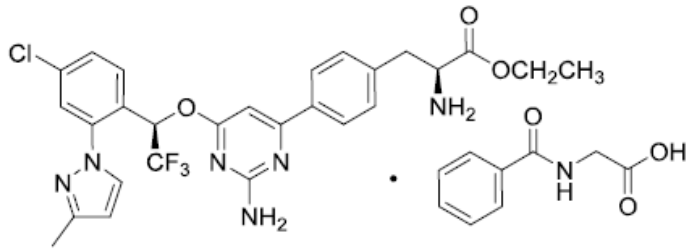
For the film-coating: polyvinyl alcohol (partially hydrolysed) (E1203), titanium dioxide (E 171), macrogol 3350 (E1521) and talc (E553b).

The product is available in PVC/PCTFE/PVC/Al blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of telotristat etiprate is [(1S)-1-[[4-[2-amino-6-[(1R)-1-[4-chloro-2-(3-methylpyrazol-1-yl)phenyl]-2,2,2-trifluoro-ethoxy]pyrimidin-4-yl]phenyl]methyl]-2-ethoxy-2-oxo-ethyl]ammonium; 2-benzamidoacetate corresponding to the molecular formula $C_{27}H_{26}ClF_3N_6O_3 \bullet C_9H_9NO_3$. Telotristat etiprate is a salt containing telotristat ethyl and hippurate. It has a relative molecular mass of 754.2 g/mol and the following structure:



The active substance is a non-hygroscopic white to off-white crystalline powder. Its solubility is pH-dependent. Due to its low permeability and low solubility, it is classified as BSC class 4.

Telotristat etiprate exhibits isomerism as it contains two chiral centre. Enantiomeric purity is controlled routinely by chiral HPLC.

Polymorphism has been observed for the active substance under certain conditions, notably under stress conditions using solvents and/or conditions not employed during active substance manufacture. The Applicant consistently produces the same polymorphic form.

The Applicant has performed comparative structural analysis to show that telotristat etiprate is to be regarded as a new active substance (NAS) in itself and that it is not a salt, complex, derivative or isomer (nor mixture of isomers) of a previously authorised substance.

Manufacture, characterisation and process controls

The active substance is synthesized by one manufacturer in a six-step synthesis using well-defined starting materials with acceptable specifications.

Since the use of class I solvent in the synthesis of one of the starting materials is avoidable, the CHMP recommended the deletion of the synthesis that uses class I solvent to manufacture the starting material.

A rework procedure has also been proposed and it is considered acceptable.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The structure of the active substance has been confirmed by the following methods: elemental analysis, ^{1}H-NMR, ^{13}C-NMR and 2-D NMR, FT-IR, UV analysis, MS, MS/MS, XRPD, optical rotation and DSC. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities including genotoxic impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in LDPE bag closed with a tie placed into a second LDPE bag, also closed with a tie and placed in a HDPE drum or equivalent secondary container. The LDPE bag complies with Ph. Eur. monograph 3.1.3 (Polyolefins) and the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance, identity (IR, HPLC, chiral HPLC), assay (HPLC), impurities (HPLC, chiral HPLC), residual solvents (GC), water content (KF), and residue on ignition (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

Justifications were provided and accepted for the omissions of a number of tests including particle size distribution, specific optical rotation, polymorphism control, microbial analysis and specific residual impurities.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data are provided for several batches of the active substance including production scale batches manufactured at the proposed manufacturing site according to the commercial process.

Batches manufactured with initial manufacturing processes show OOS results for impurities and assay. Otherwise, all batches are within specifications and demonstrate batch to batch consistency of the manufacturing process.

Stability

Stability data were provided for three production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 18 months under long term conditions at 25 ºC / 60% RH and minimum 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

The following parameters were tested: appearance, identification, assay, related substances, water content and stereoisomeric impurities. The analytical methods used were the same as for release and were stability indicating.

For the long term and accelerated storage conditions, all tested parameters were within the specifications. No significant changes were observed. A slight increasing trend is observed for impurities when stored at 25°C/ 60% RH. When stored at 40°C/ 75% RH an increase of one impurity, which is well within the specified limit, is observed.

A forced degradation study was performed on one batch in both solid and solution state (solid state: heat, photolytic stress according to ICH Q1B option 1, solution state: acid, base, oxidation, photolytic stress).

The results of stress tests showed that the active substance is susceptible to acidic, oxidative and photolytic conditions. The active substance is stable when submitted to thermal/humid and photolytic stress. Active substance solutions however showed pronounced degradation when submitted to forced degradation.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is white to off-white, film-coated oval tablet with “T-E” debossed on one side and “250” debossed on the other side.

Telotristat etiprate is an inhibitor of the enzyme tryptophan hydroxylase, and is thus a serotonin synthesis inhibitor. Telotristat ethyl is the prodrug of the pharmacologically active entity, LP-778902 (LX-1033), which is the product of hydrolysis of the ethyl ester of telotristat etiprate. Although LP-778902 (LX1033) is the active moiety, it has very low permeability and is a Pg-p substrate; therefore the prodrug, telotristat ethyl , was synthetized to increase permeability, increase exposure to the target (the enzyme tryptophane hydroxylase), and to enhance oral bioavailability for the active moiety to the systemic serotonin producing tumors.

As a starting point, the scientific approach for product development followed a Quality Target Product Profile (QTPP) which took into account the expected route of administration; the dosage form and the stability expected (refer to table 2). This development program supported product development activities and provided key inputs to the formulation and process design such as the finished product composition intended for commercial products and the general manufacturing pathway.

Table 1: Finished product QTPP

QTPP elements		**Target**
Dosage form		Tablet
Dosage design		Immediate release tablet with coating and debossing
Route of administration		Oral
Dosage strength		250 mg (based on free base)
Shelf life		≥ 3 years at 25° C/60% RH
Biocompatibility		Acceptable toleration on oral administration
Drug product quality attributes	Physical Attributes	White to off-white coated tablet appropriate for debossing.
	Identification	Complies with reference standard
	Assay	Meets pharmacopoeia requirements for oral forms
	Content Uniformity	Meets pharmacopoeia requirements for oral forms
	Dissolution	Appropriate for an immediate release oral dosage form
	Degradation Products	Below safety threshold, or qualified
	Water Content	Appropriate to achieve the target shelf-life
	Microbial Limits	Meets pharmacopoeia requirements for oral forms

Pharmacopoeia compliance	Meets pharmacopoeia requirements for oral forms
Container closure systems	Appropriate to achieve the target shelf-life and ensure tablet integrity during shipping

Physicochemical characteristics of the active substance like solid-state forms, biopharmaceutical attributes, particle size, hygroscopicity, chemical stability and compatibility with excipients have been taken into account for the pharmaceutical development.

The effect of active substance particle size distribution on dissolution of finished product batches has been determined.

The compatibility of the active substance with the excipients has been adequately demonstrated. The role, the choice of the excipients and their concentration has been satisfactorily justified.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards with the exception of the film-coating material which is tested according to an in-house specification. However all components of the film-coating material comply with Ph. Eur. standards. Additional controls are also included in the lactose anhydrous and hydroxypropyl cellulose specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Different formulations of the finished product have been produced for the clinical studies and their composition and improvements regarding product performance have been shown precisely.

The initial goal of telotristat etiprate clinical product development was to develop a capsule formulation that facilitated assessment of a range of doses. During stability studies of the telotristat etiprate capsules used in initial clinical studies, significant hydrolysis of telotristat etiprate was observed, and thus development studies were performed to create a chemically more stable tablet formulation.

The goal of telotristat etiprate product Phase 3 clinical formulation and commercial formulation development was to develop a tablet dosage form with requisite active substance stability, fast dissolution profile, high drug loading (250 mg free base per tablet), and satisfactory manufacturability.

The critical quality attributes for telotristat etiprate tablets as identification, assay, content uniformity, dissolution, related substances, water content and microbial limits which affect the safety and efficacy have been assessed during product and process development.

Bioequivalence study was performed between the 250 mg capsule formulation and the proposed 250 mg tablet commercial formulation. Bioequivalence between the two formulations could not be concluded.

Dissolution method was satisfactorily developed. The dissolution testing has been performed in different buffers covering the physiological pH range.
The dissolution method has been demonstrated to discriminate tablets with different levels of coating as well as different formulations i.e. coated tablets vs capsules.

During manufacturing process development the final manufacturing process up to production scale batch size was selected and optimised. Some QbD elements were used during the development phase to investigate the Critical Quality Attributes (CQA) that could impact the Quality Target Product Profile (QTPP) and to identify the critical process parameters (CPPs), the classical approach has been retained for the control strategy of commercial batches and no design space is claimed.

The primary packaging is a PVC/PCTFE/PVC film with paper backed push-through aluminium foil blister. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 8 main steps: pre-roller compacting blending, roller compaction and milling, final blending, tablet compression, tablet coating, primary packaging. The process is considered to be a standard manufacturing process.

Critical process parameters were identified. The in-process controls are suitable for this type of manufacturing process. Optimum operating ranges evaluated during pharmaceutical development are proven acceptable ranges. Formal validation will be performed post-approval on the first three consecutive commercial batches, prior to launching the product. An acceptable validation plan has been provided. In addition the applicant has provided the validation data for three commercial scale batches manufactured for US market to support the process validation for the EU batches. The results confirm that the process is reproducible.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form : product appearance (Visual), tablet dimensions, identification (HPLC), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution, water content (KF), microbial purity (Ph. Eur.).

The omission of chiral purity and crystallinity test from the finished product specification has been justified based on batch analysis and stability data. There is also no specification for inorganic impurities based on a risk assessment as per ICH Q3D and batch data. Absence of hardness and friability control in the specification was justified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three pilot scale batches and one production scale batch confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided for 3 pilot scale batches of finished product stored under long term conditions for 24 months at 25 ºC / 60% RH or 30 °C / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for tablet description, assay, degradation products, dissolution, water content, and microbiological quality. The analytical procedures used are stability indicating.

No significant changes have been observed.

In addition, two pilot batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results demonstrate that the product is not light sensitive.

A cycling temperature stability study has been conducted on two finished product batches. Results demonstrated that the freezing-thawing cycles do not impact the quality of the finished product as results of the test are all within the specification.

Additional stress stability studies performed at -20°C/ambient humidity for up to 24 months and at 50°C/ambient humidity and 60°C/ambient humidity for 4 weeks concluded that extreme temperatures do not impact the quality of the finished product as results remain within set specifications. The only parameter that changed significantly was appearance after 4 weeks at 60°C/ambient humidity, with tablets changing from a white tablet with a white core to a cream /tan colored tablet with a white core. Nevertheless, as the quality control testing for all other tests (including assay and degradation impurities) are well below the specification limits this change is judged to not impact the finished product quality and therefore no specific storage conditions should be set on labelling.

Samples of a full-scale production batch have been included in a study to confirm the bulk stability of the tablets in the production area. The packaging is the same as intended for commercial production. Stability of bulk tables is demonstrated.

A simulating shipping study was carried out. It was concluded that packaging configuration chosen is suitable for shipment of bulk tablet by road or by air. All results met the specifications.

Based on available stability data, the proposed shelf-life of 30 months with no specific labelling statement as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was a minor unresolved quality issues related to the active substance starting material synthesis having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Deletion of Option 1 route of synthesis for a specific the starting material through a variation at the latest before the renewal of the marketing authorisation.

2.3. Non-clinical aspects

2.3.1. Introduction

The safety pharmacology, pharmacokinetic, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity studies were performed according to GLP principles. Telotristat etiprate was evaluated in mice, rats, dogs, rabbits and monkeys models. Primary pharmacodynamics of telotristat etiprate/ethyl and/or its active metabolite LP-778902 were tested in vitro and in vivo. One enzyme (human TPH isoforms) and two cell-based (rat and human cells) in vitro assays were performed to show the inhibitory effect of telotristat etiprate, telotristat ethyl or LP-778902 on its target TPH and off target effects on human phenylalanine hydroxylase (PAH) or tyrosine hydroxylase (TH). In vivo pharmacodynamics after a single or multiple doses of telotristat etiprate/ethyl were determined in mice, rats, dogs and monkeys.

The acute and repeated-dose toxicity of etiprate was studied in mice, rats and dogs. The dog was used as the non-rodent species for toxicity studies as it had systemic exposure to both telotristat ethyl and LP-778902 after oral dosing. Developmental and reproductive toxicity studies were performed in rat and rabbit, carcinogenicity studies were performed in mice. A 2 year rat carcinogenicity study is still ongoing. The pivotal studies of this programme were conducted in compliance with GLP regulations.

The whole package of reproductive toxicity studies was conducted in accordance with ICH S5. Embryofoetal development studies in rats and rabbits were preceded by dose range finding studies (DRF), whereas dose selection for the remaining reproductive toxicity studies was based on the results of the repeated dose toxicity studies in rats and - additionally for the prenatal and postnatal development study - on the results of the embryofoetal development study, respectively. All studies including DRF studies were performed in compliance with GLP. For all studies the oral route of administration (gavage) was chosen and methylcellulose in purified water served as vehicle.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro

One enzyme (human TPH isoforms) and two cell-based (rat and human cells) *in vitro* assays were performed to show the inhibitory effect of telotristat etiprate, telotristat ethyl or LP-778902 on its target TPH and off target effects on human phenylalanine hydroxylase (PAH) or tyrosine hydroxylase (TH).

Table 2: Summary of in *vitro* inhibitory activity of prodrug – telotristat ethyl (LX1606), active metabolite (LP-778902) and minor metabolite (LP-951757)

	IC_{50} (nM)		
Target	**LP-778902**	**LX1606**	**LP-951757**
Human Tryptophan Hydroxylase Type 1 (TPH1)	28 ± 3 (7)	800 ± 90 (4)	> 10,000 (2)
Human Tryptophan Hydroxylase Type 2 (TPH2)	32 ± 4 (2)	1210 ± 20 (2)	ND
RBL-2H3 (rat leukemia cell line)	6 ± 1 (7)	11 ± 4 (4)	ND
BON (human carcinoid cell line)	180 ± 40 (5)	100 ± 20 (3)	ND
Human Phenylalanine Hydroxylase (PAH)	> 10,000 (2)	> 10,000 (2)	ND
Human Tyrosine Hydroxylase (TH)	> 10,000 (2)	> 10,000 (2)	ND
ND = not determined Data expressed as Mean ± SEM (N) Data for LX1606 and LP-778902 from P103-002, Table 1; Data for LP-951757 from 160629			

In vivo

In mice, rats and dogs telotristat etiprate/ethyl reduced blood and GI 5-HT from the lowest dose in a dose dependent fashion after single or multiple treatments throughout studies.

5 Day Oral Gavage Toxicity Study of LP-778914-02-002 in the Male Sprague-Dawley Rats, (IVT-06-021), Rodent pharmacology summary report P103-002

5 rats per group were dosed orally with vehicle (15% Captisol) or telotristat ethyl. Doses in this study were 10, 30, 150, or 400 mg/kg/day. Following the last dose, animals were sacrificed; 5-HT levels were measured in jejunum, ileum, proximal colon, distal colon, blood, and brain. Brain levels of 5-HIAA were also determined.

Telotristat ethyl caused a significant, dose-dependent reduction of 5-HT in both the small and large intestine. Approximately 70 to 80% depletion was achieved throughout the intestine at the highest dose. A statistically significant reduction in blood 5-HT levels was noted at doses ≥ 150 mg/kg/day. In contrast, no significant change in either 5-HT or 5-HIAA was observed in the brain at dose levels up to 400 mg/kg in this study.

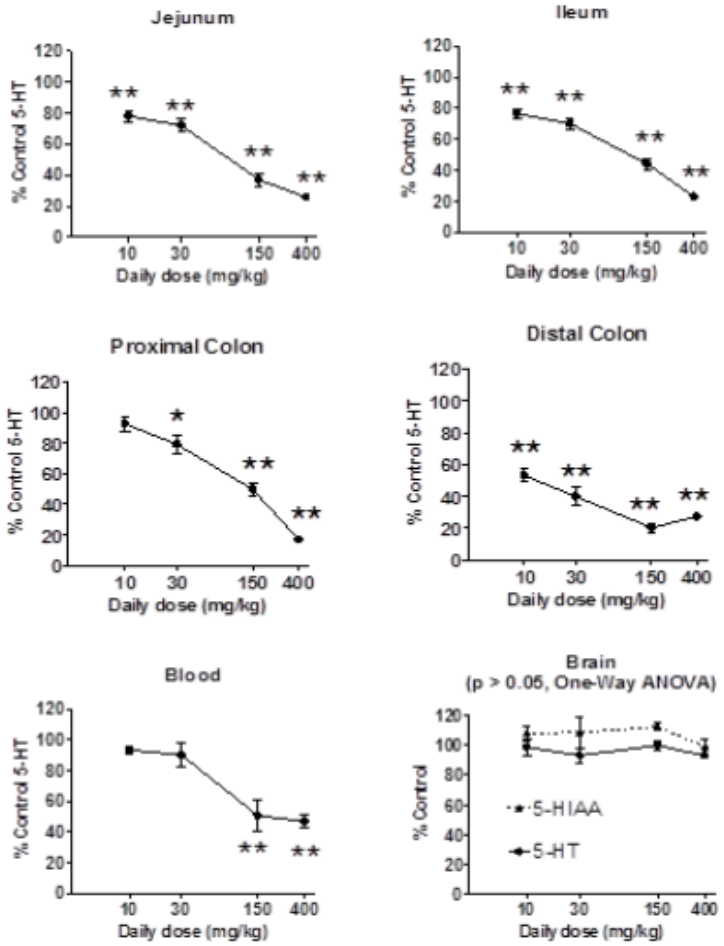
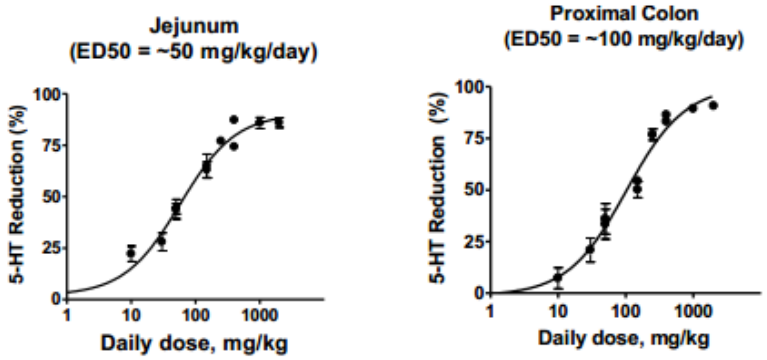


Figure 1: Change of 5-HT in blood, jejunum, ileum, proximal and distal colon and brain in rats

All data are presented as percentage of the mean of the control (vehicle-dosed) group. Error bars are S.E.M. * $p < 0.05$; ** $p < 0.01$ vs. control group (One-Way ANOVA and Dunnett's Test). N = 5/group. Source: P103-002,

Estimation of ED 50 of telotristat ethyl administration, PO in intestine in rat, (P103-002).

The data for intestinal 5-HT reduction from 3 studies in the rat were combined and used to estimate an ED50 of telotristat ethyl in the intestine. Telotristat ethyl caused a robust, sigmoid dose-dependent reduction of 5-HT in both the small and large intestine, with an ED50 of approximately 50 and 100 mg/kg/day in the jejunum and proximal colon, respectively.



Data from 3 studies are plotted. In all studies, telotristat ethyl was given by oral gavage, once daily for 5 consecutive days. All % reduction data were relative to vehicle control group of the corresponding study. Error bars are S.E.M. Source: P103-002, Figure 3

Figure 2: Estimated ED50 of administered telotristat ethyl in the intestine in rats, PO

14 Day Oral Gavage Study in Male Rats to Assess the Safety and Tolerability of LP-778914-03-005 (IVT-07-006).

Five male Sprague-Dawley rats per dose group were dosed orally with vehicle (0.25 MC) or telotristat etiprate at doses of 500, 1000, or 2000 mg/kg/day. Blood 5- HT levels were determined after the last dose of telotristat etiprate.

Results: telotristat etiprate produced a statistically significant decrease in 5-HT levels in the blood for all dose levels

Table 3: Summary of findings

	5-HT (% Reduction vs. Control)
Dose Group (mg/kg/day)	**Blood**
500	-87.9%‡
1000	-91.0%‡
2000	-86.8%‡**

‡ Significantly different ($p<0.05$) from control using One-Way ANOVA and Dunnett's Test.
** All high dose animals sacrificed moribund on Day 9. Data collected during unscheduled necropsy on Day 9 of the study.
Source: IVT 07-006, Summary of findings

Table 4: Exposure to major metabolite reached after IV administration of metabolite and PO administration of parent drug on 1, 3 and 7 days in beagle dogs

Single Dose					
Dose (mg/kg)	**Compound**	**Dose Route**	**C_{max} (ng/mL)**	**T_{max} (hrs)**	**AUC_{0-24} (hr*ng/mL)**
5	LP-778902	IV	13695 ± 4014	0.42 ± 0.14	10828 ± 3315
10	LP-778902	IV	28723 ± 5318	0.50 ± 0.00	24012 ± 4407
20	LP-778902	IV	37917 ± 1127	0.83 ± 0.29	58287 ± 4338
200	Telotristat etiprate	Oral	3497 ± 1925	3.00 ± 1.73	27696 ± 14380
3 Days of Dosing					
Dose (mg/kg)	**Compound**	**Dose Route**	**C_{max} (ng/mL)**	**T_{max} (hrs)**	**AUC_{0-24} (hr*ng/mL)**
5	LP-778902	IV	13750 ± 2924	0.33 ± 0.14	10266 ± 3952
10	LP-778902	IV	31862 ± 851	0.36 ± 0.24	27283 ± 3605
20	LP-778902	IV	33056 ± 679	1.00 ± 0.00	51461 ± 3142
200	Telotristat etiprate	Oral	4308 ± 364	3.33 ± 1.15	28819 ± 10794
7 Days of Dosing					
Dose (mg/kg)	**Compound**	**Dose Route**	**C_{max} (ng/mL)**	**T_{max} (hrs)**	**[1]AUC_{0-12} (hr*ng/mL)**
5	LP-778902	IV	13722 ± 1721	0.25 ± 0.00	10612 ± 1907
10	LP-778902	IV	29945 ± 4257	0.50 ± 0.00	25072 ± 4247
20	LP-778902	IV	31139 ± 1901	0.69 ± 0.34	44419 ± 4298
200	Telotristat etiprate	Oral	6247 ± 1469	2.67 ± 1.15	39340 ± 7050

All values represent the mean ± SD of 3 observations

For the 5 mg/kg IV and 10 mg/kg IV groups, LP-778902 was infused over 30 minutes at a dose volume of 5 mL/kg/day; for the 20 mg/kg IV group, LP-778902 was infused over 60 minutes at a dose volume of 10 mL/kg/day

[1] For single dose and 3 days of dosing, $AUC_{(0-24)}$ is presented. For 7 days of dosing, $AUC_{(0-12)}$ is presented; the 24 hour time point was eliminated from the PK parameter calculations due to an abnormally high level (>30 fold higher than the level seen at 0.25 hour time point) of LP-778902 in the 200 mg/kg telotristat etiprate oral group.

Source: LX1606-N19, Appendix 2, Table 4, Table 5, Table 6, Table 10

In rats and dogs reductions in brain 5-HT were observed at 1000 mg/kg/day and 500 mg/kg/day, respectively indicating that telostristat etiprate/ethyl and/or LP-778902 pass the blood brain barrier at higher concentrations in these species.

In monkeys telotristat etiprate also reduced blood 5-HT levels; this effect however was much weaker when compared to other animal species.

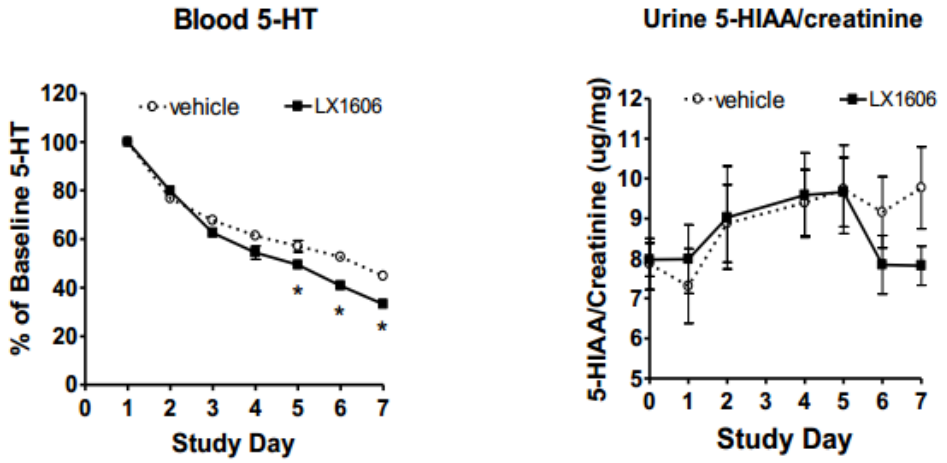
Monkeys

Collection of Samples for Determination of the Pharmacokinetics/Pharmacodynamics of LP-778914 Following Once-Daily Oral Doses for 7 Days and a Single Intravenous Dose to Monkeys , (Covance Report 7648-187).

Fourteen cynomolgus monkeys (10 males, 4 females) were divided into 2 groups (5 males, 2 females in each group). One group received telotristat ethyl at 75 mg/kg (0.25 MC), once daily for 7 days by oral gavage. The other group received vehicle only.

5-Hydroxytryptamine concentration in blood declined steadily in both the vehicle- and telotristat ethyl-dosed groups. The reason for the reduction in blood 5-HT in vehicle-dosed animals is unclear. Nevertheless, animals dosed with telotristat ethyl showed a greater decline in blood 5-HT concentrations compared to those dosed with vehicle. This effect emerged beginning on Day 3 and became statistically significant on Days 5-7. In the urine, the ratio of 5-HIAA over creatinine was similar between the groups

until Day 6, when telotristat ethyl -dosed animals started to show a lower ratio. The difference at Day 7 between the groups did not reach statistical significance (p = 0.1, t test).



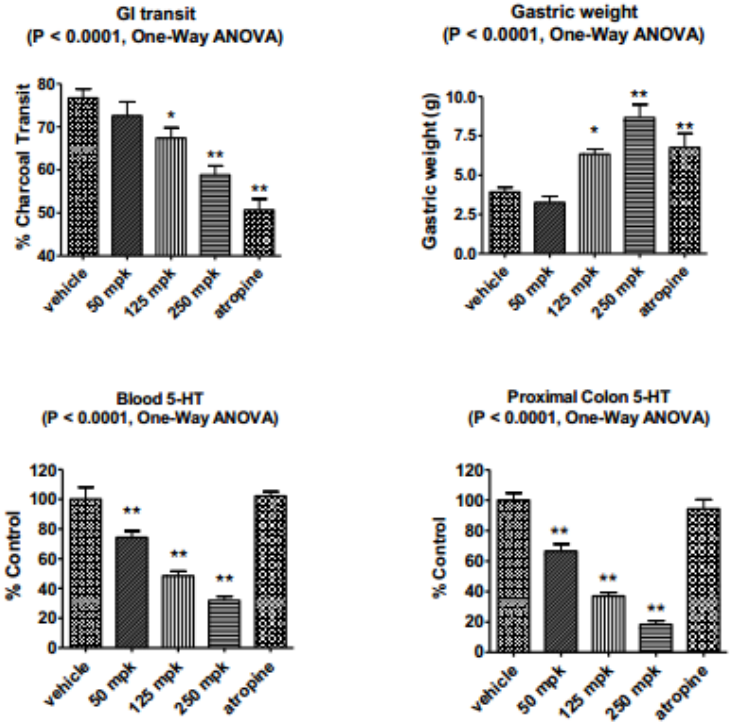
Blood 5-HT was normalized to each animal's own level on Day 1. Day 3 urinary 5-HIAA data were excluded due to dietary supplement of banana (which has high levels of tryptophan) on that day. Error bars are SEM.
* $p < 0.05$ vs. vehicle group (t test) . Source: 7648-187, Appendix 3, Figure 2, Figure 3

Figure 3: Effect of telotristat ethyl on blood 5-HT and urinary 5-HIAA in monkeys

The effect of telotristat etiprate or telotristat ethyl on GI motility was assessed in mice and rats. In mice, neither telotristat etiprate nor LP-778902 had any effect on percent charcoal transit. The effect of telotristat etiprate on GI motility was evaluated in the rat using the charcoal meal test (P103-002).

Three groups of male Sprague-Dawley rats (n = 6/group) were used in this study. One group of rats was dosed with telotristat etiprate at 250 mg/kg, once daily for 13 consecutive days while the other 2 groups were dosed once daily for 14 days with vehicle (0.25% methylcellulose). Rats in positive control group received vehicle for 13 days followed by atropine (150 mg/kg) on Day 14.

Telotristat etiprate dosed animals showed a significant decrease in GI transit and an increase in gastric weight (indicating a decrease in gastric emptying) when compared to vehicle-dosed animals. 5-Hydroxytryptamine levels in blood and colon were reduced by 73% and 81%, respectively. Atropine, delayed gastric emptying and GI transit but did not alter GI and blood 5-HT levels.



Atropine was used as a positive control for decreasing GI motility. Error bars are S.E.M. * $P < 0.05$; ** $p < 0.01$ vs. control (One-Way ANOVA and Dunnett's Test). N = 9/group (vehicle and telotristat etiprate groups). For atropine, N = 6. Source: P103-002, Figure 5

Figure 4: Change of GI Motility and 5-HT in Rats Administered Telotristat Etiprate for Two Weeks at Different Dose Levels

Secondary pharmacodynamic studies

In vitro secondary pharmacodynamic studies focused on receptor/enzyme interaction potential and cytotoxicity of telotristat ethyl and LP-778902. In vivo studies were conducted to determine if telotristat possesses any anti-tumour activity and if it is effective in chemically-induced colitis models.

Telotristat ethyl and LP-778902 were tested for their interaction potential with 75 relevant human receptors, enzymes and ion channels. Telotristat ethyl showed a more than 50% inhibition at 16 of the 75 receptors indicating a high in vitro interaction potential. In contrast LP-778902 only showed a weak interaction potential with these receptors, however, a > 50% inhibition was observed at 10 µM at the A_3, $5\text{-}HT_{1B}$ and $5\text{-}HT_{2A}$ receptors. Telotristat ethyl is rapidly converted to LP-778902 and thus only appears at low concentrations in the circulation. In addition telotristat ethyl is highly protein bound in plasma. At the maximum human dose tested of 500 mg tid. LP-778902 only reaches C_{max} levels in the nanomolar range.

No anti-tumour activities of telotristat etiprate were observed in a Hep3B human hepatocellular xenograft mouse model and a model of patient derived tumour material which was implanted subcutaneously into FOXN1 nude mice.

In study LX1606-N41, mice treated with telotristat etiprate showed significantly less weight loss compared to vehicle treated, however weight loss was not modified by the other compounds including LP-778902.

In study LX1606-N32, only telotristat etiprate had significant effects in a model of chemically induced colitis, while its active metabolite LP-778902 was less effective.

Safety pharmacology programme

A standard battery of safety pharmacology studies has been performed with telotristat etiprate. In addition LP-778902 was tested at 2 doses in the hERG assay. All studies were performed according to GLP.

Table 5: Overview and major findings of performed safety pharmacology studies with telotristat etiprate and LP-778902

Study Number	Study Type	Species	Dose (mg/kg)	Major findings
LX1606-N08	Central Nervous System	Sprague Dawley rats	Telotristat etiprate:0, 100, 500 and 2000 mg/kg	Telotristat etiprate produced no significant adverse behavioural or physiological changes when compared to vehicle.
LX1606-N17	hERG assay	In vitro, hERG transfected HEK293 cells	LP-778902: 0, 1, 10 µM telotristat etiprate: 0, 0.1, 0.3, and 1 µM	LP-778902 significantly (n=3) inhibited hERG currents by 3.7 ± 0.6% at 0.84 µM and 28.1 ± 1.1% at 10 µM. Telotristat etiprate significantly (n=3) inhibited hERG currents by 6.1 ± 1.3% at 0.1 µM, 53.2 ± 1.7% at 0.3 µM, 80.9 ± 1.5% at 1 µM and 95% at 3 µM (only n=2)
LX1606	Cardiovascular effects	Male dog, beagle 4/group	0, 30, 100, 200 mg/kg telotristat etiprate single oral dose	No ECG changes and no arrhythmias occurred at any dose tested. Heart rate and blood pressure were unaffected. No effects on QT or QTc interval.
LX1606-N07	Respiratory system	Male rat, SD 8/group	0, 100, 500, 2000 mg/kg telotristat etiprate single oral dose	No significant adverse effects on tidal volume, rate of respiration, or minute volume when compared to vehicle.
LX1606-N09	Renal function	Male rat, Han Wistar 6/group	0, 100, 500, 2000 mg/kg telotristat etiprate single oral dose	At 100 and 500 mg/kg no changes in urinalysis parameters. At 2000 mg/kg significant decrease in urine output and a significant increase in K^+ excretion at 0-6 hours post dose and a significant decrease in Na^+, K^+ and Cl excretion at the

				6-24 hour collection period.
LX1606-N10	GI function	Male rat, Han Wistar 6/group	0, 100, 500, 2000 mg/kg telotristat etiprate single oral dose	At 100 no effect on GI transit or stomach emptying. At 500 and 2000 mg/kg significant decrease in GI transit and stomach emptying.

ECG = electrocardiogram; GI = gastrointestinal; hERG = human ether-a-go-go related gene; QTC = corrected QT interval

Pharmacodynamic drug interactions

Studies on pharmacodynamic drug interactions were not submitted (see non-clinical discussion).

2.3.3. Pharmacokinetics

A range of in vitro and in vivo absorption, distribution, metabolism, and excretion (ADME) studies have been performed in various species on telotristat ethyl and its active metabolite, LP-778902.

Absorption

The in vitro permeability of telotristat ethyl in Caco-2 cells suggests that both, telotristat ethyl and LP-778902 have low intestinal absorption.

The oral bioavailability of LP-778902 in the mouse at 50 mg/kg was approximately 12%.

The PK of telotristat ethyl and LP-778902 have been studied in mice, rats, rabbits, dogs, and monkeys. Telotristat ethyl exhibited generally low systemic exposure following oral administration in all species tested.

In the dog, exposure to both telotristat ethyl and LP-778902 increased in the presence of food. In fasted dogs emetic effects were observed which is likely to contribute to the notable lower Cmax and AUC0-t values in these animals compared to that observed in dogs given the same dose of compound in the fed state.

Following 6 daily doses of telotristat ethyl in the monkey, the plasma pharmacokinetic of LP-778902 was similar compared to single administration. No significant accumulation of LP-778902 in the plasma was evident upon multiple dosing.

A summary of the data is shown in Figure 5.

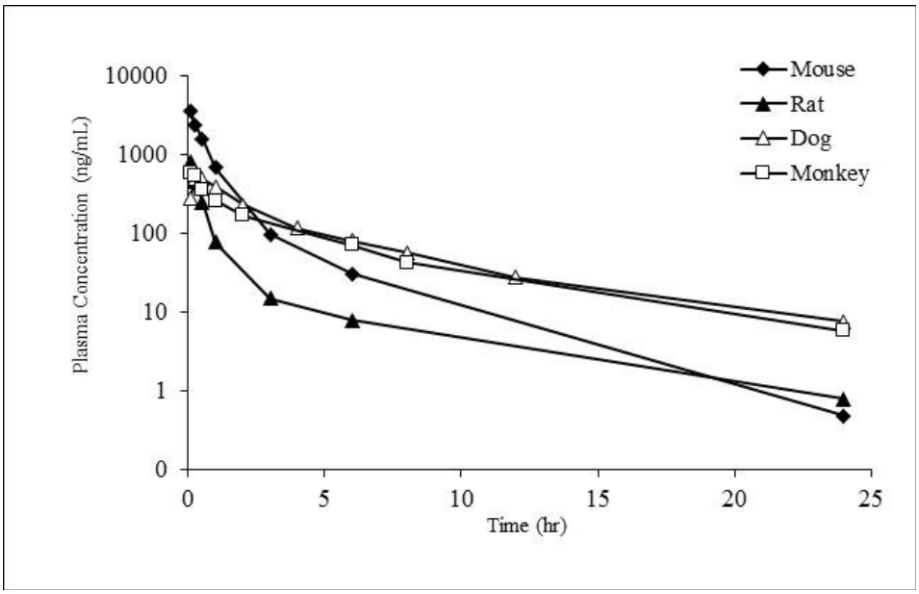


Figure 5: Plasma pharmacokinetics of LP-778902 after 1 mg/kg bolus intravenous injection of LP-778902 to rodents, telotristat etiprate to dogs and telotristat ethyl to monkeys

Distribution

In tissue distribution studies in Sprague-Dawley and Lister Hooded (partially-pigmented) rats exposure was limited to the contents of the GI tract, hepatic, and renal systems, with no measurable activity in the brain. In the Lister Hooded rat, there was no significant exposure to melanin-containing pigmented areas of the eye and skin.

No data on tissue distribution after repeated administration of telotristat ethyl has been submitted.

Both telotristat ethyl and LP-778902 exhibited very high plasma protein binding (> 96%) in all species tested, including human.

Metabolism

Telotristat ethyl is hydrolysed by carboxylesterase 1 and 2 to the corresponding acid, LP-778902. In human the conversion of telotristat ethyl to LP-778902 took place primarily in the intestine and liver and in rodents telotristat ethyl is also converted in plasma.

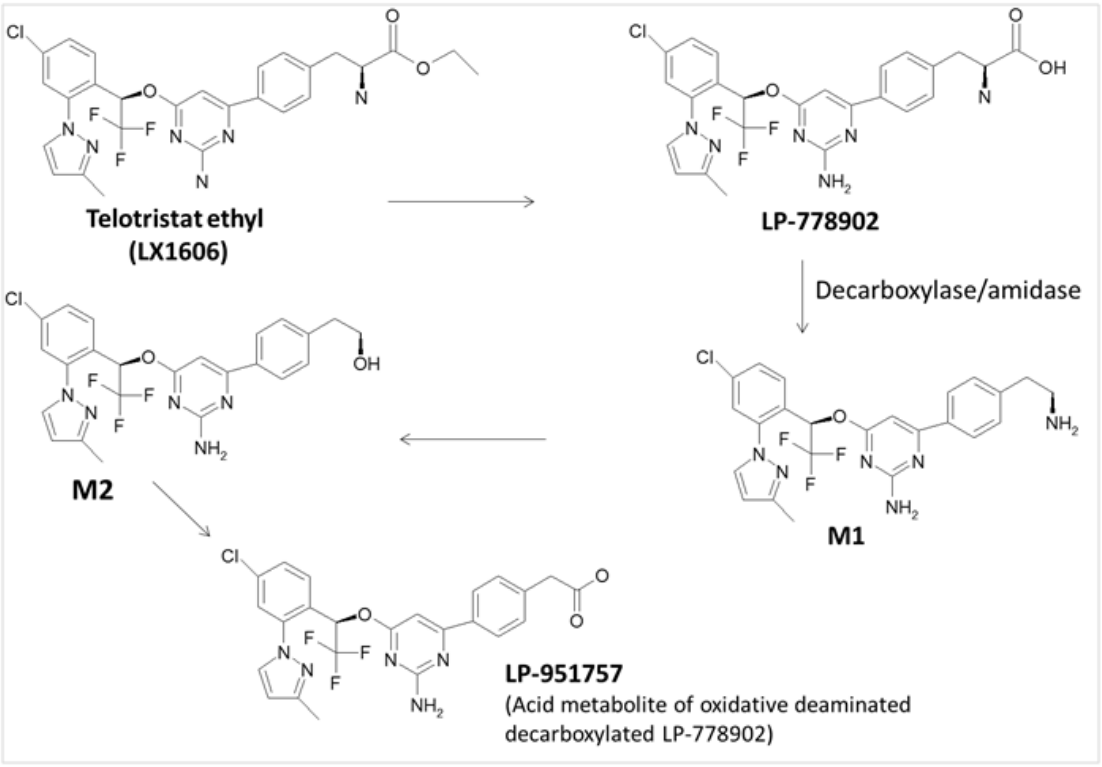


Figure 6: Proposed Metabolic Pathway of Telotristat Ethyl

In vivo metabolism studies in rats showed that exposure was markedly higher for LP-778902 when compared to LP-951757. For LP-951757, the Tmax was noticeably longer than that of LP-778902. In male and female Sprague-Dawley rats, following a once daily oral administration of telotristat etiprate for 7 days at 20, 60, and 170 mg/kg, exposure of telotristat ethyl, LP-778902 and LP-951757 was generally higher in females when compared to males, and no accumulation was observed on repeated dosing.

Excretion

In the rat, following oral administration of 14C-telotristat ethyl, radioactivity was almost exclusively eliminated in the faeces (≥ 86% of the administered dose) and less than 0.2% was excreted via the urine.

Table 6: Excretion of Radioactivity After a Single Oral Dose of 14C-Telotristat Ethyl to Male Sprague-Dawley Rats at 30 and 100 mg/kg

Dose (mg/kg)	Collection Interval (hr)	% of Radioactive Dose	
		Urine	Feces
30	0-8	0.06 ± 0.01	0.00 ± 0.00
	8-24	0.02 ± 0.01	88.1 ± 4.8
	Subtotal	0.08 ± 0.00	88.1 ± 4.8
100	0-8	0.06 ± 0.01	0.00 ± 0.00
	8-24	0.03 ± 0.00	92.1 ± 12.8
	Subtotal	0.09 ± 0.01	92.1 ± 12.8
Source: LX1606-N16 Data expressed as mean ± standard deviation of 3			

Pharmacokinetic drug interactions

Table 7: Cytochrome P450 Inhibition by Telotristat Ethyl and LP-778902 at 1 µM Concentration

P450 Isoenzyme	Telotristat Ethyl (% Inhibition)	LP-778902 (% Inhibition)	Study Reference
CYP1A2	0.0	0.0	160614
CYP2C9	73	46	160614
CYP2C19	11	28	160614
CYP2D6	23	19	160614
CYP3A4	79	18	160614
CYP2C8	15	0.6	XenoTech XT15A010
CYP2E1	-6.0	-4.0	XenoTech XT15A010
Source: 160614, XenoTech XT15A010			

Telotristat ethyl and its active metabolite (LP-778902) were not shown to be inducers of CYP3A4 at systematically-relevant concentrations, based on in vitro findings. The potential of telotristat ethyl as an inducer of CYP3A4 was not assessed at concentrations expectable at the intestinal level, due to its low solubility *in vitro*.

I*n vitro*, telotristat ethyl inhibited CYP3A4, suggesting a potential interaction with CYP3A4 substrates. For CYP1A2, there was high inter-donor variability, and it was concluded that there was little to no induction of CYP1A2 mRNA expression (<2-fold following treatment with telotristat ethyl and LP-778902).

In vitro telotristat (active metabolite) caused a concentration dependent increase in CYP 2B6 mRNA levels (>2-fold increase and >20% of the positive control, with a maximum observed effect similar to the positive control), suggesting possible CYP 2B6 induction.

The Applicant has conducted in vitro studies to assess the interaction of telotristat ethyl, its active metabolite LP-778902 and metabolite LP-951757 with the efflux transporters (P-gp, BCRP, MRP2 and BSEP), as well as the SLC transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3). In vitro telotristat ethyl inhibited P-gp, but its active metabolite did not at the clinically relevant concentrations. Telotristat ethyl inhibited MRP2-mediated transport (98% inhibition). Telotristat ethyl inhibited BCRP (IC50 = 20 µm), but its active metabolite telotristat did not show any significant inhibition of BCRP activity (IC50 > 30 µM). The potential for in vivo drug interaction via BCRP is considered low. Based on in vitro findings, no clinically-relevant interaction is expected with other transporters.

2.3.4. Toxicology

Single dose toxicity

Single dose studies were conducted in mice, rats and dogs to determine the acute toxicity of telotristat etiprate. An overview over the studies is given in Table 8.

Table 8: Single-Dose Oral Gavage Toxicity and Toxicokinetic Study with telotristat etiprate in Rats and Dogs

Study ID / Study type / GLP	Species; Number / group	Route & single dose [mg/kg]	Dosing period	Major findings	NOAEL [mg/kg/day]
Study No.: LX1606-N11 Single-Dose Oral Gavage Toxicity And Toxicokinetic GLP	Crl:CD (SD) rats 5 /sex/ group	0, 100, 500, 1000 and 2000 oral	Single dose with 14 d observation	None	NOAEL: 2000
Study No.: Lexicon LX1606-N15 Single Intravenous and Oral Doses of telotristat etiprate Non GLP	Beagle dogs Purebred beagle/ 17 ♂	Group 1 IV: 1 mg/kg Group 2 oral: 0, 50, 100, 200 and 500 +/- food	Single dose	500 mg/kg: emesis	Not determined

Repeat dose toxicity

An overview over the results of the 28-day repeat-dose study toxicity study is shown in Table 9.

Table 9: 28-Day Repeat-Dose Oral Toxicity and Toxicokinetic Study with Telotristat etiprate in Mice

Study ID / Study type / GLP	Species; Number / group	Route & dose [mg/kg/day]	Dosing period	Major findings	Maximal tolerated dose
Study No.: LX1606-N46 28 day oral Toxicity (based on 14 days dose-range-finding study) and Toxicokinetic GLP	Mouse / CByB6F1 10/group	0, 300, 750, and 1500 mg/kg/day (males); 0, 300, 750, 2000, and 3000 mg/kg/day (females) oral	28 days	All groups: nasal cavity inflammation and/or serocellular exudates ↑ 750 mg/kg/d: ♂: necrotizing inflammation ↑ 2000 mg/kg/d: ♂ : mortality ↑, ≥2000 mg/kg/d: ♀: All dead or sacrificed	300 mg/kg/day

An overview of the repeat-dose oral toxicity studies in rats is shown in Table 10.

Table 10: Repeat-dose Oral Toxicity and Toxicokinetic Studies with Telotristat etiprate in the Rat

Study ID / Study type / GLP	Species; Number / group	Route & dose [mg/kg/day]	Dosing period	Major findings	NOAEL [mg/kg/day]
Study No.: LX1606-N12 29 day oral Toxicity And Toxicokinetic GLP	Crl:CD(SD) rats 15 /sex/ Group 6 /sex/ Group	0, 100, 500, and 1000 oral	29 days with 14 days recovery	1000 mg/kg/d: 1 ♂and 4 ♀ sacrificed on day 12 all others on day 13 mean body weight↓, food consumption↓, hunched or thin appearance↑, few or liquid faeces rough ↑, discolored hair coat↑, piloerection ↑ 500 mg/kg/d: body weight↓ during first interval of recovery	NOAEL: 500
Study No.: LX1606-N22 3 Month oral Toxicity And Toxicokinetic GLP	Crl:CD(SD) rats 16 /sex/ Group	0, 50, 200 and 500 oral	13 week with 4 week recovery	500 mg/kg/d: Mean body weight↓	NOAEL: 500
Study No.: LX1606-N28 26-Week Oral Gavage Chronic Toxicity And Toxicokinetic GLP	Crl:CD(SD) rats 15 /sex/ Group 1,3 and 4 10 /sex/ Group 2	0, 50, 200 and 500 oral	26 week with 4 week recovery	≥200 mg/kg/d: degeneration/necrosis in the nonglandular and/or glandular portions of the stomach, protein droplets in the glandular portions↑ 500 mg/kg/d: ♂: mean body weight↓, mean food consumption↓, ♂ and ♀: mean absolute reticulocyte counts↓, rough hair coat↑	NOAEL: 50

An overview of the repeat-dose oral toxicity stuidies in dogs is shown in Table 11.

Table 11: Repeat-dose Oral Toxicity and Toxicokinetic Studies with Telotristat etiprate in the Dog

Study ID / Study type / GLP	Species; Number / group	Route & dose [mg/kg/day]	Dosing period	Major findings	NOAEL [mg/kg/day]
Study No.: LX1606-N20 7 repeated dose toxicity And Toxicokinetic GLP	Beagle Dog 5 /male/ Group	0, 10, 30, 100, and 200 oral	7 days	All: Dose dependent GI tract intolerance 30 and 100 mg/kg/d: Day 1 to 3: Emetic responses 500 mg/kg/d: Day 1 to 5: Emetic responses	NOAEL: 30
Study No.: LX1606-N14 4 weeks oral Toxicity And Toxicokinetic GLP	Beagle Dog 5 /sex/ Group 1 and 4 3 /sex/ Group 2 and 3	0, 30, 100 and 500/200 oral	4 week with 2 week recovery	≥100 mg/kg/d: food consumption ↑, nonformed, liquid and/or mucoid faeces, vomiting 500 mg/kg/d: decreased body weight, hypoactivity	NOAEL: 100
Study No.: LX1606-N23 3 month Oral Gavage Chronic Toxicity And Toxicokinetic GLP	Beagle Dog 5 /sex/ Group 1,3 and 4 3 /sex/ Group 2	0, 30, 100 and 200 oral	13 week with 4 week recovery	≥100 mg/kg/d: alterations in stool character hypospermatogenesis	NOAEL: 200
Study No.: LX1606-N27 39 week Oral Gavage Chronic Toxicity And Toxicokinetic GLP	Beagle Dog 6 /sex/ Group 1,3 and 4 4 /sex/ Group 2	0, 75, 150, 300	39 weeks with 4 week recovery	alterations in stool character ≥150 mg/kg/d: liquid faeces only during dosing phase, cholesterol ↑, AST ↑, liver/gallbladder weights (♂ only) ↑	NOAEL: 300

Genotoxicity

A standard battery of in vitro and in vivo genotoxicity tests was performed with telotristat etiprate. The active metabolite LP-778902 was only tested in in vitro in an Ames test and a chromosomal aberration assay. Main study details and results are summarized in Table 12.

Table 12: Overview of genotoxicity studies performed with telotristat etiprate and LP-778902

Type of test / study ID / GLP	**Test system**	**Concentrations / Concentration range / Metabolising system**	**Results Positive / negative / equivocal**
Telotristat etiprate Gene mutations in bacteria / LX1606-N03 (29093-C1; 290931-D1; 290931-D2) / Yes	Salmonella/E-Coli strains TA98/TA100/TA1535/TA1537/WP2*uvr*A	**+ S9 (TA98/TA100/TA1535/TA1537):** 3.33, 10.0, 33.3, 100, 333, 1000, 5000 µg/plate **- S9 (TA98/TA100/TA1535/TA1537):** 0.333, 1.00, 3.33, 10.0, 33.3, 100, and 333 µg/plate **+/- S9 (WP2*uvr*A):** 10.0, 33.3, 100, 333, 1000, 2500, 5000 µg/plate Plate incorporation for 52 ± 4 hours at 37 ± 2°C.	**Negative** for relevant increase in reverse mutations. + S9 (assays 1, 2): Signs of cytotoxicity at 1000 µg/plate (TA100, TA1537); at 5000 µg/plate (TA1535) -S9 (assay 2): signs of cytotoxicity at 33 µg/plate (TA98/TA100/TA1537); 10 µg/plate (TA1535); 2500 µg/plate (WP2*uvr*A) +/- S9 (assay 1): signs of cytotoxicity at 2500 µg/plate (WP2*uvr*A)
LP-778902 Gene mutations in bacteria / LX1606-N03/ Yes	Salmonella/E-Coli strains TA98/TA100/TA1535/TA1537/WP2*uvr*A	**+/- S9 (all strains):** 33.3, 100, 333, 1000, 2500, 5000 µg/plate Plate incorporation for 52 ± 4 hours at 37 ± 2°C.	**Negative** for relevant increase in reverse mutations. + S9 (assay1): Signs of cytotoxicity at 5000 µg/plate (all strains) -S9 (assays 1,2): signs of cytotoxicity at 5000 µg/plate (TA98/TA1535/TA1537/WP2*uvr*A)
Telotristat etiprate Chromosome aberration in mammalian cells / LX1606-N04 / Yes	Chinese hamster ovary (CHO) cells	- S9 20h/20h recovery: 3.75, 5.00, 6.50 µg/mL + S9 3h/20h recovery: 30.0, 60.0, 100 µg/mL	**No** clastogenicity +/- S9. 50% cytotoxicity -S9 at 6.50 µg/mL 53% cytotoxicity +S9 at 100 µg/mL and precipitation
LP-778902 Chromosome aberration in mammalian cells / LX1606-N04 / Yes	Chinese hamster ovary (CHO) cells	- S9 3h/20h recovery: 3.13, 6.25, 12.5 µg/mL + S9 20h/20h recovery: 100, 150, 300 µg/mL	**No** clastogenicity +/- S9. 55% cytotoxicity -S9 at 12.50 µg/mL Precipitation +S9 at 300 µg/mL
Telotristat etiprate / Micronucleus test / LX1606-N05 / Yes	Male SD rats (5/dose) micronuclei in bone marrow	0, 100, 500, 2000 mg/kg oral gavage once daily for 2 days Sampling 24 h after last administration	**No increase** in the number of micronucleated PCE's as compared to vehicle. Statistically significant decreases in micronucleated PCE's at 100 and 500 mg/kg/day.

			No change in PCE/NCE ratio as compared to vehicle. Clinical signs at 2000 mg/kg/day: yellow anal discharge, brown/green anal discharge, unformed faeces, red nasal discharge, red haircoat on the front legs, hunched posture, squinted eyes, irregular respiration, and/or hypoactivity.

Telotristat etiprate and its active metabolite LP-778902 were negative in in vitro Ames tests and chromosome aberration assays in CHO cells. Additionally, Telotristat etiprate was negative in the in vivo micronucleus test performed in rats.

Carcinogenicity

The carcinogenic potential of telotristat etiprate was studied in Tg.rasH2 mice. 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).

A two-year rat carcinogenicity study is ongoing (see SmPC, section 5.3).

Reproduction Toxicity

Fertility and early embryonic development

Table 13: Overview of the design and the main findings of the fertility and early embryonic development study

Study no. / Study year Species / strain No. of animals / group Dosages (mg/kg/d) Treatment duration	Main findings	NOAEL
Covance study #: 8247231 Sponsor study #: LX1606-N33 2011 Rats / Crl:CD (SD) 22 m + 22 f 0 (vehicle) – 100 – 200 – 500 m: 4 w prior to + throughout mating until necropsy f: 4 w prior to + throughout mating until gd 6	**Mortality**: 1 Co m found dead on d 34 (gavage error), 1 HD m euthanized on d 44 (tail damage) **Clinical signs**: Dose dependent ↑ in frequency + earlier onset of taste aversion (mouth rubbing, salivation, paddling) → but no effect on food consumption **bw gain**: ↓↓ in HD m d1 – 15; ↑↑ in MD f + HD f on d 1 – 15 (prepairing), ↓↓ in MD f + HD f on gd 6 – 10 → but no influence on fertility, fecundity + mating indices, pregnancy rate + embryonic development **Cycling**: 2 MD >4 d oestrus cycle: → pregnancy rate no affected **No. pregnant**: 21/22–22/22–22/22–22/22 **No. of dams with preimpl.loss ≥ 3**: 6/21–4/22–4/22–5/22	F_0 + F_1: 500 mg/kg/d

	No. of dams with postimpl.loss ≥ 3: 0/21–1/22–1/22–3/22 **Sperm count** ↑ in LD, MD+HD → not considered adverse	

Co = control; LD = low dose; MD = mid dose; HD = high dose; m = male; f = female; w = week; gd = gestation day; d = (treatment)day; bw = body weight; ↑ = increase; ↑↑ = significant increase; ↓ = decrease; ↓↓ = significant decrease

Embryo-fœtal development

Table 14: Overview of the design and the main findings of the embryo-foetal development studies in rats and rabbits

Study no. / Study year Species / strain No. of animals / group Dosages (mg/kg/d) Treatment duration	Main findings	NOAEL
Covance study #: 7648-298 Sponsor study #: LX1606-N29 2008 - 2009 Rats / Crl:CD (SD) Main study: 25 f; TK: 3 f for Co + 6 f for LD, MD + HD 0 (vehicle) – 250 – 500 – 750 gd 6 - 17	**mortality / sacrifice**: 1 HD found dead on gd 20, pregnant, but with late resorptions only, necropsy: no abnormal findings; 1 HD sacrificed on gd 18 due to moribund condition, pregnant but early resorptions only → necropsy: distended intestines; 1 HD necropsy: early resorptions only, no abnormal findings; 1 TK LD found dead on gd 7 (animal no. B42862, see p.228 of study report), no information provided; gd 6 TK values for LX1606 + LP-778902 (active moiety) about 6 to 7 times higher than mean values for MD + HD TK groups → misdosing ??? **bw + fc**: ↓↓ HD **pregnancy rate**: 1 HD not pregnant **EXT malformation**: 1 Co with rudimentary tail, 1 MD with rudimentary tail + anal atresia, 1 HD with umbilical hernia **SKEL malformation**: 1 Co with vertebrae malformations corresponding to rudimentary tail, 1 HD with vertebrae malformations corresponding to rudimentary tail + absent ribs (5th to 13th) right and left **VISC malformation**: 1 HD with retroesophageal aortic arch	F_0 + F_1: 500 mg/kg/d
Covance study no. 7648-299 Sponsor study no. LX1606-N30 2008 – 2009 Rabbits, Hra:(NZW)SPF Main study: 20 f; TK: 3 f 0 (vehicle) – 125 - 250	**mortality / morbidity**: 2 HD found dead, one doe on gd 10 without any remarkable observation, not pregnant; another doe on gd 20 following observations of thin and few or no faeces, pregnant; 1 TK HD moribund, removed from study on gd 18, thin, recumbent, laboured respiration, cold to touch, few or no faeces; necropsy: foreign material in lungs + thoracic cavity → gavage error; 1 LD found dead on gd19: both horns of gravid uterus filled with large amount of dark red fluid **bw**: dose-dependent ↓ **mean maternal bw change**: ↓↓ in MD (- 20.5%) + HD (- 42.2%)	F0 + F1: 125 mg/kg/d

– 500 gd 7 - 20	**fc**: ↓↓ in MD (13.6%) + HD (43.6%) during dosing period **mean postimplantation loss**: ↑ in MD and ↑↑ in HD **mean % of live foetuses**: ↓↓ in HD EXT malformation: 1 Co with eyes open SKEL malformation: 1 HD with vertebral anomaly; 2/2 – 4/3 – 0 – 1 foetus(es)/litter with major fusion of sternebrae SKEL variations: ↑↑ incidence of foetuses with 26 presacral vertebrae in MD (15%) + HD (22%); ↑↑ incidence of foetuses with 13th full ribs in MD (48%) + HD (47%) VISC malformation: 1 Co + 2 HD/1 litter reduced spleen; 1 HD agenesis of gallbladder; 1 MD malpositioned kidney	

Co = control; LD = low dose; MD = mid dose; HD = high dose; m = male; f = female; w = week; gd = gestation day; d = (treatment)day; bw = body weight; fc = food consumption; ↑ = increase; ↑↑ = significant increase; ↓ = decrease; ↓↓ = significant decrease

Prenatal and postnatal development, including maternal function.

Table 15: Overview of the design and the main findings of the prenatal and postnatal development study in rats

Study no. / Study year Species / strain No. of animals / group Dosages (mg/kg/d) Treatment duration	Main findings	NOAEL
Covance study #: 8300028 Sponsor study #: LX1606-N54 2014 - 2015 Rats / Crl:CD (SD) 24 f 0 (vehicle) – 100 – 200 – 500 gd 6 – ld 20	**F_0 generation:** **mortality**: 1 Co + 1 MD killed on ld 0 and 1 Co, 1 LD + 1 HD killed on ld 1 due to total litter death; clin. Signs in these animals: no visible teets, not attending to their litters → no milk in stomach of the pups → not considered treatment related as also Co dams affected 1 LD + 1 HD euthanized on gd 26 because of failure to produce a litter (not pregnant at necropsy) **bw**: ↓ in HD on gd 6 – 8 and in MD on ld 10 – 14 **fc**: ↓ in HD on gd 6 – 8, remained lower than Co by 6-11% during rest of gestation, no effect during lactation **necropsy**: 1 LD with large heart **F_1-generation:** **PND 4** pups culled to 4m + 4 f / group → developmental and functional parameters assessed, no adverse effects on pinna unfolding, surface righting, hair growth, incisor eruption, and eye opening **Viability from birth to PND 4**: ↓ in HD (↑number of dead pups, ↑number of sacrificed moribund pups and missing pups) **bw**: ↓↓ in male pups on PND 21 **PND 21**: remaining pups culled to 1m + 1f / group → randomly selected to 20 rats / sex / group → bw, fc, vaginal opening, cleavage of balantopreputial opening, locomotor activity, auditory startle habituation and prepulse inhibition, water maze performance and reproductive capacity not adversely affected **Necropsy**: 1 Co m with distended intestine, 1 Co f with dilated oesophagus and malpositioned intermediate lobe; 1 HD m with discoloured testis	F_0 + F_1: 500 mg/kg/d

Toxicokinetic data

In the initial MAA dossier safety margins for the active metabolite LP-778902 were calculated, and were based on the human steady state exposure (AUC_{0-24} of approximately 4238 ng*hr/mL) at the highest dose studied in Phase 3 of 500 mg tid from the LX1606.1-102-NRM study.

Similarly safety margins for telotristat ethyl were calculated based on human steady state exposure (AUC_{0-24} of approximately 21 ng*hr/mL) at the highest dose studied in LX1606.1-102-NRM study. An overview of the clinical safety margins for telotristat ethyl and the active metabolite LP-778902 is given in Table 16 and Table 17.

An overview of the toxicokinetic of telotristat ethyl and the active metabolite LP-778902 is shown in Table 18 and Table 19.

Table 16: Clinical Safety Margins for Telotristat Ethyl

Toxicity	Species	Sex	NOAEL (mg/kg/day)	AUC_{0-24} (ng.hr/mL)	Clinical Safety Margin (total, based on AUC)[a]	Clinical safety margin (unbound, based on AUC)[b]
13 Weeks repeat dose	Rat	M	500	73.6	3.5x	ND
		F	500	117	5.6x	ND
26 Weeks repeat dose	Rat	M	50	NA	NA	ND
		F	50	NA	NA	ND
39 Weeks repeat dose	Dog	M	300	4698	223.7x	223.7x
		F	300	5946	283.1x	283.1x
Carcinogenicity	Mice	M	300	24.5	1.2x	ND
		F	300	34.7	1.7x	ND
Fertility	Rat	Paternal toxicity	500	Not measured[c]	3.5x	ND
		Maternal toxicity	500		5.6x	ND
		Fertility and embryo/fetal viability	500*		5.6x	ND
Developmental toxicity	Rat	Maternal toxicity	500	155	7.4x	ND
		Embryo/fetal toxicity	750*	216	10.3x	ND
	Rabbit	Maternal toxicity	125	13.6	<1 (0.6)x	ND
		Embryo/fetal viability	125*	13.6	<1 (0.6)x	ND
		Embryo/fetal growth	250*	117	5.6x	ND
		Embryo/fetal development	500*	90.1	4.3x	ND
Pre- and Post-natal development	Rat	Maternal toxicity	500	Not measured[d]	7.4x	ND
		Pre- and Post-natal toxicity	500		7.4x	ND

Note: x = fold changes; * = NOEL; NA= Not applicable because of limited data; ND= Not determined; The free fraction of telotristat ethyl in plasma of rat and mouse could not be determined due to instability. The free fraction of telotristat ethyl in rabbit plasma was not determined

a Based on total telotristat ethyl in plasma. Human AUC_{0-24} is considered 21.0 ng.hr/mL at the 500 mg tid dose from the LX1606.1-102-NRM study.

b Based on free fraction of telotristat ethyl in plasma. The free fraction of telotristat ethyl for dog and human is 0.2% (160618). E.g. human AUC_{0-24} free fraction at the clinical dose of 500 mg tid dose is 0.042 ng*hr/mL [(21*0.2)/100=0.042].

c For safety margin calculation, exposures are from males and females in 13-week rat study at the same dosage.

d For safety margin calculation, exposures are from females in rat developmental toxicity study at the same dosage.

Table 17: Clinical Safety Margins for the Active Metabolite LP-778902

Toxicity	Species	Sex	NOAEL (mg/kg/day)	AUC_{0-24} (ng.hr/mL)	Clinical Safety Margin (total, based on AUC)[a]	Clinical safety margin (unbound, based on AUC)[b]
13 Weeks repeat dose	Rat	M	500	12655	3.0x	17.9x
		F	500	18948	4.5x	26.8x
26 Weeks repeat dose	Rat	M	50	2726	<1 (0.6)x	3.9x
		F	50	2729	<1(0.6)x	3.9x
39 Weeks repeat dose	Dog	M	300	132949	31.4x	31.4x
		F	300	128720	30.4x	30.4x

Note: x = fold changes; * = NOEL; ND = Not determined because the free fraction of LP-778902 in rabbit plasma was not determined.

a Based on total telotristat ethyl in plasma. Human $AUC_{0\text{-}24}$ is considered 4238 ng.hr/mL at the 500 mg tid dose from the LX1606.1-102-NRM study.

b Based on free fraction of LP-778902 in plasma. The free fraction of LP-778902 for mouse, rat, dog, and human is 0.6%, 1.2%, 0.2%, and 0.2% respectively (160618). E.g. human $AUC_{0\text{-}24}$ free fraction at the clinical dose of 500 mg tid dose is 8.476 ng*hr/mL [(4238*0.2)/100=8.476].

Table 18: Toxicokinetic Data of Telotristat Ethyl

	Steady-State $AUC_{0\text{-}24}$ (ng.hr/mL)[a]							
Daily Dose	**Mice**		**Rats**		**Dogs**		**Rabbits**	**Humans**
(Toxicokinetic studies, mg/kg/day)	**M**	**F**	**M**	**F**	**M**	**F**	**F**	
500 mg three times per day for 14 days								21.0
10					148			
30	1.31	NA			595	590		
50			NA	NA				
75					1289	1932		
100	8.75	6.74	NA	0.923	2075	1949		
125							13.6[b]	
150					3454	3148		
200			4.65	34.3	5531	4011		
250				97.7[b]			117[b]	
300	24.5	34.7			4698	5946		
500			53.5	102/ 155[b]	5019		90.1[b]	
750				216[b]				

NA= Not applicable because of limited data.

a When the same dose was tested in multiple studies, the representative data are selected from GLP and/or longer term repeat dose studies. Source of data (all studies are GLP unless otherwise specified): Mice, all doses from LX1606-N52; Rats, 50, 200, 500 mg/kg/day doses from LX1606-N28, 100 mg/kg/day dose from LX1606-N12, 250, 500, 750 mg/kg/day doses from LX1606-N29; Dogs, 10 mg/kg/day dose from LX1606-N20, 30, 100, 200 mg/kg/day doses from LX1606-N23, 75, 150, 300 doses from LX1606-N27, 500 mg/kg/day dose from LX1606-N13 (non-GLP); Rabbits, all doses from LX1606-N30; Humans, 500 mg tid dose from LX1606.1-102-NRM study.

b In pregnant animals.

Table 19: Toxicokinetic Data for the active metabolite LP-778902

	Steady-State $AUC_{0\text{-}24}$ (ng.hr/mL)[a]							
Daily Dose	**Mice**		**Rats**		**Dogs**		**Rabbits**	**Humans**
(Toxicokinetic studies, mg/kg/day)	**M**	**F**	**M**	**F**	**M**	**F**	**F**	
500 mg three times per day for 14 days								4238
10			338		4296			
30	5340	8250	909		11050	19341		
50			2726	2729				
75					34221	44139		
100	20400	29100	4954	4301	59948	65096		
125							24365[b]	
150					77835	74435		
200			9276	8421	162764	109845		
250				12880[b]			78626[b]	
300	64100	101000			132949	128720		
500			19439	29974/ 26878[b]	209473		176309[b]	
750				47563[b]				
1000			47575					

a When the same dose was tested in multiple studies, the representative data are selected from GLP and/or longer term repeat dose studies. Source of data (all studies are GLP unless otherwise specified): Mice, all doses from LX1606-N52; Rats, 10, 30 mg/kg/day doses from IVT 07-020 (non-GLP), 50, 200, 500 mg/kg/day doses from LX1606-N28, 100 mg/kg/day dose from LX1606-N12, 250, 500, 750 mg/kg/day doses from LX1606-N29, 1000 mg/kg/day dose from IVT 07-006 (non-GLP); Dogs, 10 mg/kg/day dose from LX1606-N20, 30, 100, 200 mg/kg/day doses from LX1606-N23, 75, 150, 300 doses from LX1606-N27, 500 mg/kg/day dose from LX1606-N13 (non-GLP); Rabbits, all doses from LX1606-N30; Humans, 500 mg tid dose from LX1606.1-102-NRM study.

b In pregnant animals.

Local Tolerance

In a GLP acute dermal irritation/corrosion study in rabbits, telotristat etiprate did not show to be a dermal irritant.

Other toxicity studies

A rat excretion balance and tissue distribution study was conducted with ^{14}C-LX1606 in Lister Hooded (pigmented) rat. Results from this study showed that the majority of radiolabeled material remained in the gastrointestinal tract and was rapidly eliminated. Based on these findings and according to ICH S10 no further photosafety testing was performed with telotristat etiprate.

In the chronic toxicity study in the dog (LX1606-N27), no evidence of immunosuppression or myelosuppresion was observed

2.3.5. Ecotoxicity / environmental risk assessment

The Applicant provided an environmental risk assessment Phase I. A summary of the findings are described in Table 20.

Table 20: Summary of main study results

Substance (INN / Invented Name): LP-778902 (active metabolite of the pro-drug Telotristat Etiprate			
CAS-number (if available): 1033805-28-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log P_{ow}	**No study submitted**	3.5 – 3.8 (pH 5- 9)	Potential PBT (Y/N) **OPEN**
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	OPEN		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (e.g. prevalence)	0.136	µg/L	> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate			
OPEN			

2.3.6. Discussion on non-clinical aspects

The pharmacodynamic activity of telotristat etiprate/ethyl and LP-778902 on TPH has been evaluated in rat and human in vitro models and in several in vivo models of mice, rats, dogs and monkeys. The inhibitory action of telotristat has been demonstrated in the colon of the animals tested and in the decrease of 5-HT in the blood and 5-HIAA in the urine. Based on non-clinical data package, TPH inhibition is considered highly species specific. However, it is apparent from animal studies that 5-HT and 5-HIAA reduction in brain occurs at exposures sufficiently above to the proposed clinical dose of 250 mg TID. Animal data in rats and dogs regarding brain 5-HT and 5-HIAA reduction were included in section 5.3 of the SmPC and depression and depression related events in the RMP.

In the rat, increased systemic exposure to LP-778902 was observed with escalating doses of telotristat ethyl, with saturation observed at high dose levels. Saturation was also observed for telotristat ethyl at high dose levels. The saturation at high dose levels was probably due to a limitation in the absorption process but occurs at dose levels which are not clinically relevant. In the dog, exposure to both telotristat ethyl and LP-778902 increased in the presence of food. In fasted dogs emetic effects were observed which

contributed to the notable lower C_{max} and AUC_{0-t} values in these animals compared to that observed in dogs given the same dose of compound in the fed state. In human an increase in C_{max} and AUC was also observed when telotristat etiprate is given together with high fat meal but not with a standard meal. This is consistent to the PK data in human and as such Xermelo should be taken with food (see sections 4.2, 5.1 and 5.2 of the SmPC).

Tissue distribution studies have only been performed after single administration to Sprague Dawley rats and lister hooded rats (partially pigmented). No tissue distribution after repeated administration of telotristat ethyl has been performed, which is acceptable.

No pharmacokinetic study for brain penetration was conducted. This is acceptable as pharmacology studies have shown statistically significant decrease in brain 5-HT levels in SD rats dosed with ≥ 1000 mg/kg/day and beagle dogs at 500 mg/kg/day dose. There was also a statistically significant decrease in 5-HIAA levels in the brain in the 30 and 100 mg/kg/day dose groups in dogs.

Brain distribution was not observed after highest dose tested 100 mg/kg/day (free base) in both tissue distribution studies in rats, but this dose did not reach sufficient exposure to prodrug - indicated to be responsible for 5-HT reduction in brain. However, considering the difference in PK profile and sensitivity to TPH inhibition (based on in vitro cell based assay data) between rat and human, new data would not be of value. From non-clinical point of view, inclusion of animal data regarding brain 5-HT, 5-HIAA reduction in section 5.3 are sufficient.

The in vitro and in vivo metabolism shows that telotristat is converted trough hydrolysis of esterases to the active metabolite LP-778902. Whereas in rodents conversion occurred already in plasma, in humans conversion occurred primarily in intestine and liver. A further oxidative, decarboxylated, deaminated metabolite LP-951757 (inactive) was found in rats and human.

The metabolites of telotristat ethyl have been poorly characterized in in vitro models and in vivo in animals. However, it can be assumed that the human metabolites are also present in in vitro models and in vivo in animals and that no metabolites unique to human exist. Therefore, no further studies are requested.

Telotristat ethyl and LP-778902 were investigated for their pharmacokinetic drug interaction potential in in vitro studies on a range of drug metabolizing enzymes and drug transporters. The in vitro studies show that there is interaction of telotristat ethyl, its active metabolite LP-778902 and/or minor metabolite LP-951757 with the efflux transporters (P-gp, BCRP, MRP2) Based on in vitro findings, no clinically relevant interactions is expected with other transporters. These studies have been performed according to the EMA guideline CPMP/EWP/560/95/Rev. 1 Corr. 2 (see clinical pharmacology).

In terms to toxicity observed in the rat studies, in a 26-week repeat-dose toxicity study in rats a No-Observed Adverse Effect Level (NOAEL) of 50 mg/kg/day was determined. This is approximately 0.4 times the human exposure (AUC total) at MRHD of 750 mg/day for the active metabolite LP-778902. At doses of 200 and 500 mg/kg/day degeneration/necrosis in the nonglandular and/or glandular portions of the stomach and/or increased protein droplets in the glandular portions were observed. The microscopic changes in the gastrointestinal tract reversed with a 4-week recovery period. Relevance of these gastrointestinal findings to humans is unknown. In a 39-week repeat-dose toxicity study in dogs NOAEL of 300 mg/kg/day was determined. Clinical signs were limited to increase in frequency of liquid faeces at all doses. This is approximately 20 times the human exposure (AUC total) at MRHD of 750 mg/day for the active metabolite LP-778902.

Telotristat etiprate and LP-778902 are not considered to be genotoxic in vitro and in vivo. As telotristat etiprate is rapidly metabolized in vivo to LP-778902 no further in vivo genotoxic testing of LP-778902 was performed what is acceptable.

A 2 year rat carcinogenicity study with dose levels up to 170 mg/kg/day is on-going. The CHMP agreed that carcinogenicity studies could be submitted in post-authorisation. The absence of the long-term carcinogenicity study is properly reflected in the SmPC section 5.3.

Prenatal development in rats and rabbits was affected by increased prenatal lethality (increased early and late resorptions). Therefore, information on embryonic lethality has been included in 5.3 and further recommendations have been included in section 4.6 of the SmPC where animal studies have shown reproductive toxicity (see SmPC section 5.3). Xermelo is not recommended during pregnancy and in women of childbearing potential not using contraception. There are no data from the use of telotristat in pregnant women. No studies on the effect of telotristat on human fertility have been conducted. Telotristat had no effect on fertility in animal studies (see SmPC section 5.3). It is unknown whether telotristat ethyl and its metabolite are excreted in human breast milk. A risk to newborns/infants cannot be excluded. Patients should not breast-feed during telotristat treatment.

The spectroscopic scans (200-700 nm) for telotristat ethyl and its active metabolite LP- 778902 show that both compounds absorb light in the UVB spectrum at 306 nm. The molar extinction coefficient (ε) for telotristat ethyl is 9573.8 L mol^{-1} cm^{-1} at 306 nm. For LP- 778902, corresponding value for ε is 8081 L mol^{-1} cm^{-1} (documentation in appendix). In a rat excretion balance and tissue distribution study in Lister Hooded (pigmented) rats it was demonstrated that the majority of radiolabeled material remained in the gastrointestinal tract and was rapidly eliminated. Furthermore, no persistent dermal or ocular distribution above that of plasma levels was observed. In addition, in clinical study 301 in CS patients treated at 500 mg tid no accumulation of plasma concentration of LP-778902 and no skin safety finding were observed up to 48 weeks of treatment. Based on these findings no further photosafety testing was performed with telotristat etiprate.

It is not possible to conclude on the environmental risk of telotristat (active metabolite LP 778902). The applicant provided an ERA Phase I which is acceptable. Calculation of $PEC_{SURFACEWATER}$ is based on the recommended daily dose of telotristat etiprate of 750 mg/day (3 x 250 mg) and a refined market penetration factor (Fpen) of 0.036%. The $PEC_{SURFACEWATER}$ was determined to be 0.136 µg/L. This value is above the action limit of 0.01 µg/L defined by EMA Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr.2) as the threshold above which a phase II environmental fate and effects analysis must be performed. The provided experimental values for $logK_{OW}$ including the study reports are acceptable. A PBT assessment is not required. So far, no phase II assessment is available. The missing ERA studies and an overall ERA revision shall be provided in post-authorisation.

2.3.7. Conclusion on the non-clinical aspects

The pharmacologic, pharmacokinetic, and toxicological characteristics of telotristat have been well characterised in the non-clinical aspects. In general, the non-clinical aspects are considered to be appropriately addressed. However, the applicant should submit the results of the 2 year carcinogenicity study and the missing ERA studies as post-authorisation measures.

Therefore, the CHMP considers the following measures necessary to address the non-clinical issues:

- Final study reports as well as a phase II Tier A risk assessment, expected to be available in Q3 2018.

- Final study report for the 2 year rat carcinogenicity study, expected to be available Q3 2018.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study / Source	Dose	Dosage Form[a]	Analyte	Pharmacokinetic Sampling Times
LX101	6 escalating doses of telotristat etiprate: [50, 100, 250, 500 (fed and fasted states), 1000, 1500	Capsule	Telotristat ethyl, LP-778902	Predose samples and then at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24,36, and 48 hours postdose
LX102	5 escalating doses of telotristat etiprate over 14 days: 100 mg qd, 250 mg qd, 500 mg qd, 500 mg bid, 500 mg tid or placebo (n=40)	Capsule	Telotristat ethyl, LP-778902	Day 1: Predose; 15 minutes, 30 minutes, 45 minutes postdose; and 1, 2, 4, 6, 8, and 12 hours postdose; Days 2 through 13: Morning predose; Day 14: Predose; 15 minutes, 30 minutes, 45 minutes
LX103	250 mg telotristat etiprate (n=22)	Capsule or Tablet	Telotristat ethyl, LP-778902	Predose samples and then at 30 minutes, 1, 2, 4, 6, 12, 24, and 48 hours postdose
LX104	500 mg [^{14}C]-telotristat etiprate (n=8)	Capsule	Telotristat ethyl, LP-778902	Predose samples and then at 15, 30, 45 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose [After 168 hours postdose (Day 8) samples
LX105	1500 mg telotristat etiprate or 400 mg moxifloxacin (positive control) (n=48)	Tablet	Telotristat ethyl, LP-778902	Predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 60 hours postdose
LX106	*180 mg fexofenadine administered on Days 1 and 10; and 500 mg telotristat etiprate tid x 5 days (n=24)*	*Tablet*	*Fexofenadine*	*Predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose. All times are relative to fexofenadine dosing.*
LX107	500 mg telotristat etiprate (fed and fasted state) (n=22)	Tablet	Telotristat ethyl, LP-778902	Predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 48 hours postdose
LX108	*3 mg midazolam hydrochloride administered on Days 1 and 9 mg; and 500 mg telotristat etiprate, tid x 5 days (n=24)*	*Tablet*	*Midazolam and 1'-hydroxy-midazolam*	*Predose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 hours postdose. All times are relative to midazolam dosing.*
LX109	500 mg telotristat etiprate on Days 1 and 6; 200 µg octreotide acetate tid on Day 6 (n=24)	Tablet	Telotristat ethyl, LP-778902	Predose and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, and 48 hours postdose. All times were relative to telotristat etiprate dosing. The 6- and 12-hour PK samples were to be collected prior

D-FR-01017-001	Single-dose 500 mg telotristat ethyl	Tablet	Telotristat ethyl, LP-778902	Predose and at 0.5, 1, 2, 3, 4, 6, 8 and 12 hours post-dose
LX202	Part 1: 150 mg tid, 250 mg tid, 350 mg tid, or 500 mg tid (or matching placebo) telotristat etiprate; Part 2: 500 mg tid telotristat etiprate	Capsule	Telotristat ethyl, LP-778902	Predose and at 1, 2, 3, 4, 5, 6, 8, 12, 20, 28, and 36 weeks
LX203	150 mg tid, 250 mg tid, 350 mg tid, or 500 mg tid telotristat etiprate (n=15)	Capsule	Telotristat ethyl, LP-778902	Predose and at 2, 4, 6, 8, 12, 20, 28, and 36 weeks
LX204	500 mg qd or tid (or placebo) telotristat etiprate (n=59)	Capsule	Telotristat ethyl, LP-778902	Predose and at 7, 14, 28, 42, 56 days and at the 2-week follow-up
LX301	250 or 500 mg tid (or placebo) telotristat etiprate (n=135)	Tablet	Telotristat ethyl, LP-778902	For the intensive PK subgroup, samples were collected on Day 1, Week 12, Week 24, and Week 48 at the following time points: Predose, and then at 1, 2, 4, and 6 hours after the morning dose. Samples for trough level determinations in the rest of the patients were collected on Day1 and at 6, 12, 18, 24, 36, and 48 weeks.
LX302	250 or 500 mg tid (or placebo) telotristat etiprate (n=71)	Tablet	N/A	No PK sampling
LX303	250 or 500 mg tid (or placebo) telotristat etiprate (n=)	Tablet	N/A	No PK sampling

- bid = twice daily; qd = once daily; tid = 3 times daily; a = telotristat etiprate dosage form; n= number of total enrolled subjects

2.4.2. Pharmacokinetics

At the time of MAA submission, telotristat etiprate had been studied in approximately 259 healthy volunteers as single/multiple doses in Phase 1 studies. In addition, 38 patients with CS and 48 patients with ulcerative colitis have received telotristat etiprate during Phase 2 of the clinical development programme. In the three Phase 3 studies, a total of 185 patients had completed the DBT Periods of Studies LX301 and LX302, a total of 71 patients were continuing to participate in the OLE Periods of LX301 and LX303, and a total of 60 patients were continuing to participate in Study LX302.

An additional phase I study (D-FR-01017-001) was conducted in patients with mild and moderate hepatic impairment and healthy controls (n=8 in each of the three groups).

Absorption

Study LX301:

Table 21: Summary of PK Parameters for the Intensive PK Subgroup Administered a Single Dose of 250 mg (LX301) with Additional Octreotide and Lanreotide Subgroups Summarization: Includes Day 1 for the 250 and 500 mg Treatment Arms and Week 12 for the Placebo Arm

Analyte	PK Parameter	All Patients (N = 40)		Octreotide Subgroup (N = 28)		Lanreotide Subgroup (N = 12)	
		n	Mean (SD) [%CV]	n	Mean (SD) [%CV]	n	Mean (SD) [%CV]
Telotristat Ethyl	C_{max} (ng/mL)	32	3.97 (2.83) [71.2]	23	4.18 (3.19) [76.5]	9	3.45 (1.58) [45.9]
	T_{max} (h)[a]	32	1.07 (1.00-4.08)	23	1.00 (1.00-4.08)	9	1.08 (1.00-2.07)
	AUC_{0-4} (ng × h/mL)	9	11.6 (5.15) [44.3]	4	16.2 (3.71) [22.9]	5	7.96 (2.23) [28.0]
	AUC_{0-6} (ng × h/mL)	7	15.3 (6.81) [44.5]	5	17.8 (6.33) [35.5]	2	7.21, 10.72[b]
	T_{last} (h)[a]	32	2.00 (1.00-6.08)	23	2.00 (1.00-6.08)	9	4.00 (1.08-5.97)
LP-778902	C_{max} (ng/mL)	40	523 (446) [85.2]	28	554 (451) [81.3]	12	452 (446) [98.7]
	T_{max} (h)[a]	40	2.00 (1.00-4.08)	28	2.00 (1.00-4.08)	12	2.00 (1.00-3.95)
	AUC_{0-4} (ng × h/mL)	37	1146 (939) [82.0]	26	1163 (974) [83.7]	11	1103 (893) [81.0]
	AUC_{0-6} (ng × h/mL)	30	1423 (1235) [86.8]	22	1592 (1354) [85.0]	8	958 (695) [72.6]
	T_{last} (h)[a]	40	6.00 (2.00-6.35)	28	6.00 (2.00-6.35)	12	5.95 (3.95-6.25)

a Median (range) b Individual values

Study LX107: PK results after administration of telotristat etiprate 500mg (as free base) as tablet formulation in fed and fasted states are summarised in Table 22 and graphically represented in Figure 7.

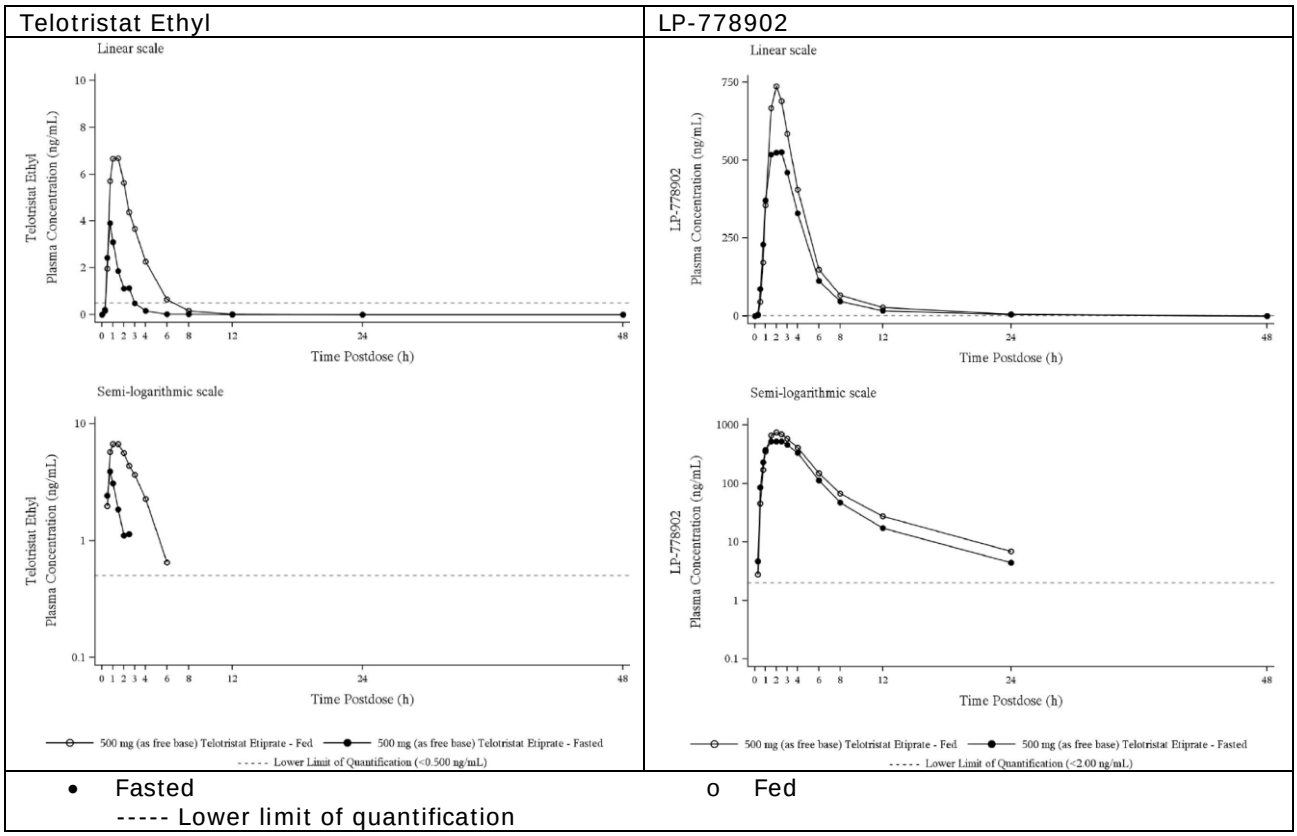


Figure 7: Arithmetic Mean Plasma Concentration Profiles for Telotristat Ethyl and LP-778902 in fed vs. fasted state

Table 22: Statistical Analysis of the Effect of Food on the Pk Parameters of Telotristat Ethyl and LP-778902 Following Administration of Telotristat Etiprate Tablets

Analyte	Parameter (Units)	Telotristat Etiprate, 500 mg, (Fed) (Test)		Telotristat Etiprate, 500 mg, (Fasted) (Reference)		Test/ Reference[c] (%)	90% CI[d] (%)	P-value[e]
		n[a]	LS Mean[b]	n[a]	LS Mean[b]			
Telotristat Ethyl	C_{max} (ng/mL)	22	8.66	22	4.09	211.8	(168.5, 266.3)	
	$AUC_{0\text{-last}}$ (hr*ng/mL)	22	18.05	22	4.86	371.5	(315.4, 437.5)	
	$AUC_{0\text{-inf}}$ (hr*ng/mL)	20	20.83	18	5.72	364.2	(302.7, 438.2)	
	T_{max} (h)	22	1.50	22	0.75	0.63	(0.25, 1.00)	0.0025
LP-778902	C_{max} (ng/mL)	22	846	22	576	146.9	(121.2, 178.0)	
	$AUC_{0\text{-last}}$ (hr*ng/mL)	22	2796	22	2114	132.3	(114.2, 153.2)	
	$AUC_{0\text{-inf}}$ (hr*ng/mL)	22	2843	22	2146	132.5	(114.5, 153.2)	
	T_{max} (hr)	22	2.27	22	2.00	0.22	(-0.24, 0.50)	0.4706

a = number of observations in each treatment used in the model

b = Least squares means for AUC0-last, AUC0-inf, and Cmax from ANOVA were calculated by transforming the natural log means back to the linear scale. (ie, geometric LS mean); the median value is presented for tmax only.

c = The ratio of LS means for natural log transformed parameters including AUC0-last, AUC0-inf, and Cmax (expressed as a percent), were natural log transformed back to the linear scale; a Hodges-Lehmann estimate was calculated for median difference between the test and reference states for tmax.

d = The 90% CI for ratio of LS means of natural log transformed parameters including AUC0-last, AUC0-inf, and Cmax (expressed as a percent), were natural log transformed back to the linear scale; the 90% CI was calculated for median difference between the test and reference states for tmax.

e = The p-value was calculated using the Wilcoxon signed-rank test for tmax.

For telotristat ethyl, the between subject variability, as assessed from the geometric CV for $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ of telotristat ethyl, was generally similar in the fed (43% and 36%, respectively) and fasted (37% and 36%, respectively) states; however, the geometric CV for C_{max} was higher in the fed state (69%) compared to the fasted state (38%).

Distribution

Following administration of [14C]-telotristat etiprate to healthy volunteers in the mass balance study (LX104), the total radioactivity in whole blood ranged from 278 – 1427 ng equivalents/mL.

Telotristat ethyl exhibited high plasma protein binding (99.8%, mean of n=2) in human as determined by equilibrium dialysis (160618).

The estimated apparent total volume of distribution for the active metabolite from the Population PK model of 428.1 L in a typical healthy fasted subject and 348.7 L in patients with CS.

Elimination

Results from the mass balance study LX104 showed that following administration of a single dose of 500 mg (as free base) [14C]-telotristat etiprate, plasma concentrations of total radioactivity reached a maximum between 2.00 and 4.00 h postdose. Thereafter, total radioactivity declined in a biphasic manner up to 24 h postdose. Half-lives of telotristat ethyl were estimated for only 2 of the 8 subjects and a true terminal half-life could not be reliably determined as telotristat ethyl plasma concentrations dropped BLQ after only 4 h. For LP-778902, half-lives were estimated for 7 out of 8 subjects with values ranging from 4.71 to 5.62 h (geometric mean of 5.022 h) and plasma concentrations falling BLQ after 24 h postdose.

The apparent oral clearance at steady state in healthy subjects (500mg tid) was estimated to be 2.67 L/hr for telotristat ethyl and 152 L/hr for LP-778902 (LX102).

Recovery of total radioactivity from all excreta (urine and faeces) was to be monitored. Reported values of cumulative excretion showed that a mean of 93.157% (range of 90.39% to 95.38%) of administered total radioactivity was recovered in urine and faeces from subjects following continuous sampling up to 240 h postdose. A mean of 92.775% was recovered from the faeces, with approximately 0.382% recovered from the urine.

The in vitro metabolism of telotristat ethyl was further studied in human male and female hepatocytes using [^{14}C]-telotristat ethyl. Telotristat ethyl was rapidly metabolised to its major metabolite, LP-778902, by both male and female human hepatocytes, which was further metabolised to LP-951757. The formation of LP-951757 was slower and less extensive when compared to LP-778902. No significant sex differences were observed in the nature and quantity of metabolites formed in this study (XenoTech XT154054).

The oxidative decarboxylated deaminated metabolite, LP-951757, represented consistency >10% of total plasma drug-related material. Systemic exposure to LP-951757 was about 35% of the systemic exposure to telotristat (active metabolite) in the mass balance study. LP-951757 was pharmacologically inactive at TPH1 in vitro.

The proposed metabolic pathway of telotristat ethyl is depicted in Figure 8.

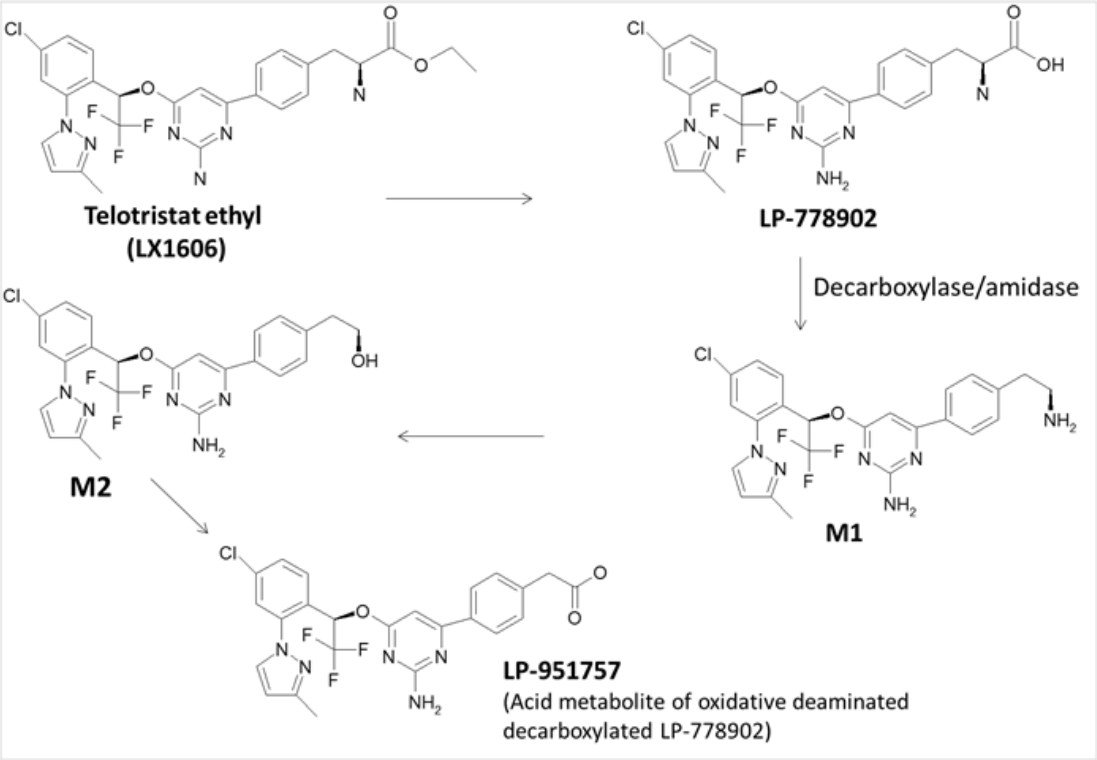


Figure 8: Proposed Metabolic Pathway of Telotristat Ethyl

Following oral administration of [^{14}C]-telotristat etiprate to 8 male subjects, at least 15 radioactive components were observed in faeces (designated F1 to F15). Two major radioactive components were observed (corresponding to >10% of the dose administered in at least 1 subject). Both components were shown to contain several metabolites including LP-778902 and metabolites of LP-778902.

Dose proportionality and time dependencies

Study LX102: Dose proportionality was investigated under single and multiple dose administration for the capsule formulation of telotristat etiprate in study LX102, a randomized, double-blind, placebo-controlled, ascending multiple-dose study to evaluate i.a. the PK of LX1606 and LP-778902 over a range of multiple oral doses in healthy subjects. Each cohort received 1 dose level for 14 days. Dose levels were 100 mg once daily (QD), 250 mg QD, 500 mg QD, 500 mg twice daily (BID), and 500 mg 3 times daily (TID) of LX1606 capsules or placebo. Standard morning meals or a snack were provided before dosing and then approximately 4 hours after study treatment administration. Forty subjects enrolled in the study and 38 completed it.

The PK parameters for both LX1606 for Cohorts 1 through 3 are summarized in Table 23.

Table 23: Dose-Adjusted (Adjusted to 100 mg) PK Parameters of LX1606 Following Administration of 100 mg QD, 250 mg QD, or 500 mg QD on Day 1 and Day 14, PK Full Population

Dose	Statistics	Day 1 C_{max} (ng/mL)	Day 1 $AUC_{0\text{-}tau}$ (ng*hr/mL)	Day 14 C_{max} (ng/mL)	Day 14 $AUC_{0\text{-}tau}$ (ng*hr/mL)
Cohort 1 100 mg QD	n	4	0	3	0
	Mean	0.731	ND	1.50	ND
	SD	0.201	ND	0.861	ND
Cohort 2 250 mg QD	n	6	2	6	0
	Mean	0.576	0.831	0.904	ND
	SD	0.333	0.158	0.467	ND
Cohort 3 500 mg QD	n	6	6	6	1
	Mean	1.07	2.68	1.01	2.90
	SD	1.07	1.43	0.427	ND

ND= Not determined; due to subjects having fewer than 3 measurable concentrations

Statistical Analysis of Dose Proportionality: Table 24 summarize the results of the statistical analysis of dose proportionality of LX1606 PK parameters, respectively, following single-dose and multiple-dose administration of 100, 250, and 500 mg QD LX1606.

Table 24: Statistical Analysis of Dose Proportionality of LX1606 $AUC_{0\text{-}tau}$ and C_{max}, Pharmacokinetic Full Population

Day	Parameter	Number of Subjects	Slope Estimate and 95% CI
1	$AUC_{0\text{-}tau}$ (ng*hr/mL)	8	2.56 (1.31, 3.80)
1	C_{max} (ng/mL)	16	1.06 (0.519, 1.60)
14	$AUC_{0\text{-}tau}$ (ng*hr/mL)	1	NA
14	C_{max} (ng/mL)	15	0.803 (0.325, 1.28)

NA= Not Applicable. Only 1 subject had an estimable $AUC_{0\text{-}tau}$ for Day 14.

Time dependency

Healthy subjects: In healthy subjects (study LX102), there was no apparent accumulation of LP-778902 after multiple doses of once-daily 100 mg through 500 mg 3 times daily telotristat etiprate based on the Day 14 AUC0-tau/Day 1 AUC0-tau ratio (Ro) being close to 1 (<1.2).

The mean t1/2 of LP-778902 after multiple doses of telotristat etiprate ranged from 3.65 to 11.7 hours between dose groups with similar mean apparent clearance at steady-state values for all dose groups.

Patients with CS: A posthoc noncompartmental PK evaluation (1606-301-nca-pk-011084) of single- and multiple-dose oral administration of telotristat etiprate (LX1606 hippurate) in patients with CS not adequately controlled by somatostatin analog therapy (study LX301) was conducted.

Table 25: Mean (SD) [%CV] PK Parameters of Telotristat Ethyl and LP-778902 at Week 24 and Week 48 for All Patients Administered Multiple Doses of 500 mg Telotristat Etiprate From All Treatment Arms

Analyte	Pharmacokinetic Parameter	Week 24[a] (N = 26)		Week 48[a] (N = 14)	
		n	Mean (SD) [%CV]	n	Mean (SD) [%CV]
Telotristat Ethyl	C_{max} (ng/mL)	26	7.25 (5.41) [74.6]	13	7.43 (6.06) [81.6]
	T_{max} (h)[b]	26	1.04 (0.00-2.08)	13	1.00 (0.967-4.08)
	AUC_{0-4} (ng × h/mL)	17	17.8 (8.72) [49.1]	9	16.9 (10.4) [61.4]
	AUC_{0-6} (ng × h/mL)	13	22.9 (12.5) [54.4]	6	21.6 (12.9) [59.6]
	T_{last} (h)[b]	26	5.00 (1.00-6.50)	13	6.00 (1.00-6.17)
	$RacAUC_{0-4}$	5	1.19 (0.315) [26.5]	3	1.08 (0.646) [60.1]
	$RacAUC_{0-6}$	4	0.848 (0.493) [58.2]	0	NC
LP-778902	C_{max} (ng/mL)	26	924 (484) [52.4]	13	906 (570) [63.0]
	T_{max} (h)[b]	26	2.00 (0.717-4.00)	13	2.00(0.967-4.08)
	AUC_{0-4} (ng × h/mL)	24	2326 (1298) [55.8]	13	2423 (1689) [69.7]
	AUC_{0-6} (ng × h/mL)	22	3006 (1785) [59.4]	12	3031 (2146) [70.8]
	T_{last} (h)[b]	26	6.00 (2.00-6.50)	13	6.00 (5.25-6.27)
	$RacAUC_{0-4}$	16	2.15 (3.04) [141.8]	10	1.39 (1.11) [79.6]
	$RacAUC_{0-6}$	11	1.74 (1.99) [114.2]	7	1.99 (1.27) [64.0]

a Includes patients from placebo arm receiving telotristat etiprate treatment since Week 12.
b Median (range).

Accumulation ratio (R_{ac}) calculations were made based upon individual-calculated AUC_{0-4} and AUC_{0-6} after dose administration on Weeks 24 and 48 divided by corresponding Day 1 values with appropriate adjustment for differences in dose administration between study days (Table 26).

Table 26: Accumulation ratio $R_{ac}AUC_{0-4}$ and $R_{ac}AUC_{0-6}$ for Telotristat ethyl and LP-778902 after 24 and 48 weeks

Analyte	Week	Pharmacokinetic Parameters	N	Mean	SD	Min	Median	Max	%CV	Geo.Mean	%CV Geo.Mean
Telotristat ethyl	Week 24	$RacAUC_{0-4}$	5	1.189	0.3149	0.7430	1.194	1.592	26.5	1.153	29.1
		$RacAUC_{0-6}$	4	0.8479	0.4933	0.1507	1.013	1.215	58.2	0.6539	129.4
	Week 48	$RacAUC_{0-4}$	3	1.076	0.6464	0.3851	1.177	1.666	60.1	0.9107	89.2
		$RacAUC_{0-6}$	0	NC	NC	NC	NC	NC	NC	NC	NC
LP-778902	Week 24	$RacAUC_{0-4}$	16	2.146	3.042	0.2740	1.095	11.46	141.8	1.179	141.8
		$RacAUC_{0-6}$	11	1.740	1.988	0.2345	1.197	7.409	114.2	1.170	112.4
	Week 48	$RacAUC_{0-4}$	10	1.393	1.109	0.1945	1.175	3.551	79.6	1.020	108.4
		$RacAUC_{0-6}$	7	1.992	1.274	0.4041	1.854	4.194	64.0	1.609	89.4

Special populations

Impaired renal function

In the overall population analysed, the range of renal function was mostly normal (>= 90 mL/min, 60.5%) followed by mild renal impairment (60-89 mL/min, 24.1%), moderate renal impairment (30-59 mL/min, 8.2%) and severe renal impairment (15-29 mL/min, 2.6%). The majority of subjects in the Phase 1 studies had normal renal function. In LX301, 34 (31.8%) patients were normal, 43 (40.2%) were mild, 16 (15.0%) were moderate, and 5 (4.7%) had severe renal impairment.

Renal function (as assessed by creatinine clearance) was not identified as a significant covariate on the PK of LP-778902 in the PopPK analysis (002479); patients with normal, mild, and moderate renal impairment had comparable exposures.

Impaired hepatic function

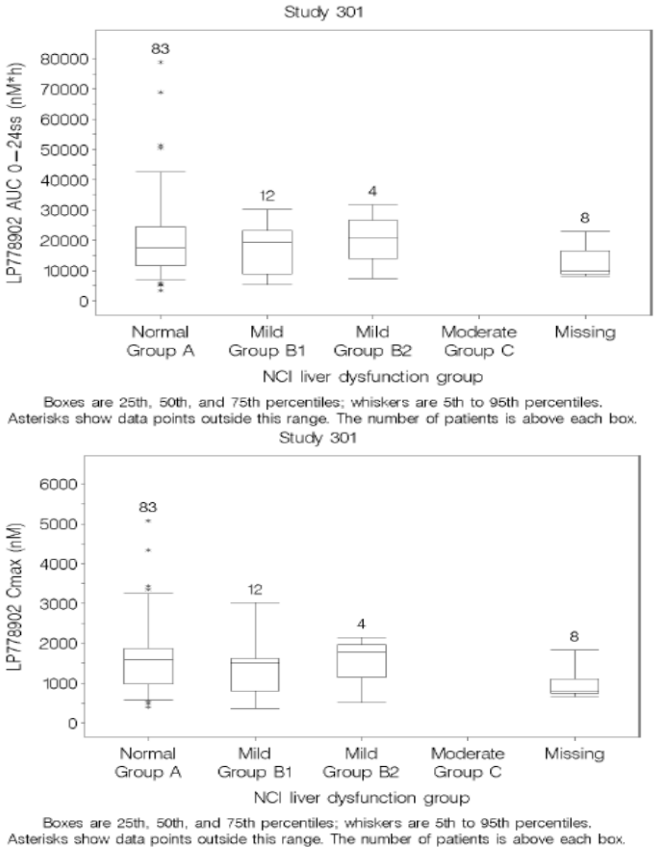


Figure 9: Boxplots Showing Relationship Between LP-778902 PK and Hepatic Function in Patients with Carcinoid Syndrome

In a hepatic impairment study (D-FR-01017-001) conducted at a single dose of 500 mg, exposures to the parent compound (telotristat ethyl) and its active metabolite, LP-7789012, (based on $AUC_{0\text{-tlast}}$) were higher in patients with mild hepatic impairment (2.3- and 2.4-fold, respectively) and in patients with moderate hepatic impairment (3.2- and 3.5-fold, respectively) compared with healthy subjects. Administration of a single dose of 500 mg was well tolerated. The use of telotristat is not recommended in patients with severe hepatic impairment as no data are available.

Age

Table 27: Summary Statistics of Age Characteristics, by Study, in the PK Analysis of LP 778902

Subject Characteristic		Study				
		LX101 (n = 36)	LX102 (n = 30)	LX103 (n = 22)	LX301 (n = 107)	Overall (n = 195)
Age (y)	Mean (SD)	29.0 (10.0)	32.0 (8.0)	35.0 (9.0)	63.0 (9.0)	49.0 (18.0)
	Median	26.0	31.0	33.0	64.0	51.0
	Min, Max	18, 50	19, 48	21, 54	37, 83	18, 83

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trial LX301	32 /107 (29.9%)	8 /107 (7.47%)	0 /107

Pharmacokinetic interaction studies

SSA treatment: Coadministration of telotristat etiprate and immediate-release octreotide acetate was previously shown to reduce systemic exposure and delay T_{max} of telotristat ethyl and LP-778902 in healthy subjects (LX109). It was not possible to evaluate SSA treatment as a covariate in the population PK analysis due to confounding with health status. Indeed, all healthy subjects from the 3 Phase 1 studies did not have SSA treatment and all patients from Study LX301 had SSA treatment. At study entry, 26 patients had received Lanreotide long acting and 81 patients had received Octreotide long acting formulation.

Based on the post-hoc individual PK parameters from the pop PK model, exposure ($AUC_{0\text{-}24\ h}$ and C_{max}) was comparable whatever the concomitant SSA treatment Figure 10.

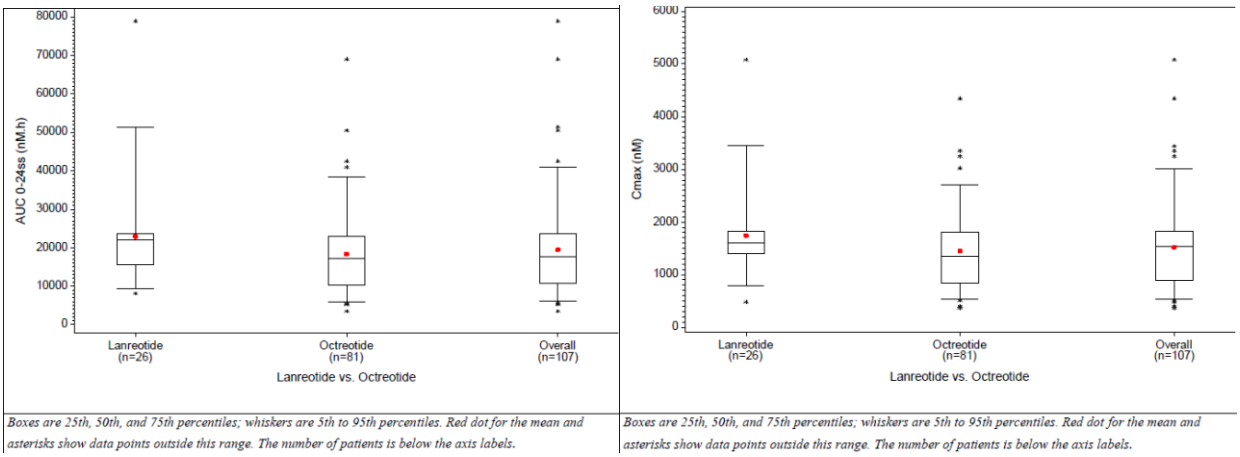


Figure 10: Boxplot of exposure LP-778902 PK parameters and Concomitant SSA treatment in Patients with Carcinoid Syndrome

Induction of CYPs:

In vitro telotristat (active metabolite) caused a concentration dependent increase in CYP2B6 mRNA levels (>2-fold increase and >20% of the positive control, with a maximum observed effect similar to the positive control), suggesting possible CYP2B6 induction. Concomitant use of Xermelo may decrease the efficacy of medicinal products that are CYP2B6 substrates (e.g. valproic acid, bupropion, sertraline) by decreasing their systemic exposure. Monitoring for suboptimal efficacy is recommended in the SmPC.

Telotristat ethyl and its active metabolite were not shown to be inducers of CYP3A4 at systematically relevant concentrations, based on in vitro findings. The potential of telotristat ethyl as an inducer of CYP3A4 was not assessed at concentrations expectable at the intestinal level, due to its low solubility in vitro.

Based on in vitro findings, no clinically-relevant induction is expected with other cytochromes P450.

In vitro, telotristat ethyl inhibited CYP3A4 suggesting a potential interaction with CYP3A4 substrates. A clinical DDI study was conducted with midazolam (a CYP3A4 substrate) to clarify this interaction (see LX108 below).

Based on in vitro findings, no clinically-relevant inhibition is expected with other cytochromes P450.

Transporters

P-glycoprotein (P-gp) and Multi-drug Resistance associated Protein 2 (MRP-2)

In vitro telotristat ethyl inhibited P-gp, but its active metabolite did not at the clinically relevant concentrations.

Telotristat ethyl inhibited MRP2-mediated transport (98% inhibition).

Breast Cancer Resistance Protein (BCRP)

In vitro telotristat ethyl inhibited BCRP (IC_{50} = 20 µM), but its active metabolite telotristat did not show any significant inhibition of BCRP activity (IC_{50} > 30 µM). The potential for in vivo drug interaction via inhibition of BCRP is considered low.

Other transporters

Based on in vitro findings, no clinically-relevant interaction is expected with other transporters.

Carboxylesterases (CES) inhibitors

In vitro loperamide (CES2 inhibitor) had a moderate effect on the metabolism of telotristat ethyl, reducing the formation of telotristat by <30%. *In vitro*, telotristat ethyl inhibited CES2 with an IC50 approximately of 6.4 µM. In phase 3 clinical trials, telotristat was routinely combined with loperamide with no evidence of safety concerns.

LX108: in vivo DDI study with Cyp3A4 substrate midazolam

This phase 1 study was an open-label, 2-period, single-sequence, drug-drug interaction study to assess the effects of steady-state telotristat ethyl, resulting from dosing with 2 x 250-mg (as free base) telotristat etiprate tablets tid for 5 days on the pharmacokinetics of single-dose midazolam (1 x 3 mg [1.5 mL oral syrup (2 mg/mL)]), a sensitive cytochrome P450-3A4 substrate, in healthy male and female subjects. A total of 24 healthy subjects were enrolled in the study and all subjects completed the study.

Following the first administered Midazolam single dose on Day 1 in a fasted state, all subjects were to complete a washout period of 3 nondosing days (Days 2 to 4). On Day 5, subjects were to begin a 5-day

telotristat etiprate regimen (2 x 250-mg [as free base] tablets tid) administered within 1 hour following a standard (non high-fat) meal, except on Day 9 (final dosing day of telotristat etiprate tid), the morning telotristat etiprate dose was to be administered to subjects in the fasted state concomitantly with a single dose of midazolam. The 2 final doses of telotristat etiprate were to be administered again with food on Day 9 throughout the PK sampling collection. Blood samples were collected up to 48 h following administration.

The arithmetic mean plasma concentration profiles for Midazolam are presented in Figure 11.

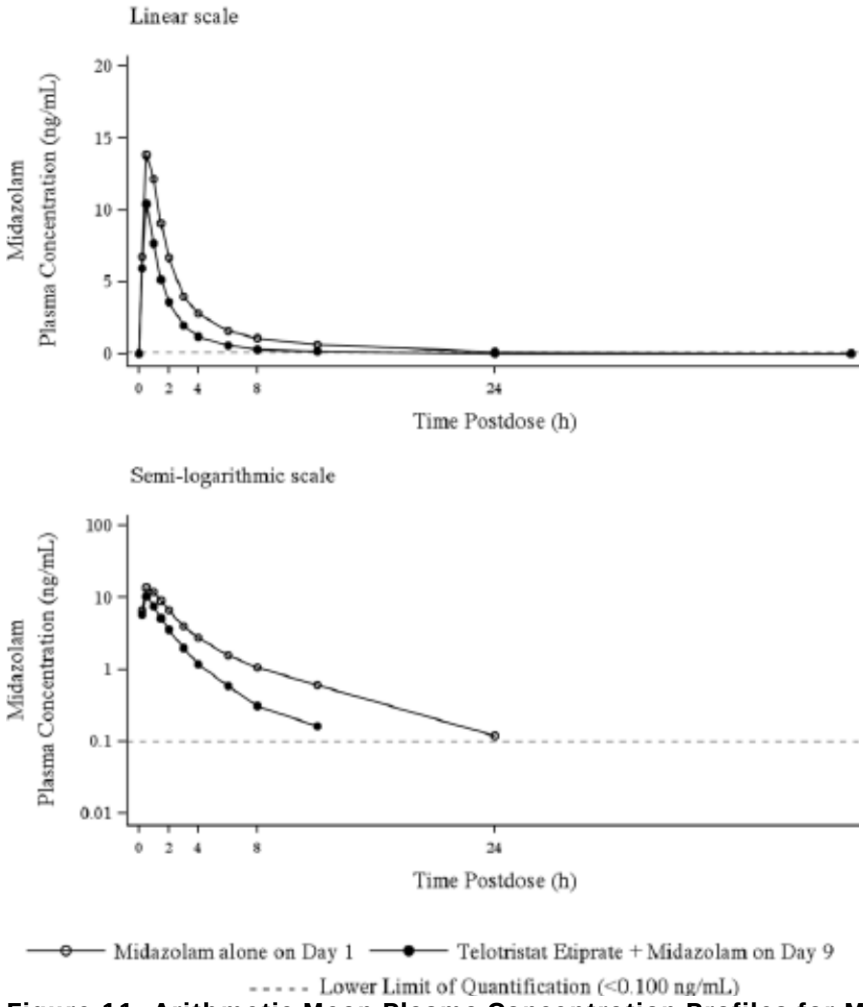


Figure 11: Arithmetic Mean Plasma Concentration Profiles for Midazolam Following Administration of Midazolam Alone and Following Coadministration with Telotristat Etiprate

Arithmetic mean PK parameters from study LX108 are summarized in Table 28.

Table 28: Summary of Arithmetic Mean Pk Parameters from Phase 1 Study LX108

Study	Analyte	Treatments	Arithmetic Mean Parameters (± SD)						
			C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}last}$[a] (hr•ng/mL)	$AUC_{0\text{-}inf}$ (hr•ng/mL)	$t_{1/2}$ (hr)	CL/F (L/hr)	Vz/F (L)
LX108[8]	Midazolam	Midazolam alone (3 mg)	14.8 ± 5.34	0.50 (0.50 - 1.50)	40.4 ± 18.8	42.7 ± 19.8	4.71 ± 2.02	82.5 ± 32.2	516 ± 241
		Telotristat etiprate (500 mg tid) + Midazolam (3 mg)	11.0 ± 3.01	0.50 (0.25 - 2.00)	20.2 ± 4.68	21.1 ± 4.86	2.90 ± 0.86	151 ± 41.6	621 ± 224
	1'-Hydroxymidazolam	Midazolam alone (3 mg)	5.87 ± 2.33	0.50 (0.50 - 1.50)	13.4 ± 4.60	14.7 ± 5.13	4.19 ± 2.89		
		Telotristat etiprate (500 mg tid) + Midazolam (3 mg)	3.86 ± 1.81	0.50 (0.25 - 2.00)	7.21 ± 2.55	7.45 ± 2.60	1.54 ± 0.39		

Following administration of multiple doses of telotristat ethyl, the systemic exposure to concomitant midazolam was significantly decreased. When 3 mg midazolam was coadministered orally after 5-day treatment with telotristat ethyl 500 mg tid (twice the recommended dose), the mean C_{max}, and AUC0-inf for midazolam were decreased by 25%, and 48%, respectively, compared with administration of midazolam alone. The mean C_{max}, and AUC0-inf for the active metabolite, 1'-hydroxymidazolam, were also decreased by 34%, and 48%, respectively. Concomitant use of Xermelo may decrease the efficacy of medicinal products that are CYP3A4 substrates (e.g. midazolam, everolimus, sunitinib, simvastatin, ethinyloestradiol, amlodipine, cyclosporine…) by decreasing their systemic exposure (see section 5.2). Monitoring for suboptimal efficacy is recommended.

LX106: in vivo DDI study with P-gp / MRP2 substrate fexofenadine:

This phase 1 study was an open-label, 2-period, single-sequence DDI study to evaluate the effects of steady-state telotristat ethyl, resulting from dosing with 2 x 250 mg telotristat etiprate tablets tid x 5 days, on the PK of single-dose fexofenadine (1 x 180 mg tablet), a sensitive P-gp and MRP2 substrate, in healthy subjects. A total of 24 healthy subjects were enrolled in the study of which 23 completed the study.

The mean plasma concentration profiles of fexofenadine following administration of fexofenadine alone and following coadministration with telotristat etiprate is represented in and PK parameters are summarized in Table 29.

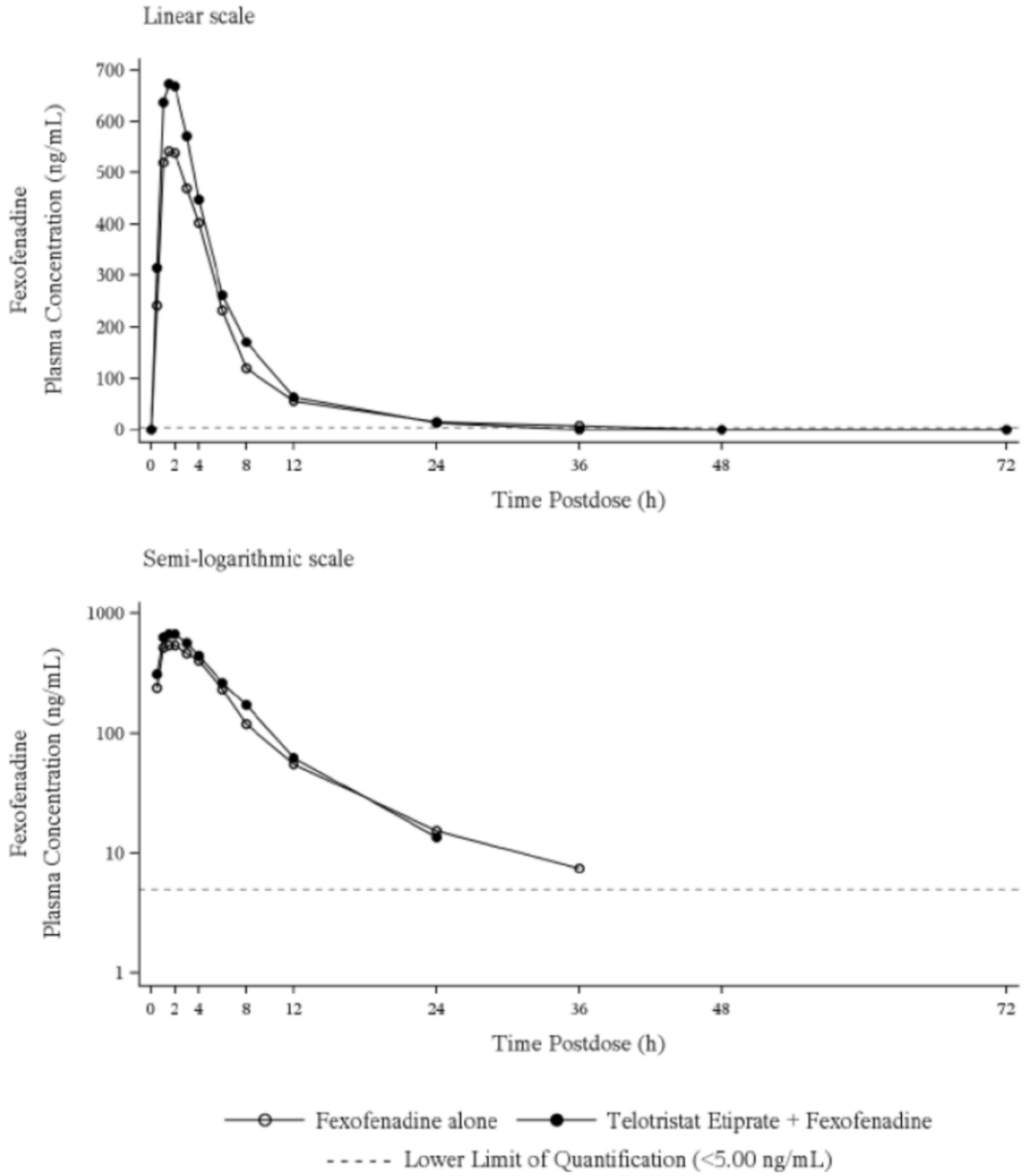


Figure 12: Arithmetic Mean Plasma Concentration Profiles for Fexofenadine Following Administration of Fexofenadine Alone and Coadministration with Telotristat Etiprate

Table 29: Summary of Pharmacokinetic Parameters from LX106

Study	Analyte	Treatments	Arithmetic Mean Parameters (± SD)						
			C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}last}$[a] (hr•ng/mL)	$AUC_{0\text{-}inf}$ (hr•ng/mL)	$t_{1/2}$ (hr)	CL/F (L/hr)	Vz/F (L)
LX106[6]	Fexofenadine	Fexofenadine alone (180 mg)	682 ± 389	2.00 (1.00-4.00)	3590 ± 1440	3690 ± 1440	9.59 ± 3.98	57.6 ± 25.8	1200 ± 1090
		Telotristat etiprate (500 mg tid) + fexofenadine (180 mg)	756 ± 329	1.50 (1.00-6.00)	4130 ± 1520	4210 ± 1530	8.07 ± 3.80	50.1 ± 23.8	567 ± 388

The C_{max} and AUC of fexofenadine (a P-gp and MRP-2 substrate) increased by 16% when a single 180 mg dose of fexofenadine was co-administered orally with a dose of telotristat ethyl 500 mg administered tid (twice the recommended dose) for 5 days. Based on the small increase observed, clinically meaningful interactions with P-gp and MRP-2 substrates are unlikely.

LX109: DDI study with IR octreotide acetate injection (200µg tid).

This was an open-label, 2-period, single-sequence DDI study in healthy male and female subjects to evaluate the effect of octreotide acetate injections (immediate release, administered 200 µg tid) on the PK of telotristat ethyl and its metabolite LP-778902 relative to administration of single-dose telotristat etiprate (administered as 2 x 250 mg tablets) alone in healthy subjects. A total of 24 healthy subjects were enrolled in the study and all subjects completed the study.

For all time points when telotristat etiprate was coadministered with octreotide acetate, ≥50% of telotristat ethyl plasma concentration values were BLQ; therefore, arithmetic mean plasma concentrations were not calculated and are not displayed and the terminal elimination phase could not be adequately characterised.

The mean plasma concentration profiles of LP-778902 following administration of telotristat etiprate alone and following coadministration with octreotide acetate are represented in Figure 13 and the PK parameters are summarized in Table 30.

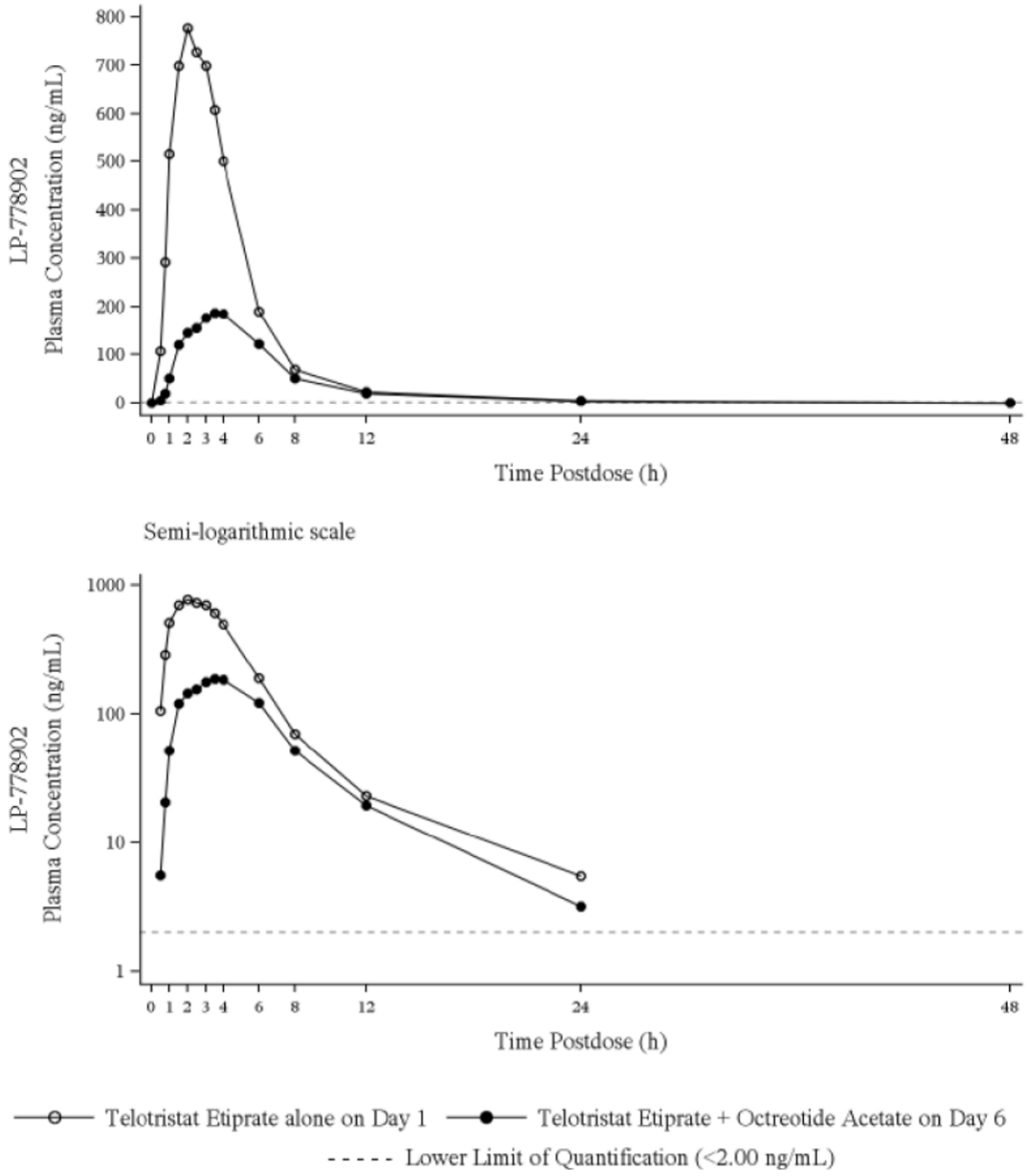


Figure 13: Arithmetic Mean Plasma Concentration Profiles for LP-778902 Following Administration of Telotristat Etiprate Alone and Following Coadministration with Octreotide Acetate

Table 30: Summary of Pharmacokinetic Parameters from LX109

Study	Analyte	Treatments	Arithmetic Mean Parameters (± SD)						
			C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}last}$[a] (hr•ng/mL)	$AUC_{0\text{-}inf}$ (hr•ng/mL)	$t_{1/2}$ (hr)	CL/F (L/hr)	Vz/F (L)
LX109[9]	Telotristat ethyl	Telotristat etiprate alone (500 mg)	6.62 ± 3.90	1.00 (0.50 - 2.50)	8.65 ± 5.09	10.6 ± 5.64	0.62 ± 0.14	56400 ± 20900	50600 ± 25000
		Telotristat etiprate (500 mg) + octreotide acetate (200 µg tid)	1.12 ± 0.51	1.50 (0.75 – 3.50)	2.34 ± 1.27	NC	NC	NC	NC
	LP-778902	Telotristat etiprate alone (500 mg)	865 ± 277	2.03 (1.02 – 3.50)	3350 ± 1140	3380 ± 1140	5.18 ± 1.58		
		Telotristat etiprate (500 mg) + octreotide acetate (200 µg tid)	209 ± 129	3.50 (2.00 – 6.00)	1190 ± 651	1280 ± 647	3.61 ± 1.25		

Study data showed an 83% and 81% decrease in Cmax and AUC of telotristat ethyl and telotristat, respectively. Reduced exposures were not observed in a 12◦week double-blind, placebo-controlled, randomised, multicentre clinical trial in adult patients with carcinoid syndrome on long-acting SSA therapy.
Consequently, short-acting octreotide should be administered at least 30 minutes after administration of Xermelo if treatment with short-acting octreotide is needed in combination with Xermelo.

Pharmacokinetics using human biomaterials

Following incubation of 14C-telotristat ethyl with human male and female hepatocytes, LP-778902 was formed by both male and female human hepatocytes, which was further metabolized to LP-951757. The formation of LP-951757 was slower and less extensive when compared to LP-778902. No significant gender differences were observed in the nature and quantity of metabolites formed.

Addiitional in vitro studies were submitted to investigate the potential of telotristat ethyl and LP-778902 to induce CYP1A2, 2B6 and 3A4/5 expression in cultured human hepatocytes from three different donors and to evaluate the potential of telotristat ethyl and LP-778902 to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4/5 in human liver microsomes. The range of telotristat ethyl and LP-778902 concentrations tested was from 0.003 to 10 µM and from 0.03 to 10 µM, respectively, which covers the maximum human plasma concentration. These studies have been performed according to the EMA guideline CPMP/EWP/560/95/Rev. 1 Corr. 2. The results showed that telotristat ethyl and LP-778902 were not inducers of CYP1A2, but showed concentration-dependent down-regulation of this enzyme. (see non-clinical section).

2.4.3. Pharmacodynamics

Mechanism of action

The applicant did not submit clinical studies on the mechanism of action of telotristat etiprate (see clinical discussion).

Primary and Secondary pharmacology

Serotonin (5-HT) levels

In the study LX1606.1-102-NRM a statistically significant (P<0.05) decrease in 5-HT blood levels compared to placebo was observed following treatment with the 500 mg doses (BID, TID, and QD) starting on Days 7, 9, and 10, respectively. A statistically significant decrease in 5-HT blood levels compared to placebo was observed with all of the 500 mg doses on Day 14. The decrease in 5-HT levels for the 500 mg dose groups was maintained through the 48-hour post-Day 14 dose sample for the 500 mg QD and TID dose groups and 24 hours post-Day 14 dose for the 500 mg BID dose group.

In the study LX1606.1-202-CS the 5-HT levels had high variability over a range of multiple oral doses. In the core phase whole blood 5-HT levels tended to increase with placebo and telotristat etiprate 150 mg tid, while 5-HT levels remained close to baseline for telotristat etiprate 250 mg tid, 350 mg tid, and 500 mg tid. In the extension phase levels of 5-HT varied throughout the treatment period but tended to remain near baseline values with no clear trend over time. The mean baseline whole blood 5-HT level was 850.3778 ng/mL (n=19); it varied throughout the extension with minimal mean changes from baseline ranging from -298.7 to +432.0 ng/mL. The lowest mean whole blood 5-HT level was 523.1 ng/mL (week 8; n=17) with an average telotristat etiprate dose of 1088.8 mg/d and the highest mean whole blood 5-HT level was 1259.0 ng/mL (week 147/148; n=2) with an average dose of telotristat etiprate of 1390.5 mg/d.

In the study LX1606.1-203-CS the mean whole blood 5-HT concentration remained below Baseline during the Core Phase and Extension Period over a range of multiple oral doses (however the mean change from Baseline and percent change from Baseline in whole blood 5-HT was not statistically significant at any time point during the Core Phase).

5-hydroxyindolacetic acid (5-HIAA) levels

In the study LX102, all decreases (from Day 1 measurement) in urinary 5-HIAA excretion were statistically significantly different (most P values were <0.01) in terms of greater reductions for all cohorts on Days 5, 10, 13, and 14, with the exception of Cohort 1 at Day 13 (no data were collected) and Day 14.

In the study LX202, mean u5-HIAA values were generally lower in treatment groups versus placebo in the Core Phase. In the core phase mean 5-HIAA values in urine were generally lower in the telotristat etiprate treatment groups versus placebo. Minimal mean changes from baseline ranging from -74.16 to +0.03 mg/24 h were seen in the telotristat etiprate 150 mg tid, 250 mg tid, and 500 mg tid groups. In the extension phase mean decreases from baseline for u5-HIAA ranged from -1.6 to -86.0 mg/24 h at all time-points with data available.

In the study LX203, for Core Phase, mean u5-HIAA levels decreased from Baseline from Week 2 through Week 12, and the change from Baseline (reduction) in u5-HIAA was statistically significant at Week 6 by signed-rank test (p = 0.012) and at Week 8 and Week 12 by both tests (p = 0.015 and p = 0.032 at Week

8 and p = 0.008 and p = 0.016 at Week 12 by paired t-test and signed-rank test, respectively). For the extension period, mean u5-HIAA values remained below Baseline throughout the Extension Period with the exception of Week 60.

In the study LX301, reductions in u5-HIAA values from baseline were statistically significant at week 12 for telotristat etiprate 250 mg and 500 mg tid compared to placebo in the ITT population. The estimate of the treatment difference versus placebo (Hodges-Lehmann) was -30.100 mg/24 h (97.5% CI: -56.000, -8.100) for telotristat etiprate 250 mg (p<0.001) and -33.800 (97.5% CI: -66.200, -14.600) for the telotristat etiprate 500 mg (p<0.001); p-values were obtained from a blocked WRS Wilcoxon rank sum test (van Elteren test). In the ITT population the mean change from baseline in 5-HIAA plasma levels averaged across all time points during the double-blind treatment period was -59.1 ng/mL (n=44) for telotristat etiprate 250 mg tid, -133.9 ng/mL (n=41) for 500 mg tid, and 58.8 ng/mL (n=40) for placebo. The treatment difference versus placebo demonstrated statistical significance for both telotristat etiprate groups [250 mg tid -63.5 ng/mL (95% CI: -116.4, -35.4; p<0.001), 500 mg tid -92.1 ng/mL (95% CI: -128.6, -56.6; p<0.001), Wilcoxon rank sum test). In the open-label extension period samples were analysed for urinary 5-HIAA levels (mg/24 h) at weeks 18, 24, and 48. Reductions in u5-HIAA were observed at all assessed time-points in the ITT population.

In the study LX302, plasma 5-HIAA levels were stable over the first 24 weeks of the study (baseline: mean 187.6 ng/mL, median 37.2 ng/mL; week 12: mean 181.4 ng/mL, median 32.0 ng/mL; week 24: mean 146.3 ng/mL, median 38.3 ng/mL) in the PP Population.

In the study LX303, there was a statistically significant greater percent reduction in the urine of u5-HIAA levels for both telotristat etiprate 250 mg and 500 mg tid compared to placebo (p<0.001 each). Estimates (Hodges-Lehmann) of treatment differences versus placebo were -54.0% (95% CI: -85.0, -25.1) for telotristat etiprate 250 mg tid and -89.7% (95% CI: -113.1, -63.9) for 500 mg tid. The majority of patients in the telotristat etiprate 250 mg and 500 mg groups showed reductions in percent change from baseline at week 12 in u5-HIAA while the majority of patients in the placebo group showed increases in percent change. The mean changes from baseline in plasma levels of 5-HIAA averaged across all time points during the double-blind treatment period were -187.3 ng/mL for telotristat etiprate 250 mg tid (n=22), -194.4 ng/mL for 500 mg tid (n=24), and 69.4 ng/mL for placebo (n=24) in the ITT population. Estimates (Hodges-Lehmann) of treatment differences versus placebo were -142.379 ng/mL (95% CI: -242.583, -60.050) for telotristat etiprate 250 mg and -124.355 ng/mL (95% CI: -201.650, -70.950) for 500 mg. Correlations between urinary and plasma 5-HIAA levels were positive and statistically significant during the double-blind treatment period DBT Period at baseline, week 6, and week 12 for all groups (p<0.001 for all comparisons) in the ITT population. Reductions in u5-HIAA levels in patients previously assigned to placebo and telotristat etiprate 250 mg tid approached similar percentage changes to those seen in patients receiving telotristat etiprate 500 mg tid during the double-blind treatment phase.

Exposure-Response Analysis of Urinary 5-HIAA

The analysis was restricted to patients on active treatment, resulting in 187 observations from 67 individuals (250 mg: 37 patients, 103 observations; 500 mg: 30 patients, 84 observations). Due to the limited u5-HIAA data available from study LX301 the exposure-response model with the best fit was a linear model that related the maximum plasma concentration of the active metabolite LX1033 at steady-state ($C_{max,ss}$) to u5-HIAA levels. The model predicted u5-HIAA reduction at the 500 mg tid dose in general agreement with the study data, but due to its linear nature the 250 mg tid dose was under predicted (approximately 50%). The median average u5-HIAA level at baseline was 31.3 mg/24h with a range of 0 to 786.2 mg/24 h. The influence of age, weight, BMI, race, sex, renal impairment, hepatic impairment, and short-acting SSA treatment (octreotide), as well as average bowel movements, u5-HIAA, and SSA treatment (octreotide or lanreotide) at baseline were evaluated in the model but none

of the covariates was found to be a statistically significant predictor of variability in u5-HIAA.
The only covariate that was identified as being predictive of u5-HIAA variability was the chromogranin A (CgA) level at baseline. Patients with baseline CgA ≥39 ng/mL had an u5-HIAA baseline of 61.09 mg/24 h compared to the typical value of 7.09 mg/24 h. The population mean estimates of the slope for $C_{max,ss}$ in patients with baseline CgA ≥39 ng/mL was -0.016 mg/24 h compared to -0.00206 mg/24 h in patients with baseline CgA <39 ng/mL corresponding to expected decreases in u5-HIAA of 16.1 mg/24 h and 2.06 mg/24 h in subjects with baseline CgA ≥39 ng/mL and for subjects with baseline CgA <39 ng/mL, respectively, for every 1000 nM increase in $C_{max,ss}$ due to the drug effect.

Exposure-Response Relationship for Weekly Bowel Movements

Exposure-response analyses of bowel movements included patients on telotristat etiprate with LX1033 exposure estimates available and on placebo; patients included needed to have a baseline and at least 1 documented post-first dose weekly bowel movement measurement. A total of 1454 observations from 119 patients were included.
Median average bowel movements at baseline were 5.29 counts/day with a range of 3.5 to 12.5 counts/day and approximately 28% of the weekly bowel movement records were in the presence of rescue short-acting SSA octreotide in addition to a long-acting SSA.
The final exposure-response model for bowel movements averaged at each study week was an inhibitory maximal effect (E_{max}) time-course model including parameters estimating the baseline average bowel movements, maximum reduction in bowel movements (E_{max}), and time to 50% of the maximum effect (T_{50}).
An exposure-response relationship was found whereby 2 separate linear functions described the relationship between E_{max} and T_{50} with predicted LX1033 C_{max}. Assuming the median steady-state C_{max} of 836 and 1780 nM for a typical patient administered telotristat etiprate 250 and 500 mg tid, E_{max} in bowel movements taking into account drug effect are 1.46 (28% reduction from baseline) and 1.90 (36% reduction from baseline) counts/day for 250 mg and 500 mg tid, respectively, compared to a reduction of 1.055 counts/day for placebo from a baseline of 5.27 counts/day.
The typical value estimate for T_{50} was 3.74 weeks for placebo patients. Additionally, as C_{max} increased the reduction in bowel movements was more rapid with T_{50} being slightly shorter in patients administered 500 mg tid (T_{50} of 2.16 weeks) as compared to 250 mg tid (T_{50} of 3 weeks). No statistically significant influence of age, baseline weight, baseline BMI, sex, race, baseline average bowel movements, baseline u5-HIAA, baseline CgA, renal function category, hepatic function category, or concomitant long- and short-acting SSA medications was found for weekly bowel movements.

2.4.4. Discussion on clinical pharmacology

The plasma PK of telotristat ethyl and LP-778902 has been investigated in nine Phase 1 studies in healthy subjects over a range of single (up to 1500 mg) and multiple oral doses (up to 500 mg tid), (capsule and tablet formulations; alone and coadministered with immediate-release octreotide; with and without food), in hepatic impairment and in 2 Phase 2 and 1 Phase 3 studies in patients with CS.

In Phase 1 studies, dosing with telotristat ethyl in healthy subjects (dose range: 100 mg once daily to 500 mg tid) produced statistically significant reductions from baseline in whole blood serotonin and 24-hour urinary 5-hydroxyindoleacetic acid (u5-HIAA) compared with placebo.

In patients with carcinoid syndrome, telotristat resulted in reductions in u5-HIAA. Statistically significant reductions in u5-HIAA were seen for telotristat ethyl 250 mg tid compared with placebo in both Phase 3 studies.

The pharmacokinetics of telotristat ethyl and its active metabolite have been characterised in healthy volunteers and patients with carcinoid syndrome. Overall, high variability in telotristat ethyl and LP-778902 PK parameters was observed and precluded in part statistical significant extrapolations. After oral administration, telotristat ethyl undergoes hydrolysis *via* carboxylesterases to its active and major metabolite. The only metabolite of telotristat (active metabolite) representing consistently > 10% of total plasma drug-related material was its oxidative decarboxylated deaminated metabolite, LP-951757. Systemic exposure to LP-951757 was about 35% of the systemic exposure to telotristat (active metabolite) in the mass balance study. LP-951757 was pharmacologically inactive at TPH1 *in vitro*.

After oral administration to healthy volunteers, telotristat ethyl was rapidly absorbed, and almost completely converted to its active metabolite. Peak plasma levels of telotristat ethyl were achieved in 0.53 to 2.00 hours and those of the active metabolite in 1.50 to 3.00 hours after oral administration.

In patients with carcinoid syndrome on long-acting SSA therapy, there was also a rapid conversion of telotristat ethyl to its active metabolite. A high variability (% CV range of 18% to 99%) in telotristat ethyl and its active metabolite parameters was observed within the overall PK. The mean PK parameters for telotristat ethyl and the active metabolite appeared unchanged between week 24 and week 48, suggesting the achievement of steady-state conditions at or prior to week 24. In patients treated at 250 mg tid, a slight accumulation of telotristat levels was observed with a median accumulation ratio based on AUC0-4 h of 1.55 [minimum, 0.25; maximum, 5.00; n=11; week 12], with a high inter-subject variability (%CV=72%). In patients treated at 500 mg tid (twice the recommended dose), a median accumulation ratio based on AUC0-4 h of 1.095 (minimum, 0.274; maximum, 11.46; n=16; week 24) was observed, with a high inter-subject variability (%CV=141.8%).

Based on the high inter-subject variability observed, accumulation in a subset of patients with CS cannot be excluded.

A significant food effect has been observed in healthy subjects with an up to 5.5 fold increase in exposure of telotristat ethyl and a lesser increase in exposure of LP-778902 (<1.5 fold); administration of telotristat etiprate with food is recommended in the proposed SmPC. In a food effect study administration of telotristat ethyl 500 mg with a high-fat meal resulted in higher exposure to the parent drug (C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$ being 112%, 272%, and 264% higher, respectively compared with the fasted state) and its active metabolite (C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$, 47%, 32%, and 33% higher, respectively compared with the fasted state).

Both telotristat ethyl and its active metabolite are > 99% bound to human plasma proteins. After oral administration, telotristat ethyl undergoes hydrolysis via carboxylesterases to its active and major metabolite.

Following a single 500 mg oral dose of ^{14}C-telotristat ethyl, approximately 93% of the dose was recovered. The majority was eliminated in the faeces, with less than 1% in the urine.

The apparent half-life of telotristat ethyl in normal healthy volunteers following a single 500 mg oral dose ^{14}C-telotristat ethyl was approximately 0.6 hour and that of its active metabolite was 5 hours. Following administration of 500 mg three times daily, the apparent terminal half-life was approximately 11 hours.

Renal excretion is a minor elimination pathway. Telotristat etiprate is intended for chronic administration and is likely to be used in patients with impaired renal function (see SmPC section 5.2). As per Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function, a PK study in renally impaired subjects is considered necessary and should be conducted as a post authorisation measure with the results submitted as a variation.

The results of the PK study in patients with liver impairment indicate that liver impairment leads to a clinically relevant increase in plasma levels, with more than a doubling of overall exposure in mild impairment, and more than tripling with moderate impairment (see SmPC section 5.2). Severely liver impaired patients were finally not tested within the study, due to potential safety concerns, as it could be anticipated that the increases in exposure would be even higher for these patients.

Regarding interactions with potential CYP3A4 inhibitor or inducers and uptake transporters, these have been adequately described in the SmPC section 4.5 and 5.2.

Concomitant use of gastric acid reducers such as PPIs on PK of telotristat ethyl and LP-778902 from the PopPK analysis is lacking. Since solubility of telotristat ethyl is markedly pH dependent in the physiological range, a DDI study to evaluate the effect of multiple doses of concomitant gastric acid reducers such as PPIs on the PK of telotristat ethyl and LP-778902 is considered necessary in line with the guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev.1 Corr.2**). Therefore, the CHMP has requested that a study should be performed and the results submitted as a variation. In vitro data demonstrated a moderate effect of loperamide, a CES2 inhibitor. Because Xermelo is being used in a chronic manner, the chance of patients taking other medications such as Loperamide concomitantly is higher. Therefore, the CHMP recommends further exploration on the interaction between concomitant inhibitors of CES2 and the PK of telotristat ethyl and LP-778902.

Coadministration of single dose telotristat etiprate and immediate-release octreotide acetate injections in normal healthy subjects significantly reduced systemic exposure of telotristat ethyl and LP-778902 compared to administration of single-dose telotristat etiprate alone. However, such an effect was not observed in patients with CS on long acting formulation SSA therapy in which mean steady-state exposures of LP-778902 were comparable to exposures observed in healthy subjects at steady-state in study LX102 (non-compartmental analysis). Overall, based on the absorption, distribution, metabolism and excretion (ADME) properties of octreotide, it is unlikely that coadministration of telotristat with octreotide will affect the PK of octreotide.

As regards primary pharmacology of telotristat etiprate, effects on urinary (u5-HIAA) and plasma 5-HIAA as well as on serotonin (5-HT) levels have been investigated. Higher doses of telotristat etiprate (500 mg qd, bid, tid) led to a decrease in 5-HT blood levels compared to placebo and at these doses the effect was maintained throughout the studies. Urinary excretion of 5-HIAA was reduced with telotristat etiprate administration. Effects on u5-HIAA levels were consistently seen in subgroups by age, sex, baseline u5-HIAA, daily BM frequency, daily flushing, stool consistency, and proportion of days with nausea. As with urinary excretion of 5-HIAA, mean changes from baseline of 5-HIAA levels in plasma showed a statistically significant reduction compared to placebo.

As regards secondary pharmacology no clinically meaningful effects of telotristat etiprate on heart rate or other ECG parameters have been identified.

The influence of age on the pharmacokinetics of telotristat ethyl and its active metabolite has not been conclusively evaluated. No specific study has been performed in the elderly population. No statistically significant influence of age, baseline weight, baseline BMI, sex, race, baseline average BMs, baseline u5-HIAA, baseline CgA, renal function category, hepatic function category, or concomitant long- and short-acting SSA medications was found for weekly BMs. The substantial variability in baseline u5-HIAA and baseline CgA likely contributed to the inability to identify relationships between biomarkers and weekly BMs. Thus the results cannot provide adequate information on the relationship between plasma concentration and effect.

Missed doses

In the event of a missed dose, patients should take their subsequent dose at the next scheduled time point. Patients should not take a double dose to make up for a missed dose.

Elderly patients (65 years of age and above)

No specific dose recommendations are available for elderly patients (see section 5.2).

Renal impairment

No specific study has been performed in patients with renal impairment.

Patients with mild or moderate renal impairment should be treated with caution. No specific dose recommendations are available for patients with mild or moderate renal impairment.

The use of telotristat is not recommended in patients with severe renal impairment and in patients with end-stage renal disease requiring dialysis (see section 5.2).

Hepatic impairment

In patients with mild hepatic impairment (Child Pugh score A), it may be necessary to reduce the dose to 250 mg twice daily according to tolerability. In patients with moderate hepatic impairment (Child Pugh score B), it may be necessary to reduce the dose to 250 mg once daily according to tolerability. The use of telotristat is not recommended in patients with severe hepatic impairment (Child Pugh score C) as no data are available (see section 5.2).

Paediatric population

There is no relevant use of telotristat in the paediatric population in the indication of carcinoid syndrome.

Method of administration

Oral use.

2.4.5. Conclusions on clinical pharmacology

Overall, the available pharmacokinetic and pharmacodynamic data adequately characterise the pharmacology of telotristat. However, as the treatment of CS may be for long term use if the patient derives clinical benefit, some outstanding issues would need to be addressed as post authorisation measures.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- Conduct and submit the results of an in vivo drug interaction study to evaluate the effect of multiple doses of concomitant gastric acid reducers such as PPIs on the PK of telotristat ethyl, LP-778902. Expected date of submission: Q3 2018
- Conduct and submit the results of a PK study in subjects with mild, moderate and severe renal impairment in line with the recommendations given in EMA/CHMP/83874/2014, including analysis of protein binding. For subjects with end-stage renal disease requiring dialysis, in- or exclusion should be thoroughly justified. Expected date of submission: Q4 2018

The CHMP recommends the following measures to address the issues related to pharmacology:

- Submission of results of in vitro study XT174037 initiated to investigate the role of CYP enzymes in the metabolism of LP-778902.

- To evaluate the clinical significance of the observed CYP2B6 induction by LP-778902, the applicant should consider further exploration of CYP2B6 interaction once a well validated probe drug of the enzyme becomes available. It is advised to follow the scientific literature.
- The applicant should consider further exploration of concomitant inhibitors of CES2 on the PK of telotristat ethyl and LP-778902.
- Telotristat ethyl showed some inhibition towards carboxylesterase (CES) 2 in vitro. Since the clinical relevance is unclear, the applicant should consider further exploration.
- In consequence of the results from in vivo DDI study LX108 with CYP3A4 substrate midazolam, it is recommended to evaluate the inductive potential of LX1606, LP-778902 and LP-951757 on the mRNA expression of intestinally expressed UDP-glucuronosyltransferase (UGT) enzymes in vitro.
- In consequence of the results from in vivo DDI study LX108 with CYP3A4 substrate midazolam, it should be evaluated in vitro whether telotristat ethyl and midazolam bound to CYP3A undergo cooperative interaction; the 1'-OH-MDZ/4-OH-MDZ ratio may serve as a biomarker of such an interaction.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Dosages for the phase 3 studies were primarily based on data from phase 2 studies LX202 and LX203 in patients with CS not adequately controlled by SSA.

In the phase 2, dose-escalation, open-label study LX203 without placebo-control, most patients were titrated up to telotristat etiprate 500 mg tid. Clinical responses were seen at both telotristat etiprate 250 mg and 500 mg tid dose levels, although 500 mg tid produced slightly more reductions in u5-HIAA compared to 250 mg.

In study LX202 (double-blind, placebo-controlled study) telotristat etiprate 500 mg tid was associated with nausea in 44% of patients early after treatment initiation versus none on 250 mg tid, but in study LX203 500 mg tid was not associated with nausea after titration from lower doses. Therefore the 500 mg dose level was to be titrated from telotristat etiprate 250 mg tid for 7 days in a blinded manner in the phase 3 studies.

Although 500 mg tid telotristat etiprate was identified as the dosage most likely to deliver a clinical benefit in the selected population based on clinical response (slightly more reductions in the PD marker u5-HIAA levels than other doses studied), telotristat etiprate 250 mg tid was selected as a starting dose based on the favourable safety profile in relation to efficacy.

2.5.2. Main study(ies)

Study LX1606-301: A Phase 3, randomized, placebo-controlled, parallel-group, multicenter, double-blind study to evaluate the efficacy and safety of telotristat etiprate (LX1606) in patients with carcinoid syndrome not adequately controlled by somatostatin analog (SSA) Therapy.

Results described in this assessment report are based on the interim data submitted in the MAA filed in June 2016 (complete data for the 12-week double-blind portion of the study and partial data for the 36-week open-label portion of the study). Updates with final results were also provided (data not shown).

Methods

Study Participants

Inclusion Criteria

Patients were required to fulfil the following inclusion criteria:

1. Patients ≥18 years of age at the time of screening visit

2. Histopathologically confirmed, well-differentiated, metastatic NET with extent documented by computed tomography (CT), magnetic resonance imaging (MRI, or radionuclide imaging

3. Documented history of CS, and experiencing an average of ≥4 BMs/day during run-in

4. On stable-dose of SSA therapy defined as LAR or depot SSA therapy or continuous subcutaneous infusion via a pump (same dose level and frequency for at least 3 months before run-in)

5. Minimum doses of LAR or depot SSA therapy approved for use in CS in the patient's country of residence or prescriber's country of practice (Octreotide LAR at 30 mg every 4 weeks; Lanreotide depot at 120 mg every 4 weeks), however, patients not tolerating SSA therapy at this level were allowed to enter at their highest tolerated dose

6. Adequate method of contraception in patients of childbearing potential

7. Ability and willingness to provide written informed consent

Exclusion Criteria

Patients fulfilling the following criteria were excluded:

1. Diarrhoea other than CS related

2. More than 12 watery BMs/day associated with volume contraction, dehydration, or hypotension compatible with a "pancreatic cholera"-type clinical syndrome, as judged by investigator

3. Positive stool examination for enteric pathogens, pathogenic ova or parasites, or clostridium difficile

4. Karnofsky Performance Status ≤60%

5. Absolute neutrophil count ≤1500 cells/mm^3 or platelets ≤75,000 cells/mm^3 or haemoglobin ≤9 g/dL for males and ≤8 g/dL for females

6. AST, or ALT ≥5.5 x ULN if documented history of hepatic metastases or ≥2.5 x ULN without documented history of hepatic metastases; total bilirubin >1.5 x ULN (unless documented history of Gilbert's Syndrome); ALP ≥5 x ULN if total bilirubin was >ULN, no upper limit of ALP if the total bilirubin ≤ULN

7. Serum creatinine ≥1.5 x ULN

8. Treatment with tumour-directed therapy including (not limited) interferon, chemotherapy, mTOR inhibitors <4 weeks before screening or hepatic embolization, radiotherapy, radiolabeled SSA, or tumour debulking <12 weeks before screening

9. Major surgery (procedures requiring general anaesthesia or major regional anaesthesia within 8 weeks before screening)

10. History of short bowel syndrome

11. Pregnant or nursing

12. Positive pregnancy test

13. Life expectancy <12 months from screening

14. Presence of clinically significant findings in medical history or physical examination that would have compromised patient safety or the outcome of the study in investigator's or medical monitor's opinion

15. Clinically significant laboratory abnormality at screening that would have compromised patient safety or the outcome of the study in investigator's or medical monitor's opinion

16. Clinically significant cardiac arrhythmia, bradycardia, or tachycardia that would have compromised patient safety or the outcome of the study in investigator's or medical monitor's opinion

17. History of substance or alcohol abuse within 2 years before screening

18. Administration of any investigational agent within 30 days or investigational therapeutic protein or antibody within 90 days before screening

19. Previous exposure to telotristat etiprate

20. Currently committed to an institution by virtue of an order issued either by judicial or administrative authorities

Treatments

During the double-blind treatment period patients received either telotristat etiprate 250 mg, 500 mg, or placebo tid. For patients assigned to telotristat etiprate 500 mg tid a blinded titration was used during the first 7 days. Upon completion of the double-blind treatment period, patients received telotristat etiprate 500 mg tid in the open-label extension period with a titration during the first 7 days (week 13) for all patients. During the open-label extension period downward dose adjustment was permitted in case of intolerability; patients down titrated to 250 mg tid could resume a 500 mg tid dose at the discretion of the investigator. Patients intolerant to 250 mg tid were discontinued from the study.

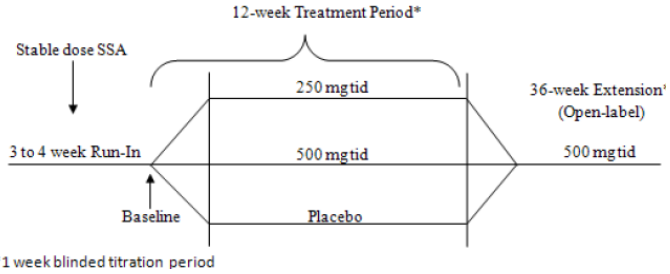


Figure 14: Treatment Schema

Study dosing schema

Assigned Dose Regimen	Week 1 (Double-blind Titration Period)	Weeks 2-12 Treatment (Double-blind Treatment Period)	Week 13 (Double-blind Titration Period)	Weeks 14+ (Open-label Extension Period)
Placebo	Placebo	Placebo	250 mg tid	500 mg tid
Telotristat etiprate 250 mg tid	250 mg tid	250 mg tid	500 mg tid	500 mg tid
Telotristat etiprate 500 mg tid	250 mg tid	500 mg tid	500 mg tid	500 mg tid

Abbreviation: tid = 3 times daily

Duration of treatment: Up to 48 weeks of treatment (12-week DBT Period and 36-week OLE Period).

Objectives

Primary Objectives:

The primary objective of the study was to confirm that at least 1 or more treatment groups of telotristat etiprate compared with placebo was effective in reducing the number of BMs/day from Baseline averaged over the 12-week double-blind portion of the study (DBT Period) in patients not adequately controlled by current SSA therapy .

Secondary Objectives:

The secondary objectives were to assess the effects of telotristat etiprate versus placebo over the DBT Period of the study in patients who were not adequately controlled by current SSA therapy as determined by:

- Change from Baseline in: urinary 5-hydroxyindoleacetic acid (u5-HIAA) levels at Week 12, the daily number of cutaneous flushing episodes averaged across all time points, abdominal pain averaged across all time points.

The other efficacy objectives were to assess the effects of telotristat etiprate versus placebo over the DBT Period of the study in patients not adequately controlled by current SSA therapy as determined by:

- Proportion of: patients with durable response, defined as the proportion of responders with ≥30% reduction in daily number of BMs for ≥50% of time over the DBT Period of the study; weeks in which patients reported adequate relief of carcinoid syndrome (CS) symptoms associated with gastrointestinal (GI) symptoms; patients that reported adequate relief of CS symptoms associated with GI symptoms at each study week; days where urgency/immediate need to defecate was reported; days with reports of nausea; days with ≥30% reduction in number of BMs from individual Baseline mean; and days with ≥1.5 reduction in number of BMs from individual Baseline mean
- Change from Baseline in: overall and domain scores of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and Gastrointestinal Symptoms of Carcinoid Neuroendocrine Tumors (GI.NET21) averaged across all time points and at each study visit where collected; the daily number of cutaneous flushing episodes averaged at each study week; abdominal pain averaged at each study week; in BM frequency averaged at each study week; stool consistency averaged across all time points and averaged at each study week; subjective global assessment of CS symptoms on an 11-point numeric rating scale averaged across all time

points and at each study week; the sensation/severity of nausea averaged across all time points and at each study week; u5-HIAA averaged across all time points and at Week 6; and plasma levels of 5-HIAA averaged across all time points and at each study week

- Time to: first ≥30% worsening in BM frequency, defined as time to the first day of 2 consecutive weeks with a mean BM frequency at least 30% above the individual Baseline mean; first sustained ≥30% improvement from Baseline in BM frequency, defined as time to the first day of 2 consecutive weeks with a mean BM frequency at least 30% below the individual Baseline mean; and a 3-point reduction in the weekly global assessment of severity of CS symptoms sustained for at least 50% of the subsequent weeks (evaluated in patients with at least 4 weeks of data from the week where they responded)
- Relationship of change from Baseline in BMs to changes from Baseline in stool consistency, adequate relief, nausea, urgency, and abdominal pain
- Relationship of changes from Baseline plasma and u5-HIAA levels to changes from Baseline in number of BMs, subjective global assessment, time to first improvement in BM frequency, time to first worsening in BM frequency, and change in symptoms (abdominal pain, stool consistency, urgency to defecate, and reports of nausea) over the DBT Period
- Correlation between 5-HIAA levels in urine and plasma over time
- Change in the frequency of rescue short-acting SSA used to treat bowel-related CS symptoms averaged across all time points and at each study week

Outcomes/endpoints

The objectives of the study were identical as study endpoints.

The primary efficacy endpoint was the change from baseline in the number of daily BMs averaged over the 12-week double-blind phase of the trial.

Secondary efficacy endpoints were the change from baseline in urinary 5-HIAA levels at week 12, the change from baseline in the number of daily cutaneous flushing episodes averaged across all time points, and the change from baseline in abdominal pain averaged across all time points.

Efficacy assessments include the following patient reported measures: number of daily BMs, EORTC QLQ-C30 & GI.NET21, subjective global assessment of symptoms associated with CS, need for rescue short-acting SSA therapy to treat bowel-related symptoms associated with CS, number of cutaneous flushing episodes, stool consistency, urgency to defecate, sensation/severity of nausea, and abdominal pain/discomfort.

Daily and weekly diaries completed by patients were used to collect all efficacy assessments (number of daily BMs, number of daily cutaneous flushing episodes experienced, sensation of urgency to defecate, abdominal pain).

A subjective global assessment of symptoms associated with CS will be evaluated using 2 methods in the diary.

1)Patients will first be asked to respond to the following question: “In the past 7 days, have you had adequate relief of your carcinoid syndrome bowel complaints such as diarrhea, urgent need to have a bowel movement, abdominal pain, or discomfort?”

2) Then patients will be asked the following question to assess global symptoms associated with CS on an 11-point scale: “Rate the severity of your overall carcinoid symptoms over the past 7 days on a scale from 0-10, where 0=no symptoms and 10 = worst symptoms ever experienced.”

Patients will record the frequency and dose of subcutaneous injections of rescue, short-acting octreotide, if taken, in the daily diary.

To assess sensation/severity of nausea on a daily basis, patients will record their response using a 4-point scale: 0=none, 1=mild, 2=moderate, 3=severe.

Patients will record in the daily diary the level of any abdominal pain they feel on a daily basis using an 11-point NRS. “Rate your worst abdominal (belly or tummy) pain in the past 24 hours, with “0” being “no pain” and “10” being “worst pain ever experienced”.”

A telephone exit interview will be conducted on a subset of patients upon completion or withdrawal from the placebo-controlled, double-blind treatment period.

The purpose of the exit interview will be to gain insight and understanding of patients’ experiences with symptoms of CS and to assess relevance and clinical meaningfulness of symptom improvements (eg, reduction in BM frequency).

Fasting (⩾6 hours) blood samples for measurement of 5-HIAA in plasma will be collected and analyzed by a specialty laboratory.

24-hour urine samples will be collected and analyzed for 5-HIAA concentrations.

Overall severity of carcinoid symptoms was measured using 2 methods. Patients were first asked to respond to the following question (Adequate Relief of Symptoms Score): “In the past 7 days, have you had adequate relief of your carcinoid syndrome bowel complaints such as diarrhoea, urgent need to have a bowel movement, abdominal pain, or discomfort?” A “Yes” answer was deemed to indicate a responder and a “No” answer indicated a nonresponder.
Patients were then asked the following question to assess global symptoms associated with CS on an 11-point scale (Global Symptom Score): “Rate the severity of your overall carcinoid symptoms over the past 7 days on a scale from 0-10, where 0 = no symptoms and 10 = worst symptoms ever experienced.”

Sample size

The sample size was calculated using the following assumptions for the primary endpoint. The endpoint was derived per patient and expressed as a rate i.e. change from baseline in the number of BMs/day averaged over the 12 weeks double-blind period. The statistical testing strategy aimed at finding 1 or more telotristat etiprate treatment groups that differed from placebo requiring statistical adjustment for multiple comparisons. The targeted treatment effect size specified under the alternative hypothesis was -1.5 BMs/day and the expected common standard deviation was 1.0 BMs/day. With a type I error of 0.025 for each comparison of telotristat group to placebo (single-step Bonferroni multiple comparison procedure to ensure a family-wise type I error of 0.05), these values resulted in a sample size estimate of 22 patients per group. A 20% dropout rate was assumed for the double-blind period.

A statistical power of the study was set to 96% and reflected a need to assure reliable detection of the effect size of -1.5 BMs/day but also to provide added confidence that a smaller effect size could also be detected. A sample size of 35 patients per group allowed for detection of an effect size as small as -0.563 BMs/day at a 2-sided α=0.025, resulting in a total sample size requirement of 105 patients. It was assumed that dropouts occurred uniformly across groups and that telotristat etiprate patients who dropped out responded in a similar manner to placebo patients.

The sample size of 35 patients per group was used for the subgroup of patients receiving a stable dose of octreotide (US registration requirement). Since randomisation was open to all patients at the investigational sites who qualified for the study regardless of their SSA therapy, randomisation was to be continued until the goal of 105 patients on octreotide was achieved. As such, the total number of patients randomised was not capped and was a random variable.
The study randomised 135 unique patients in total (45 patients per group), in order to meet the smaller sample size requirement of 35 patients by treatment group on stable octreotide therapy.

Randomisation

Centralised randomisation was performed using a SAS-generated randomisation schedule. Patients were enrolled in consecutive order at each study site and assigned a patient number in their order of inclusion in the study. After determination of eligibility patients were assigned via interactive web response system (IWRS).

Randomisation was stratified by baseline u5-HIAA levels categorised as ≤ULN, >ULN, and unknown. Balance in patient assignments groups was ensured using randomly permuted blocks of a fixed size within each of the 3 strata of u5-HIAA.

Blinding (masking)

This was a double blind study. The blinding was to all personnel and patients involved in the trial until extraction of the database except for predefined unblinding procedures. The IWRS was to provide for these unblinding procedures, if needed. Circumstances of a premature unblinding were to be documented in the source records. An independent Data Safety Monitoring Board (DSMB) performed reviews of unblinded interim safety data on a quarterly basis and ad hoc at the discretion of the DSMB or the Sponsor (e.g. in the event of unexpected SAEs).

Statistical methods

Analysis populations

The ITT Population was to include all randomized patients. Patients were to be analysed according to their randomized treatment. The ITT Population was to be used for all analyses of efficacy endpoints.

The PP Population was to include all ITT patients who received study drug and had no major protocol violation that would interfere with the collection or interpretation of the efficacy data during the DBT Period. The PP Population was to be used for a sensitivity analysis of the primary efficacy endpoint.

The Safety Population was to be defined as all patients who received any fraction of a dose of study drug during the study. Patients were to be summarized in the safety analyses based on their actual treatment received on Day 1 of the DBT Period. Patients randomized to receive telotristat etiprate 500 mg tid were to be summarized in that group despite undergoing dose titration during the first study week.

Adjustment for multiplicity

The efficacy endpoints were grouped in primary, secondary, and other endpoints.

A Bonferroni-based method was used to adjust for multiplicity in testing the primary and secondary endpoints. Furthermore, a hierarchical order for testing was applied; i.e., primary and secondary endpoints were analysed in a hierarchical order with a nominal 0.025 level for each of the 2 doses (once

a treatment comparison was not significant at the 0.025 level, formal testing stopped for this dose). The order of testing the secondary endpoints was as follows: 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.

Analyses of all other efficacy endpoints were made in a descriptive manner using statistical tests each with a nominal 2-sided α-level = 0.05.

Analysis of primary and secondary endpoints

The primary and secondary analyses of the efficacy data were limited to the DBT Period. The primary endpoint (change from Baseline in the number of BMs/day averaged over the 12-week DBT Period) was evaluated using blocked 2-sample Wilcoxon rank sum (WRS) statistic (ie, van Elteren test) stratified by the Baseline u5-HIAA levels (≤ULN, >ULN, and Unknown). The Hodges-Lehman (H-L) estimator of location shift with its 97.5% Confidence Limit (CL) was reported for each comparison of telotristat etiprate and placebo. The difference in arithmetic means between treatment groups and the corresponding 95% CLs was also calculated and reported as a descriptive measure of treatment effect. Since the blocked WRS statistics lacked flexibility in modeling the impact of other variables on the test of treatment effect, a supplemental analysis was performed using a generalised linear model (GLM) based on the negative binomial (NB) distribution; the model included the number of BMs/day as the dependent variable and included treatment group and u5-HIAA stratification at randomization as fixed effects, and the Baseline number of BMs as a fixed covariate, and the natural log value of the number of days with nonmissing diary data was used as an offset term to adjust for variable number of days. The relative risk ratio (telotristat etiprate dose group: placebo) of treatment effect was derived from the model along with the 97.5% 2-sided CLs for each contrasted risk ratio.

Secondary efficacy endpoints were evaluated using a blocked WRS statistic and H-L estimators of location shift. Supplemental analyses were performed including a similar model as for primary analysis for cutaneous flushing, and a mixed model with repeated measurements (MMRM) for change from Baseline in u5-HIAA levels and for change from Baseline in abdominal pain.

The "other endpoint" durable response was compared between treatment groups using a logistic regression model with “durable response” (yes/no) coded as the dependent variable including the treatment group and Baseline urinary 5-HIAA levels (≤ULN, >ULN, and Unknown) as fixed effects, and the Baseline number of BMs as a fixed covariate. The odds ratio (telotristat etiprate 250 mg vs. placebo, and telotristat etiprate 500 mg vs. placebo) with its 95% CLs were reported.

Handling of missing data

For the primary analyses (ie, a blocked 2-sample WRS statistics) of the primary and the secondary efficacy endpoints that use the change from Baseline averaged over the 12- week double-blind portion (Treatment Period), the change from Baseline was imputed as zero when a patient has 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). Otherwise the observed data was used and the mean response was based on the number of days with valid, non-missing data.

For variables analyzed weekly, if diary data in any weekly interval was at least 80% complete, the analysis was to use the mean response over that week, deriving the mean of the non-missing data. If <80% of the data are available, the mean response was considered missing for that week. For Baseline, at least 80% of days used to calculate Baseline means must have had no missing data.

While patients were encouraged to continue study-related visits after the decision to withdraw, few patients (n=4) completed additional visits after stopping study drug.

Sensitivity analysis to further assess the robustness of inferences made from the primary analysis:

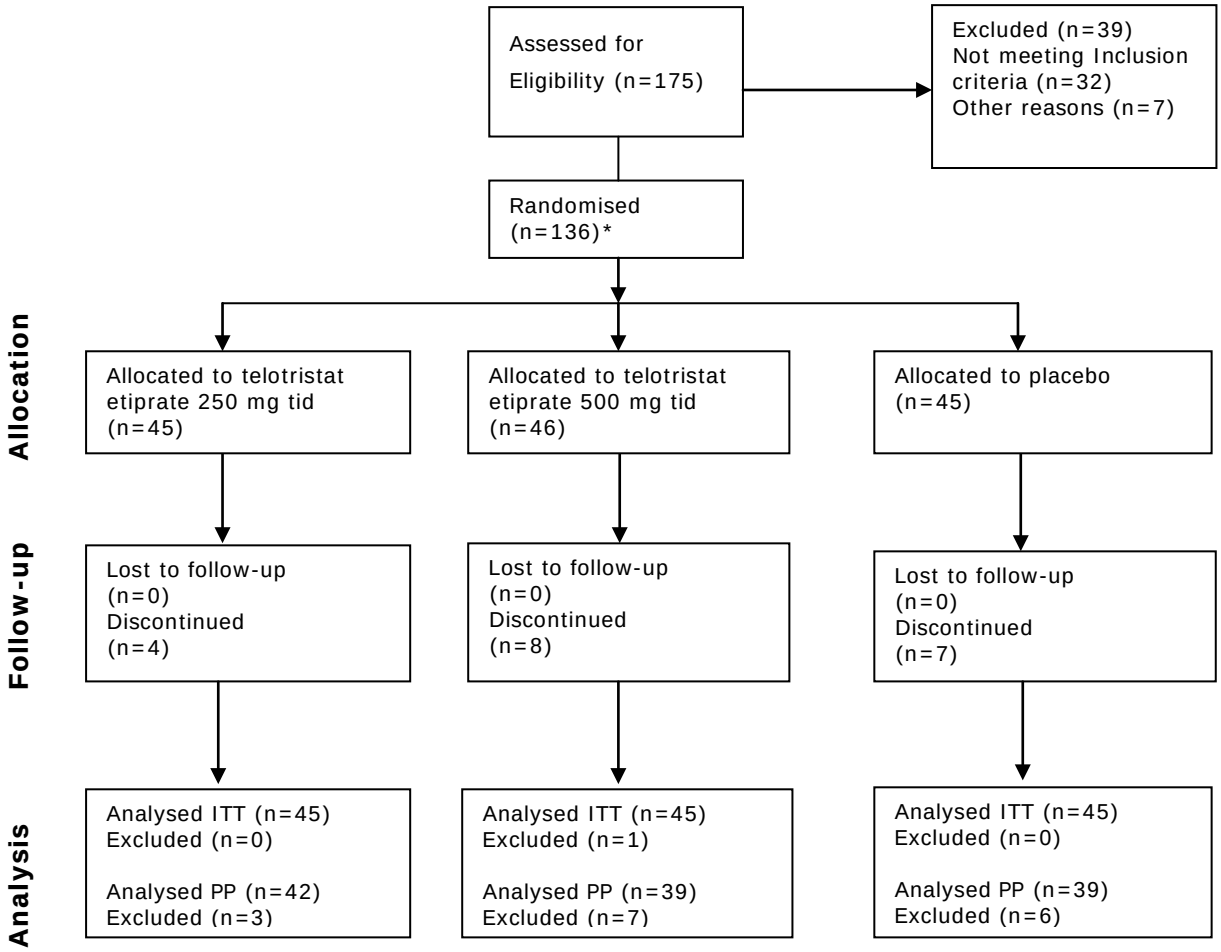
- An analysis assigning the mean baseline score to missing post baseline observations, effectively assigning a change score of 0 to missing post baseline observations
- An analysis including just those patients completing the Double-blind Treatment Period and assigning the mean baseline score to missing post baseline observations, effectively assigning a change score of 0 to missing post baseline observations
- An analysis censoring the observation (number of daily BMs) on the day a rescue short-acting SSA therapy is used and
    - Method 1: assign the mean baseline score to the censored observations.
    - Method 2: assign the highest value recorded for the patient during the Double-blind Treatment Period to the censored observations.

Subgroup analysis

Subgroup analyses were conducted on the primary efficacy endpoint and were exploratory in nature. The following subgroup categories were evaluated: age (<65 and ⩾65 years), sex (male and female), Baseline u5-HIAA levels (⩽ULN, >ULN, and Unknown), and region (North America, Europe, and Rest of the World).

Results

Participant flow



* One patient initially randomly assigned to receive telotristat 500 mg was designated a screen failure because of bruising found during the physical examination. This patient was subsequently rescreened, met all eligibility criteria and was subsequently randomly assigned a second time to telotristat 250 mg. Therefore, this patient was counted as randomized to each of treatment group, but was analysed in the telotristat 250 mg group.

Recruitment

According to the study report the double-blind treatment phase started on 08 January 2013 and the last patient visit for the double-blind period was on 29 May 2015. First data extraction was performed on 07 July 2015, including final data from all patients randomised into the double-blind phase. However, for the provided interim study report data were again extracted on 24 September 2015 including data up to patient visits on 31 July 2015 at the latest in order to ensure that a single dataset extracted on the same date would support all analyses in the interim report including preliminary information from the open-label extension.

Conduct of the study

No interim analyses were performed on the DBT Period efficacy data, and the efficacy data for the primary, secondary, and all other efficacy outcomes. The last patient visit for the DBT Period occurred 29

May 2015 and the data extraction was planned to include, at a minimum, all patient visits in the DBT and OLE Periods which occurred until 31 Jul 2015.

Protocol amendments

Major protocol amendments (main changes) included:

Amendment 1 (01 August 2012): Added 2 exclusion criteria for the purposes of screening patients who may not have had CS-related diarrhea. Specifically, exclusion criteria #15 and #16 were revised to clarify that only clinically significant findings that would compromise patient safety or the outcome of the study were to result in patient exclusion;

Amendment 2 (11 April 2013): Modified the secondary endpoint describing durability and additional endpoints for changes in BM frequency to reflect a 30% change in response of desired criteria. Based on review of new data from completed Phase 2 studies by key opinion leaders in the field, a 30% change in response criteria was considered clinically relevant.

Amendment 3 (06 September 2013): Revised the wording of the primary endpoint to correctly reflect that the planned analysis was to evaluate individual treatment groups versus placebo for a reduction of BMs from an initial Baseline value; Secondary endpoints were revised to align with the clinical importance of additional pathological and physical manifestations of CS. The other efficacy objectives were adjusted to accommodate changes to the planned analysis. Replaced the term "refractory" with the term "not adequately controlled" for the patient population expected to participate. Although early signs of tachyphylaxis were exhibited in the planned

patient population, patients who were eligible to participate in this study may have experienced some benefit from their background somatostatin analog therapy and, thus, were no longer adequately controlled. Allowed patients who had undergone tumor-directed therapies and experienced little or no reduction in BMs to participate. Clarified sample size calculations and statistical testing.

Amendment 5 (20 January 2015): Modified the exclusion criterion to remove the corrected QT interval using Fridericia's formula (QTcF) limitation of 450 msec.

Protocol Deviations

Double-blind Treatment Period

Significant protocol deviations during the DBT Period occurred in 17 patients (12.6%) in the Safety Population. 4 patients (8.9%) in the telotristat etiprate 250 mg group, 6 patients (13.3%) in the telotristat etiprate 500 mg group, and 7 patients (15.6%) in the placebo group. Sixteen of the significant deviations involved study drug; of these, all but 2 were related to study drug compliance <75% during the DBT Period. Ten patients had 11 major protocol deviations during the OLE Period; deviations included study drug (5), missing assessments (4), and safety reporting (2).

Baseline data

Double-blind treatment phase

Demographics and baseline characteristics for patients in the double blind treatment phase are shown in Table 31. Disease characteristics at baseline on symptoms and conditions associated with Carcinoid Syndrome (Intent-to-Treat Population) is shown in Table 32.

Table 31: Demographics and Baseline Characteristics (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

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)

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).

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

Table 32: Baseline Data for Symptoms and Conditions Associated with Carcinoid Syndrome (Intent-to-Treat Population)

Characteristic	Statistic	Placebo N=45	LX1606 250 mg N=45	LX1606 500 mg N=45
u5-HIAA (mg/24 hours)	n	44	**42**	44
	Mean (SD)	80.968 (161.0143)	92.645 (114.8958)	89.502 (144.4695)
	Median	26.100	67.000	28.250
	Min, Max	000, 786.20	2.20, 637.80	0.00, 608.00
BMs (count/day)	n	45	45	45
	Mean (SD)	5.200 (1.3500)	6.085 (2.0703)	5.805 (1.9624)
	Median	5.059	5.485	5.393
	Min, Max	3.50, 9.00	3.52, 12.97	3.61, 12.46
Flushing (count/day)	n	45	45	45
	Mean (SD)	1.791 (1.9344)	2.788 (3.7362)	2.712 (3.3608)
	Median	1.207	1.467	1.643
	Min, Max	0.00, 7.43	0.00, 19.29	0.00, 19.42
Abdominal pain (weekly)	n	45	45	45
	Mean (SD)	2.473 (2.3201)	2.615 (2.2657)	2.633 (2.1779)
	Median	1.385	2.000	2.643
	Min, Max	0.00, 8.04	0.00, 7.83	0.00, 7.83
Nausea (weekly)	n	45	45	45
	Mean (SD)	0.447 (0.5910)	0.664 (0.6168)	0.725 (0.6687)
	Median	0.143	0.552	0.500
	Min, Max	0.00, 2.43	0.00, 2.13	0.00, 2.14
Stool consistency (weekly)	n	45	45	45
	Mean (SD)	5.917 (0.6993)	5.934 (0.5031)	5.970 (0.6886)
	Median	6.000	6.034	6.095
	Min, Max	3.83, 6.95	4.32, 6.91	4.00, 7.00

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation; u5-HIAA = urinary 5-hydroxyindoleacetic acid

As regards to the medical history, the most frequent conditions reported were in the System Organ Class (SOC) GI disorders (98.5% of patients), specifically diarrhoea and abdominal pain (91.1% and 41.5%, respectively).

CS was reported by 44.4% of patients overall, 48.9% on telotristat etiprate 250 mg, 53.3% on 500 mg, and 31.1% on placebo. The most frequently reported symptoms related to CS were diarrhoea, flushing, various types of abdominal pain, fatigue, and nausea. Neoplasms were reported for >95% of patients and had generally similar proportions across groups, except for metastases to the lymph nodes, which were higher in the telotristat etiprate 250 mg tid group. A history of psychiatric disorders was reported by 41.5% of patients overall.

Table 33: History of Individual Conditions Related to Carcinoid Syndrome in >10% of Patients Overall at Baseline (Safety Population)

System Organ Class Preferred Term	Placebo N=45 n (%)	LX1606 250 mg N=45 n (%)	LX1606 500 mg N=45 n (%)
Gastrointestinal disorders	42 (93.3)	42 (93.3)	45 (100)
Diarrhoea[a]	40 (88.9)	40 (88.9)	44 (97.8)
Abdominal pain[b]	11 (24.4)	16 (35.6)	14 (31.1)
Nausea	1 (2.2)	5 (11.1)	7 (15.6)
Vascular disorders	30 (66.7)	23 (51.1)	29 (64.4)
Flushing[c]	30 (66.7)	22 (48.9)	29 (64.4)
General disorders and administration site conditions	6 (13.3)	13 (28.9)	15 (33.3)
Fatigue	3 (6.7)	6 (13.3)	9 (20.0)

Source: Listing 16.2.4.3

[a] Includes preferred terms of diarrhoea and frequent BMs, where the same patient reported more than 1 preferred term only the first indication was counted

[b] Includes preferred terms of abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort, where the same patient reported more than 1 preferred term only the first indication was counted

[c] Includes preferred terms of flushing and hot flush, where the same patient reported more than 1 preferred term only the first indication was counted

Note: Medical history was coded using MedDRA Version 15.1. Patients were counted once at each system organ class and preferred term level regardless of the number of medical history entries within that system organ class and preferred term.

Abbreviations: LX1606 = telotristat etiprate; MedDRA = Medical Dictionary for Regulatory Activities

Table 34: History of neoplasms in >10% of patients overall (safety population)

System Organ Class Preferred Term	Placebo N=45 n (%)	LX1606 250 mg N=45 n (%)	LX1606 500 mg N=45 n (%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	43 (95.6)	45 (100)	44 (97.8)
Metastases to liver	24 (53.3)	20 (44.4)	23 (51.1)
Carcinoid tumour	19 (42.2)	16 (35.6)	16 (35.6)
Neuroendocrine tumour	17 (37.8)	16 (35.6)	15 (33.3)
Metastases to lymph nodes	7 (15.6)	14 (31.1)	6 (13.3)
Metastatic carcinoid tumour	6 (13.3)	6 (13.3)	8 (17.8)
Metastases to bone	4 (8.9)	8 (17.8)	6 (13.3)

Source: Table 14.1.3 and Listing 16.2.4.3

Note: Medical history was coded using MedDRA Version 15.1. Patients were counted once at each system organ class and preferred term level regardless of the number of medical history entries within that system organ class and preferred term.

Abbreviations: LX1606 = telotristat etiprate; MedDRA = Medical Dictionary for Regulatory Activities

All patients (100%) received at least 1 concomitant medication during the study (see Table 35).

Table 35: Concomitant medication taken by >10% of patients overall during the double-blind treatment period, by ATC level 2 and preferred term (safety population)

ATC Level 2 Code Preferred Term	Placebo N=45 n (%)	LX1606 250 mg N=45 n (%)	LX1606 500 mg N=45 n (%)
Analgesics	19 (42.2)	27 (60.0)	29 (64.4)
Paracetamol	11 (24.4)	11 (24.4)	12 (26.7)
Antianemic preparations	10 (22.2)	11 (24.4)	13 (28.9)
Cyanocobalamin	7 (15.6)	9 (20.0)	7 (15.6)
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	15 (33.3)	23 (51.1)	24 (53.3)
Loperamide	9 (20.0)	7 (15.6)	12 (26.7)
Loperamide hydrochloride	6 (13.3)	11 (24.4)	7 (15.6)
Antithrombotic agents	12 (26.7)	10 (22.2)	11 (24.4)
Acetylsalicylic acid	7 (15.6)	3 (6.7)	8 (17.8)
Digestives, including enzymes	16 (35.6)	19 (42.2)	16 (35.6)
Pancreatin	14 (31.1)	16 (35.6)	12 (26.7)
Drugs for acid related disorders	13 (28.9)	19 (42.2)	27 (60.0)
Omeprazole	5 (11.1)	10 (22.2)	13 (28.9)
Mineral supplements	16 (35.6)	11 (24.4)	17 (37.8)
Potassium chloride	6 (13.3)	6 (13.3)	7 (15.6)
Calcium carbonate w/vitamins NOS	4 (8.9)	6 (13.3)	7 (15.6)
Pituitary and hypothalamic hormones and analogues	45 (100)	45 (100)	45 (100)
Octreotide acetate	30 (66.7)	35 (77.8)	24 (53.3)
Octreotide	6 (13.3)	9 (20.0)	14 (31.1)
Lanreotide	9 (20.0)	4 (8.9)	6 (13.3)
Lanreotide acetate	6 (13.3)	1 (2.2)	7 (15.6)
Vitamins	17 (37.8)	15 (33.3)	18 (40.0)
Colecalciferol	7 (15.6)	5 (11.1)	9 (20.0)

Source: Table 14.1.7.1 and Listing 16.2.4.4
In the DB Period, concomitant medications were defined as medications that were taken on or after the first dose date of double-blind study medication.
Abbreviations: ATC = Anatomical Therapeutic Chemical; LX1606 = telotristat etiprate; NOS = not otherwise specified

All 135 patients in the safety population reported ongoing SSA usage at the time of study entry (octreotide n=103, 76.3%; lanreotide n=32, 23.7%). Since investigators have used octreotide and octreotide acetate interchangeably in the reporting of concomitant medications, it is not possible to differentiate between long-acting release and short-acting formulations. Lanreotide and lanreotide acetate are also used interchangeably, but both refer to depot/autogel formulations. The following table summarises SSAs by name and dosage / formulation at baseline.

Table 36: Concomitant SSA Therapy by Dose Taken by All Patients at Baseline (Safety Population)

SSA Therapy Dosage	Placebo N=45 n (%)	LX1606 250 mg N=45 n (%)	LX1606 500 mg N=45 n (%)
Octreotide	30 (66.7)	40 (88.9)	33 (73.3)
20 mg	0 (0.0)	0 (0.0)	3 (6.7)
30 mg	23 (51.1)	33 (73.3)	24 (53.3)
40 mg	2 (4.4)	3 (6.7)	4 (8.9)
60 mg	3 (6.7)	2 (4.4)	1 (2.2)
90 mg	0 (0.0)	1 (2.2)	0 (0.0)
Octreotide pump	2 (4.4)	1 (2.2)	1 (2.2)
Lanreotide	15 (33.3)	5 (11.1)	12 (26.7)
90 mg	0 (0.0)	0 (0.0)	3 (6.7)
120 mg	15 (33.3)	5 (11.1)	9 (20.0)

A total of 32 patients (23.7%) reported ≥1 concomitant medication to treat depression, anxiety, or insomnia prior to the first dose of study drug (14 telotristat etiprate 250 mg, 9 telotristat etiprate 500 mg, 9 placebo). Of the 25 patients with a medical history of depression, 8 of 10 (80.0%) on telotristat etiprate 250 mg, 5 of 9 (56%) on 500 mg, and 2 of 6 (33%) on placebo received treatment for depression at study entry.

Table 37: Concomitant therapy indicated for depression, anxiety or insomnia at Baseline (safety population)

Indication[a] ATC Level 3 Code[a,b]	Placebo N=45 n (%)	LX1606 250 mg N=45 n (%)	LX1606 500 mg N=45 n (%)
Total patients receiving treatment	9 (20.0)	14 (31.1)	9 (20.0)
Depression	2 (4.4)	8 (17.8)	5 (11.1)
Antidepressants	2 (4.4)	8 (17.8)	5 (11.1)
Antipsychotics	0 (0.0)	1 (2.2)	1 (2.2)
Anxiety	3 (6.7)	6 (13.3)	3 (6.7)
Antidepressants	1 (2.2)	3 (6.7)	1 (2.2)
Antipsychotics	1 (2.2)	0 (0.0)	0 (0.0)
Anxiolytics	2 (4.4)	3 (6.7)	2 (4.4)
Insomnia	6 (13.3)	1 (2.2)	4 (8.9)
Antidepressants	0 (0.0)	0 (0.0)	1 (2.2)
Antiepileptics	0 (0.0)	1 (2.2)	0 (0.0)
Anxiolytics	2 (4.4)	0 (0.0)	1 (2.2)
Hypnotics and Sedatives	4 (8.9)	0 (0.0)	2 (4.4)

Source: Listing 16.2.4.4

[a] Where the same concomitant medication was reported for more than 1 indication in the same patient only the first indication was counted.

[b] Patients receiving multiple concomitant medications for the same indication are counted 1 time for each medication

Abbreviations: LX1606 = telotristat etiprate

Numbers analysed

Overall, 15 patients were excluded from the PP population due to significant protocol deviations.

Table 38: Analysis Populations for the Double-blind Treatment Period (All Enrolled Patients)

Analysis Populations Double-blind Treatment Period	Placebo n (%)	LX1606 250 mg n (%)	LX1606 500 mg n (%)	Total[a] n (%)
Randomized[b]	45	45	46	136
Safety Population	45 (100.0)	45 (100.0)	45 (97.8)	135 (99.3)
Intent-to-treat Population	45 (100.0)	45 (100.0)	45 (97.8)	135 (99.3)
Per-protocol Population	39 (86.7)	42 (93.3)	39 (84.8)	120 (88.2)

a Total=placebo, LX1606 250 mg, and LX1606 500 mg.

b Percentages are based on the number of patients randomized.

Abbreviation: LX1606 = telotristat etiprate

Outcomes and estimation

Primary endpoint

The mean numbers of BMs/day averaged over the baseline period were 6.085, 5.805, and 5.200 for telotristat etiprate 250 mg, 500 mg, and placebo, respectively. The observed reductions from baseline in BMs/day for telotristat etiprate 250 mg and 500 mg were statistically significant compared to placebo ($p<0.001$ each). The estimate of treatment difference telotristat etiprate minus placebo (Hodges-Lehmann) was -0.813 (97.5% CI: -1.256, -0.290) for telotristat etiprate 250 mg and -0.689 (97.5% CI: -1.170, -0.223) for 500 mg. A supplemental analysis of the primary efficacy endpoint used a generalised linear model (GLM) based on the negative binomial (NB) probability process. This analysis adjusted for baseline variables with u5-HIAA stratification as fixed effect and number of BMs as fixed covariate. A summary of the results are shown in Table 39.

Table 39: Analysis of Bowel Movements (counts/day) During Double-blind Treatment Period (ITT Population)

	Statistic	Placebo N=45	LX1606 250 mg N=45	LX1606 500 mg N=45
Average number of BMs at Baseline	Mean (SD)	5.200 (1.3500)	6.085 (2.0703)	5.805 (1.9624)
	Median	5.059	5.485	5.393
	Min, Max	3.50, 9.00	3.52, 12.97	3.61, 12.46
Change from Baseline in the number of BMs averaged over the DBT Period	Mean (SD)	-0.623 (0.8275)	-1.434 (1.3646)	-1.455 (1.3098)
	Median	-0.614	-1.338	-1.209
	Min, Max	-2.65, 0.80	-6.06, 1.63	-6.66, 0.58
	Differences in arithmetic means (LX1606-placebo)	---	-0.811	-0.833
	95% CL	---	-1.284, -0.338	-1.292, -0.374
Primary analysis[a]	Hodges-Lehmann estimator of treatment difference (LX1606-placebo)	---	-0.813	-0.689
	97.5% CL	---	-1.256, -0.290	-1.170, -0.223
	p-value	---	**<0.001**	**<0.001**
Supplemental analysis[b]	Adjusted rate (counts/day)	4.656	4.097	4.006
	95% CL	4.308, 5.033	3.794, 4.423	3.709, 4.326
	Rate ratio (LX1606:placebo)	---	0.880	0.860
	97.5% CL for rate ratio	---	0.781, 0.991	0.764, 0.969
	p-value	---	**0.016**	**0.005**

The baseline value was defined as the mean of the responses recorded during the Run-in Period prior to the first dose of study drug.

a The primary analysis used a blocked 2-sample WRS statistic (ie, van Elteren test) stratified by the u5-HIAA levels at randomization.

b The supplemental analysis used a generalized linear model based on the NB distribution. The model included the number of BMs/day as the dependent variable and included treatment group and u5-HIAA stratification at randomization as fixed effects, and the baseline number of BMs as a fixed covariate. The natural log value of the number of days with nonmissing diary data were used as an offset term to adjust for variable number of days.

Abbreviations: BMs = bowel movements; CL = confidence limit; DBT = Double-blind Treatment; ITT = intent-to-treat; LX1606 = telotristat etiprate; Max = maximum; Min = minimum; NB = negative binomial; u5-HIAA = urinary 5-hydroxyindoleacetic acid

Interpretation of difference in arithmetic means is possible only on population level but difficult at an individual patient level when data do not have a normal distribution. In addition, the difference in arithmetic means is neither adjusted for the covariate used for stratification factor (u5-HIAA level) nor for baseline value. Therefore, a post-hoc ANCOVA analysis adjusting for baseline value was provided upon request during the review. The difference in arithmetic means was calculated based on an ANCOVA with adjustment for baseline and stratification factor. The difference between telotristat 250 mg versus placebo and telotristat 500 mg versus placebo are -0.609 (97.5% CI: -1.159, -0.059) and -0.695 (97.5% CI: -1.239, -0.150), respectively. The result of this analysis is the one provided in the SmPC accompanied by 97.5% CIs (see SmPC section 5.1).

Change and Percent Change From Baseline in Bowel Movement Frequency Averaged at Each Study Week During the Double-blind Treatment Period

In the 12-week DBT period of the study, average weekly reductions in BM frequency on telotristat were observed as early as 3 weeks, with the greatest reductions occurring during the last 6 weeks of the DBT period, compared with placebo (refer to Figure 15).

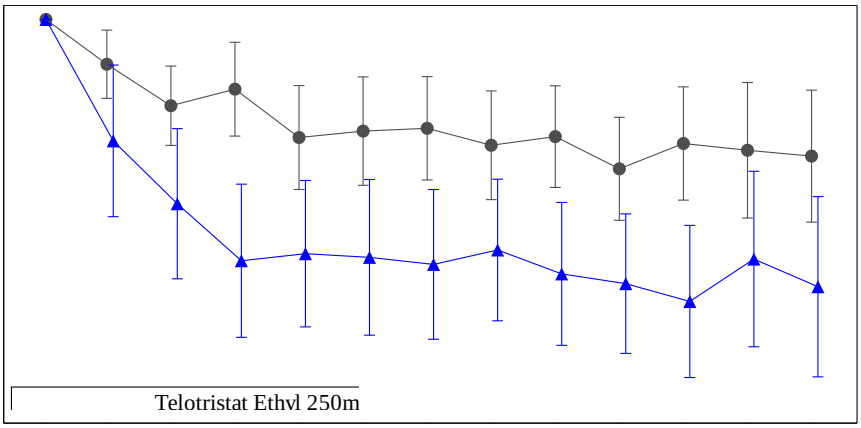


Figure 15: Mean change from baseline in BMs by study week during the DBT period, Intent-to-Treat Population

The proportions of patients reporting reductions from baseline in daily BM frequency (averaged over 12 weeks) were:

- Patients with a mean reduction of at least 1 BM per day: 66.7% (telotristat ethyl 250 mg) and 31.1% of patients (placebo);
- Patients with a mean reduction of at least 1.5 BM per day: 46.7% (telotristat ethyl 250 mg) and 20.0% of patients (placebo);
- Patients with a mean reduction of at least 2 BM per day: 33.3% (telotristat ethyl 250 mg) and 4.4% of patients (placebo).
-

Secondary endpoints

Change from Baseline in Urinary 5-HIAA Levels at Week 12 During the Double-blind Treatment Period (ITT Population)

Mean baseline u5-HIAA levels were 80.968, 92.645, and 89.502 mg/24 h for placebo, telotristat etiprate 250 mg, and 500 mg groups, respectively. At week 12 reductions of u5-HIAA levels from baseline were statistically significant for both telotristat etiprate groups compared to placebo. A summary of the analyses are presented in Table 40.

Table 40: Analysis of Urinary 5-HIAA Levels (mg/24 hours) at Week 12 during the Double-blind Treatment Period (ITT Population)

	Statistic	Placebo N=45	LX1606 250 mg N=45	LX1606 500 mg N=45
Baseline u5-HIAA levels (mg/24 hours)	n	44	42	44
	Mean (SD)	80.968 (161.0143)	92.645 (114.8958)	89.502 (144.4695)
	Median	26.100	67.000	28.250
	Min, Max	0.00, 786.20	2.20, 637.80	0.00, 608.00
Change from Baseline in u5-HIAA levels (mg/24 hours) at Week 12	n	29	32	31
	Mean (SD)	11.466 (35.6489)	-40.134 (84.7663)	-57.729 (82.1749)
	Median	1.400	-21.650	-19.000
	Min, Max	-35.80, 155.00	-458.60, 77.20	-301.00, 1.00
	Difference in arithmetic means (LX1606-placebo)	---	-51.600	-69.195
	95% CL	---	-85.547, -17.653	-102.332, -36.057
Primary analysis[a]	Hodges-Lehmann estimator of treatment difference (LX1606-placebo)	---	-30.100	-33.800
	97.5% CL	---	-56.000, -8.100	-66.200, -14.600
	p-value	---	**<0.001**	**<0.001**
Supplemental analysis[b]	Least squares mean	4.053	-33.811	-47.105
	95% CL	-24.444, 32.551	-61.558, -6.065	-75.394, -18.816
	Least squares mean difference	---	-37.865	-51.159
	97.5% CL	---	-79.279, 3.550	-92.953, -9.365
	p-value	---	**0.040**	**0.006**

The baseline value was defined as the last nonmissing assessment prior to the first dose of study drug.

a The primary analysis used a blocked 2-sample WRS statistic (ie, van Elteren test) stratified by the u5-HIAA levels at randomization.

b The supplemental analysis used a mixed model with repeated measurements (MMRM). The model used the change from baseline in u5-HIAA levels as the dependent variable, and included treatment group, u5-HIAA stratification at randomization, time (week 12) treatment-by time interaction as fixed effects, and patient as a random effect. An unstructured (general) covariance matrix was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom.

Abbreviations: CL = confidence limit; DBT = Double-blind Treatment; LX1606 = telotristat etiprate; ITT = intent-to-treat; Max = maximum; Min = minimum; SD = standard deviation; u 5-HIAA = urinary 5-hydroxyindoleacetic acid; WRS = Wilcoxon rank sum

Change from Baseline in Number of Cutaneous Flushing Episodes Averaged Across all Time Points during the Double-blind Treatment Period (ITT Population)

Mean baseline values for cutaneous flushing averaged over the run-in period (counts/day) were 2.788, 2.712, and 1.791, for telotristat etiprate 250 mg, 500 mg, and placebo, respectively. Neither telotristat etiprate 205 mg or 500 mg showed statistically significant differences in cutaneous flushing versus placebo at an α-level of 0.025.

The estimate (Hodges-Lehmann) of the treatment difference of telotristat etiprate minus placebo was 0.036 counts/day (97.5% CI: -0.230, 0.330) for telotristat etiprate 250 mg (p=0.39) and 0.000 (97.5% CL: -0.345, 0.209) for 500 mg (p=0.84). The point estimates of the rate ratios from the GLM were 0.923 for telotristat etiprate 250 mg (p=0.74) and 1.105 for 500 mg (p=0.69) versus placebo.

Change from Baseline in Abdominal Pain Averaged Across all Time Points During the Double-blind Treatment Period

Mean baseline values for abdominal pain scores averaged over the run-in period were 2.615, 2.633, and 2.473 for telotristat etiprate 250 mg, 500 mg, and placebo groups, respectively. Neither telotristat etiprate 250 mg nor 500 mg comparisons versus placebo were statistically significant at an α-level of 0.025.

The H-L estimate (Hodges-Lehmann) of the treatment difference of telotristat etiprate minus placebo was -0.167 (97.5% CI: -0.541, 0.224) for telotristat etiprate 250 mg (p=0.28) and -0.047 (97.5% CI: -0.462, 0.333) for 500 mg (p=0.87). The point estimates of the differences in LS means versus placebo were -0.283 for telotristat etiprate 250 mg (p=0.24) and -0.105 for 500 mg (p=0.66).

Ancillary analyses

Double-blind treatment phase

Subset of Patients on a Stable Dose of Octreotide as SSA Therapy (Analysis)

Concerning the number of bowel movements per day results for patients on a stable dose of octreotide as SSA therapy were similar to those of the overall population. There were 40 on telotristat etiprate 250 mg, 33 on 500 mg, and 30 patients on placebo in this subpopulation. Point estimates (Hodges-Lehmann) of the change from baseline versus placebo were -0.830 BMs/day (97.5% CI: -1.386, -0.241) for telotristat etiprate 250 mg and -0.662 BMs/day (97.5% CI: -1.206, -0.150) for 500 mg. Sensitivity analyses were similar with this finding.

Likewise, reductions in u5-HIAA at week 12 in this subpopulation were comparable to effects seen in the overall population and there were no effects of telotristat etiprate on cutaneous flushing episodes or abdominal pain.

Bowel Movement Frequency by Week

The applicant has also performed an analysis of changes from baseline in average BM frequency calculated for each study week. By week 3 compared to placebo telotristat etiprate 250 mg and 500 mg showed mean reductions of approximately 1 BM/day (p<0.001) with a slight further increase in mean reductions thereafter. At most timepoints reductions were comparable between telotristat etiprate 250 mg and 500 mg groups. At week 12, the 500 mg group had numerically the greatest reduction in BM frequency with a mean change from baseline of 2.1 BM/day; however, results also fluctuated across the treatment period in both telotristat etiprate groups beyond week 3. At week 12, mean percent reductions in BM/day were 27.5%, 34.3%, and 18.5% for telotristat etiprate 205 mg, 500 mg, and placebo treatment, respectively.

Bowel Movement Frequency Durable Response

Proportion of Responders with ≥30% reduction in number of BMs/day for ⩾50% of time, Proportion of Days with ⩾30% Reduction from Baseline or ⩾1.5 BM Reduction from Baseline, and Proportion of Days with a ≥1.5 reduction in BMs Observed per Patient

As a measure of the durability of BM changes over the 12 weeks double-blind phase of the trial “durable response” was defined as a ≥30% reduction in number of BMs/day for ≥50% of time. The results of the analyses are presented in Table 41.

Table 41: Proportion of Patients With Durable Response During the Double-blind Treatment Period (ITT Population)

	Statistic	Placebo N=45	LX1606 250 mg N=45	LX1606 500 mg N=45
Proportion of patients with durable response	Number of patients assessed	45	45	45
	Responder, n (%)	9 (20.0)	20 (44.4)	19 (42.2)
	Nonresponder, n (%)	36 (80.0)	25 (55.6)	26 (57.8)
Primary analysis[a]	Odds ratio (LX1606/placebo)	---	3.49	3.11
	95.0% CL	---	1.33, 9.16	1.20, 8.10
	p-value	---	**0.011**	**0.020**
Supplemental analysis	95% CL of responder rate[b]	0.07, 0.33	0.29, 0.60	0.27, 0.58
	Treatment difference in responder rate	---	0.24	0.22
	95.0% CL	---	0.04, 0.45	0.01, 0.43
	p-value[c]	---	**0.024**	**0.040**

Patients with durable response were the responders with ⩾30% reduction in number of BMs/day for ≥50% of time over theDBT Period. The percentage was calculated based on the number of patients assessed.

a The primary analysis used a logistic regression model with responder as the dependent variable, treatment group and u5-HIAA stratification at randomization as fixed effects, and baseline mean number of BMs (counts/day) as a covariate.

b 95% CLs were calculated based on normal, approximation using a correction for continuity.

c P-value was calculated based on continuity-adjusted chi-square test.

Abbreviations: BM = bowel movement; CL = confidence limit; DBT = Double-blind Treatment; LX1606 = telotristat etiprate; ITT = intent-to-treat; u5-HIAA = urinary5-hydroxyindoleacetic acid

When the full effect of telotristat is observed (during the last 6 weeks of the DBT period) the proportion of responders with at least 30% BM reduction was 51% (23/45) in the 250 mg group versus 22% (10/45) in the placebo group (*post-hoc* analysis).
Also the proportion of days with ≥30% reduction in the number of BMs/day from baseline was analysed as additional measure of response durability. The mean proportions of days with ≥30% reductions in BMs were 0.441 (n=45) and 0.440 (n=45) for telotristat etiprate 250 mg and 500 mg, respectively, compared to 0.282 (n=45) for placebo. The estimates of the treatment differences (Hodges-Lehmann) for telotristat etiprate versus placebo were 0.184 (95.0 % CI: 0.055, 0.298) and 0.167 (95.0% CI: 0.039, 0.296) for 250 mg and 500 mg, respectively (p≤0.019).

In addition the mean proportion of days during which a reduction in BMs ≥1.5 BM/day was observed for each patient was analysed. The mean proportions of days with a reduction ≥1.5 BM/day were 0.498 (n=45) and 0.451 (n=45) for telotristat etiprate 250 mg and 500 mg, respectively, compared to 0.317 (n=45) for placebo. The H-L estimate of the treatment differences (Hodges-Lehmann) for telotristat etiprate versus placebo were 0.202 and 0.132, respectively (p≤0.022).

Time to First Occurrence of Sustained ≥30% Reduction in BM Frequency from Baseline and Time to First Occurrence of ⩾30% worsening in BM Frequency from Baseline

The time to first sustained ≥30% reduction in BM frequency was defined as time from the first double-blind dose date to the first day of 2 consecutive weeks with BM frequency ≤30% of the individual baseline mean. Median times were 19 days (n=45) and 27 days (n=45) for telotristat etiprate 250 mg and 500 mg, respectively. The median time could not be estimated for the placebo group because less than

half of the patients (19/45=42.2%) achieved sustained ≥30% improvement. A test of the HRs indicated statistically significant differences in time to event between each telotristat etiprate treatment group and placebo (p≤0.004) with HRs of 2.29 and 2.15 for telotristat etiprate 250 mg and 500 mg, respectively.

Urgency to Defecate

The mean proportions of days with urgency to defecate were 0.664, 0.603, and 0.753 for telotristat etiprate 250 mg (n=45), 500 mg (n=45), and placebo (n=45), respectively. Differences were statistically significant for telotristat etiprate 500 mg versus placebo (H-L estimate -0.129; p=0.006), but not 250 mg (H-L estimate -0.024; p=0.35). In a supplemental analyses using a generalised linear mixed model fitted to a binomial distribution results were statistically significant for both telotristat etiprate groups versus placebo (p<0.001).

Stool Consistency

The mean changes from baseline in stool consistency averaged across all time points using the Bristol Stool Form Scale were -0.264 (n=45), -0.361 (n=45), and -0.216 (n=45) for telotristat etiprate 250 mg, 500 mg, and placebo groups, respectively. Differences between telotristat etiprate groups and placebo were not statistically significant; there was a trend towards greater reductions in stool form scores in patients on telotristat etiprate 500 mg compared to placebo.

Urinary 5-HIAA Percentage Change from Baseline and Plasma 5-HIAA

Changes in urinary and plasma 5-HIAA levels were also calculated and analysed as percentage changes at week 6 and 12.

Urinary 5-HIAA showed a statistically significant reduction versus placebo in both telotristat etiprate groups at week 6 (WRS statistic p<0.001 both groups; MMRM p=0.004 for 250 mg, p<0.001 for 500 mg) and week 12 (WRS statistic and MMRM p<0.001 both groups).

The mean changes from baseline in plasma levels of 5-HIAA averaged across all time points were -59.129 ng/mL (n=44), -133.921 ng/mL (n=41), and 58.794 ng/mL (n=40) for telotristat etiprate 250 mg, 500 mg, and placebo, respectively, in the ITT population. The treatment difference versus placebo was statistically significant for both groups [H-L estimator 250 mg -63.523 ng/mL (95% CI: -116.425, -35.440); p<0.001; 500 mg -92.138 ng/mL (95% CI: -128.550, -56.550; p<0.001)]. Using MMRM results were only statistically significant for telotristat etiprate 500 mg (p=0.022) but not 250 mg (p=0.15).

Cutaneous Flushing

Patients experiencing ≥2 flushing episodes per day at baseline were analysed separately for changes in flushing. In this subgroup, mean changes from baseline in the number of cutaneous flushing episodes averaged across all time points were -0.823 (n=20), -1.345 (n=19), and -0.399 (n=13) for telotristat etiprate 250 mg, 500 mg, and placebo, respectively. Differences between telotristat etiprate and placebo did not reach statistical significance.

Abdominal Pain

Patients with a mean baseline level of abdominal pain scores ≥3 were analysed separately for changes in abdominal pain. In this subgroup, mean changes from baseline in abdominal pain scores averaged across all time points were -1.232 (n=17), -0.991 (n=18) and -0.832 (n=17) for telotristat etiprate 250 mg, 500 mg, and placebo respectively. Differences between telotristat etiprate and placebo were not statistically significant.

Subjective Measures of Carcinoid Symptoms

The proportions of patients reporting adequate relief of carcinoid symptoms (responders) in the ITT population at baseline were 15.6% (n=45), 15.6% (n=45), and 22.7% (n=44) for telotristat etiprate 250 mg, 500 mg, and placebo, respectively. Generally no statistically significant treatment differences were observed. The mean proportion of weeks during the 12 weeks double-blind period in which patients reported adequate relief of CS symptoms associated with GI symptoms was 0.388, 0.385, and 0.263 for the telotristat etiprate 250 mg, 500 mg, and placebo, respectively (n=45 per group). Differences were not statistically significant.

Since baseline global assessment was not collected mean changes from day 6 in the subjective global assessment of CS symptom relief (11-point numeric scale) for patients who responded "No" on day 6 for adequate relief was averaged across all time points in the ITT population. Changes from day 6 were -0.723 (n=30), -1.419 (n=24), and -0.591 (n=29) for telotristat etiprate 250 mg, 500 mg, and placebo, respectively. Differences were not statistically significant. The proportions of patients who had a ≥3-point reduction in subjective global symptom assessment scores from day 6 were 4/31 (12.9%), 7/27 (25.9%), and 5/30 (16.7%) for patients on telotristat etiprate 250 mg, 500 mg, and placebo, respectively. Differences were not statistically significant.

Analysis of Nausea

The mean proportions of days with reports of nausea during the double-blind period were 0.365, 0.452, and 0.324 for telotristat etiprate 250 mg, 500 mg, and placebo, respectively in the ITT population(n=45 each). The mean proportion of days that patients reported nausea was numerically greater for patients on telotristat etiprate compared to placebo and particularly in the 500 mg group.

Rescue Short-Acting SSA

The mean usage of rescue short-acting SSA at baseline (injections counts/day) was comparable across groups (0.450 injections/day telotristat etiprate 250 mg; 0.505 injections/day 500 mg; 0.470 injections/day placebo) (Figure 16).

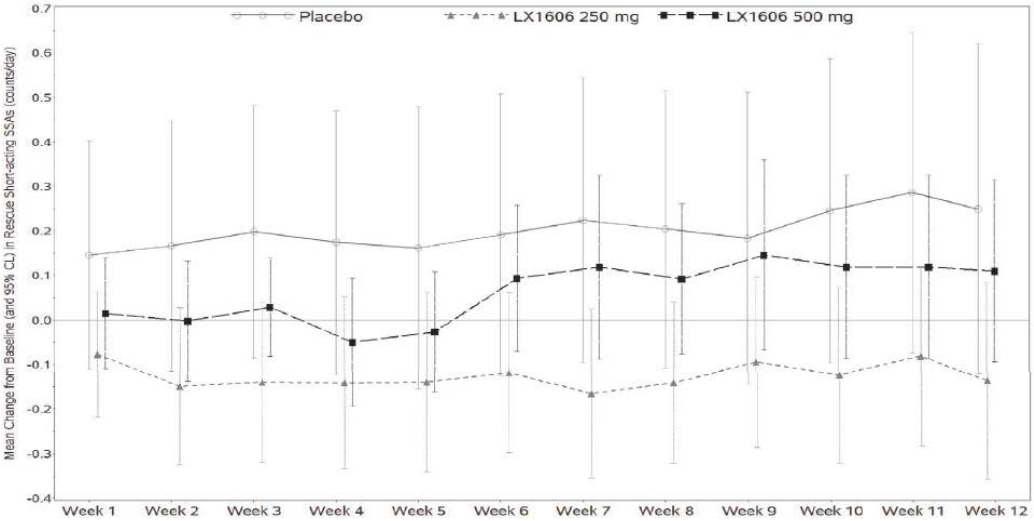


Figure 16: Mean Change from Baseline in the Daily Frequency of Daily Rescue Short-acting Somatostatin Analogue (SSA) (counts/day) Averaged at Each Week During the Double-blind Treatment Period (ITT Population)

Note: Figure plots arithmetic mean and 95% CI based on normal approximation of change from baseline in frequency of rescue short-acting SSA (counts/day) averaged at each week during double-blind period by group

A *post-hoc* analysis showed that the average number of daily short-acting SSA injections used for rescue therapy over the 12-week DBT period was 0.3 and 0.7 in the telotristat ethyl 250 mg and placebo groups, respectively.

Quality of Life: EORTC QLQ-C30 and GI.NET21 Scores

Treatment differences for mean changes for the EORTC QLQ-C30 scores for Global Health Status/QOL and the individual domain scores of physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea and vomiting, pain, dyspnoea, appetite loss, constipation, and financial difficulties averaged across all visits were not statistically significant.
Effects were only seen for the individual subscales of insomnia and diarrhoea. Mean changes from baseline in scores of the diarrhoea subscale across all visits were -19.231, -21.622, and -8.547 for telotristat etiprate 250 mg, 500 mg, and placebo, respectively. Mean scores at baseline were 80.83, 78.05, and 74.60 versus 60.00, 59.26, and 62.86 at week 12, respectively.
The comparison between both telotristat etiprate groups and placebo for insomnia across all visits showed an improvement in insomnia of 7.69 points from baseline for patients on placebo, while patients receiving telotristat etiprate 250 mg and 500 mg experienced mean worsening of insomnia of 3.33 and 4.39 points, respectively.

The mean change from baseline in the EORTC GI.NET21 scores averaged across all visits for the individual subscales endocrine, GI symptoms, treatment, social function, muscle/bone pain symptom, sexual function, information/communication function, and body image were not statistically significant.
The subscale of disease-related worries showed fewer disease-related worries for placebo compared to telotristat etiprate 250 mg and 500 mg, although the latter did not reach statistical significance. The analysis by study week showed improvement for placebo and stable results for telotristat etiprate 250 mg and 500 mg at week 12; differences compared to placebo reached statistical significance.

Exit Interview Substudy

In the Exit Interview Substudy patients described a high bowel movement frequency as the most important symptom of CS. It adversely affected their lives by interfering with emotional, social, and physical activities. During the trial, 21 out of 35 patients interviewed noted a reduction in bowel movement frequency. In 20 cases the reduction was described as meaningful by the patient (sense of freedom from bathroom, being better able to enjoy life and participate in physical and social activities).

Among the 35 interview participants, 33 answered a question on satisfaction with the ability of blinded study drug to treat CS. There were 12 patients who were “very satisfied”, all on telotristat etiprate. Proportions of patients who were “very satisfied” were 5/9 (56%) on telotristat etiprate 250 mg, 7/15 (47%) on 500 mg, and 0/9 (0%) on placebo.

Among the interview participants, 9 patients met the durable response criteria during the double-blind treatment period, including 8 patients on telotristat etiprate (all “very satisfied”). There was 1 interview participant who experienced a durable response on placebo, who did not report satisfaction with treatment.

Open label extension (OLE) period

Weekly Bowel Movements

Reductions in mean BM counts/day were maintained during the open-label extension period; reductions from baseline were in the range of approximately -1.6 to -2.0 from week 13 through week 33. A reduction in the mean BMs counts/day and in percent change from week 12 through week 48 was observed throughout the open-label extension.

Patients previously assigned to placebo and telotristat etiprate 250 mg showed reductions in mean BMs counts/day (-0.311 and -0.257, respectively) and percent change from week 12 (-3.803 and -3.111, respectively) beginning at week 13. By week 15, patients originally assigned to placebo showed BM reductions similar to those on telotristat etiprate 500 mg at week 3 of the double-blind period. Patients originally assigned to telotristat etiprate 250 mg showed additional reductions.

An analysis of weekly BMs (counts/day) in patients on a stable dose of octreotide at study entry during the open-label extension period showed results comparable to those for the ITT population.

Urinary 5-HIAA

Urinary 5-HIAA levels (mg/24 h) were analysed at weeks 18, 24, and 48 during the open-label extension. Reductions in u5-HIAA were observed at all measured time-points, although the week 48 data reflect fewer patients at the time of data extraction.

Results for patients on a stable dose of octreotide at study entry during the open-label period were comparable to those for the ITT population.

In an analysis of change from week 12 by study visits week 18, 24, and 48 reductions in mean u5-HIAA levels were seen at week 18 for patients previously assigned to placebo and telotristat etiprate 250 mg. Reductions in mean u5-HIAA levels were seen for all patients at weeks 24 and 48.

Cutaneous Flushing

Only minimal reductions from week 12 in mean flushing episodes (counts/day) were seen throughout the open-label extension; results were comparable to those seen during the double-blind period.

Abdominal Pain

Results for changes in weekly abdominal pain (11-point NRS) during the open-label extension period were similar to those observed during the double-blind period, with minimal reductions in mean scores from baseline.

Stool Consistency

In general, improvements in stool consistency in the range of -0.5 to -0.7 were observed during the open-label extension period and the magnitude of change from baseline was sustained during this period.

Subjective Global Assessment of CS Symptoms

For the subjective global assessment of CS symptoms (11-point NRS) during the open-label extension period result were in similar ranges (3.2 to 3.7) to those observed at most time points for all treatment groups during the double-blind period.

Nausea

A summary of weekly sensation/severity of nausea during the open-label extension period was comparable to results from the double-blind period; there were no significant observations in the nausea data for the open-label extension period.

Plasma 5-HIAA

In general, reductions in plasma 5-HIAA levels were sustained during the open-label extension period.

Rescue SSA

The frequency of rescue SSA showed minimal changes during the open-label extension period.

EORTC QLC-C30

As regards EORTC QLQ-C30 scores reductions from baseline in the insomnia subscale were seen at weeks 24 (-1.92) and 48 (-7.69), and in the diarrhoea subscale at week 24 (-27.59) and week 48 (-28.21).

EORTC GI.NET21

In the EORTC GI.NET21 scores improvements of 5.82 and 5.33 were seen in the GI symptoms subscale at weeks 24 and 48, respectively. Similar improvements were seen in the endocrine, social, and disease-related worries scales.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 42: Summary of efficacy for trial LX301

Title: A Phase 3, Randomized, Placebo-controlled, Parallel-group, Multicenter, Double-blind Study to Evaluate the Efficacy and Safety of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome not Adequately Controlled by Somatostatin Analog (SSA) Therapy			
Study identifier	LX1606.301-CS		
Design	Randomised, placebo-controlled, parallel-group, multicentre, double-blind study in patients with CS not adequately controlled by SSA therapy		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks 3 to 4 weeks 36 weeks
Hypothesis	Superiority of telotristat etiprate to placebo		
Treatments groups	Telotristat etiprate 250 mg		Telotristat etiprate 250 mg tid. 12 weeks, n=45
	Telotristat etiprate 500 mg		Telotristat etiprate 500 mg tid. 12 weeks, n=45
	Placebo		Placebo tid. 12 weeks, n=45
Endpoints and definitions	Primary endpoint	BMs/d	Change from Baseline in frequency of BMs per day averaged over the 12 week double-blind treatment period
	Secondary endpoint	u5-HIAA	Change in daily urinary excretion of 5-HIAA from baseline to week 12
	Secondary endpoint	cutaneous flushing	Change from Baseline in number of daily cutaneous flushing episodes averaged over the 12 week double-blind treatment period

	Secondary endpoint	abdominal pain	Change from Baseline in daily abdominal pain averaged over the 12 week double-blind treatment period		
Database lock	Study ongoing at the time of initial submission (open-label extension only), predefined interim analysis provided, cut-off date for interim report 24 September 2015				
Results and Analysis					
Analysis description	**Primary Analysis** **Change from Baseline in number of BMs/day averaged over the 12 week double-blind treatment period**				
Analysis population and time point description	Intent to treat 12 week double-blind treatment period				
Descriptive statistics and estimate variability	Treatment group	Telotristat etiprate 250 mg	Telotristat etiprate 500 mg	Placebo	
	Number of subject	n=45	n=45	n=45	
	Baseline number BMs/d Mean (SD)	6.085 (2.0703)	5.805 (1.9624)	5.200 (1.3500)	
	Median	5.485	5.393	5.059	
	Min, Max	3.52, 12.97	3.61, 12.46	3.50, 9.00	
	Change from baseline to week 12 BMs/d Mean (SD)	-1.434 (1.3646)	-1.455 (1.3098)	-0.623 (0.8275)	
	Median	-1.338	-1.209	-0.614	
	Min, Max	-6.06, 1.63	-6.66, 0.58	-2.65, 0.80	
Effect estimate per comparison	Differences versus placebo Mean 95% CI	-0.811 -1.284, -0.338	-0.833 -1.292, -0.374		
	Primary endpoint Hodges-Lehmann estimator difference P-value 97.5% CI	 -0.813 <0.001 -1.256, -0.290	 -0.689 <0.001 -1.170, -0.223		
Notes	None				
Analysis description	**Secondary Analysis** **Change in urinary excretion of 5-HIAA from baseline to week 12**				
Analysis population and time point description	Intent to treat Week 12				
Descriptive statistics and estimate variability	Treatment group	Telotristat etiprate 250 mg	Telotristat etiprate 500 mg	Placebo	
	Number of subject	n=45	n=45	n=45	
	Baseline u5-HIAA levels (mg/24 h) n Mean (SD)	 42 92.645 (114.8958)	 44 89.502 (144.4695)	 44 80.968 (161.0143)	
	Median	67.000	28.250	26.100	

	Min, Max	2.20, 637.80	0.00, 608.00	0.00, 786.20
	Change baseline to week 12 u5-HIAA (mg/24 h) n Mean (SD)	 32 -40.134 (84.7663)	 31 -57.729 (82.1749)	 29 11.466 (35.6489)
	Median	-21.650	-19.000	1.400
	Min, Max	-485.60, 77.20	-301.00, 1.00	-35.80, 155.00
Effect estimate per comparison	Differences versus placebo Mean 95% CI	 -51.600 -85.547, -17.653	 -69.195 -102.332, -36.057	
	Primary endpoint Hodges-Lehmann estimator difference P-value 97.5% CI	 -30.100 <0.001 -56.000, -8.100	 -33.800 <0.001 -66.200, -14.600	
Notes	None			
Analysis description	**Secondary Analysis** **Change from baseline in number of cutaneous flushing episodes averaged over the week 12 double-blind treatment period**			
Analysis population and time point description	Intent to treat 12 week double-blind treatment period			
Descriptive statistics and estimate variability	Treatment group	Telotristat etiprate 250 mg	Telotristat etiprate 500 mg	Placebo
	Number of subject	n=45	n=45	n=45
	Baseline cutaneous flushing counts/d Mean (SD)	 2.788 (3.7362)	 2.712 (3.3608)	 1.791 (1.9344)
	Median	1.467	1.643	1.207
	Min, Max	0.00, 19.29	0.00, 19.42	0.00, 7.43
	Change from baseline averaged over the week 12 double-blind treatment period counts/d Mean (SD)	 -0.296 (1.3097)	 -0.525 (1.3413)	 -0.164 (1.1572)
	Median	-0.082	0.000	-0.069
	Min, Max	-5.14, 3.25	-6.12, 1.44	-3.64, 5.14
Effect estimate per comparison	Differences versus placebo Mean 95% CI	 -0.132 -0.650, 0.386	 -0.361 -0.886, 0.164	

	Primary endpoint Hodges-Lehmann estimator difference P-value 97.5% CI	 0.036 0.39 -0.230, 0.330	 0.000 0.84 -0.345, 0.209	
Notes	None			
Analysis description	**Secondary Analysis** **Change from baseline in abdominal pain averaged over the week 12 double-blind treatment period**			
Analysis population and time point description	Intent to treat 12 week double-blind treatment period			
Descriptive statistics and estimate variability	Treatment group	Telotristat etiprate 250 mg	Telotristat etiprate 500 mg	Placebo
	Number of subject	n=45	n=45	n=45
	Baseline numeric rating scale (11-point) Mean (SD)	 2.615 (2.2657)	 2.633 (2.1779)	 2.473 (2.3201)
	Median	2.000	2.643	1.385
	Min, Max	0.00, 8.28	0.00, 8.04	0.00, 7.83
	Change from baseline to week 12 numeric rating scale (11-point) Mean (SD)	 -0.489 (1.4426)	 -0.333 (1.1784)	 -0.226 (1.1601)
	Median	0.000	-0.213	0.000
	Min, Max	-7.48, 1.95	-4.33, 2.26	-3.79, 2.84
Effect estimate per comparison	Differences versus placebo Mean 95% CI	 -0.264 -0.812, 0.285	 -0.107 -0.597, 0.383	
	Primary endpoint Hodges-Lehmann estimator difference P-value 97.5% CI	 -0.167 0.28 -0.541, 0.224	 -0.047 0.87 -0.462, 0.333	
Notes	None			

Supportive study(ies)

Study LX202

Introduction

The phase 2 study LX202 titled 'A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Ascending, Multidose Study to Determine the Safety and Tolerability of Orally Administered LX1606 in

Subjects with Symptomatic Carcinoid Syndrome Refractory to Stable-dose Octreotide Long-acting Release Depot Therapy' was conducted at 11 study sites in the USA between 19 August 2009 and 12 June 2014; the study report is dated 18 August 2015.

The study included patients with symptomatic CS on stable-dose octreotide long-acting release depot therapy. The study was conducted in 2 parts; a dose-escalation or dose-finding and a confirmation of dose selection via an expansion cohort of 8 additional patients. Both parts had a pretreatment period of up to 6 months including screening and run-in, a 28 days double-blind treatment period, and a 14 days follow-up period.

Patients who completed the initial 28-day double-blind treatment period and were at least 75% compliant with dosing and daily diary completion could participate in an optional 8-week open-label extension and if eligible in a further 172-week open-label extension.

In part 1, 4 cohorts of 4 patients each were given ascending doses of 150 mg, 250 mg, 350 mg, and 500 mg telotristat etiprate tid or placebo in a 3:1 ratio. In the absence of dose-limiting toxicities, dose selection for part 2 was to be confirmed at the optimal dose level determined by complete response to treatment; complete response was defined as less than 4 BMs/day, or a decrease in daily BMs ≥50% from baseline, or a positive response to global assessment question ("In the past 7 days, have you had adequate relief of your carcinoid syndrome bowel complaints …?") for the last 2 weeks of the 28-day period.

With the exception of cohort size and number of patients part 2 was conducted similar to part 1 and used the same study procedures, durations, and schedules.

The study recruited adults of both gender with biopsy-proven metastatic carcinoid tumour with disease extent confirmed by CT scan, MRI, or radionuclide imaging who were refractory to a stable-dose of octreotide therapy.

The primary efficacy measure was the number of daily BMs. Secondary efficacy measurements included description of the average stool form for BMs, sensation of urgency to defecate, subjective global assessment of symptoms associated with CS, description of abdominal pain or discomfort, CgA levels, number of cutaneous flushing episodes, and frequency of rescue, short-acting octreotide dosing. Pharmacodynamic assessments included determinations of 5-HT levels in blood and 5-HIAA levels in urine and plasma and other assessments the use of concomitant medications for relief of symptoms associated with CS in the extension period. Furthermore, safety and PK assessments were included.

Twenty-three (23) patients were enrolled and analysed for the core phase; 22 patients completed the core phase and 19 patients were eligible for and entered the open-label extension.

Results

All telotristat etiprate groups had a mean reduction in BMs/day each week during the core phase of -0.20 to -2.17 BMs/day except for the telotristat etiprate 500 mg group at week 3, while on placebo patients showed no reduction in weekly mean number of BMs/day from baseline at any week.

Seven (7/14; 50%) patients on telotristat etiprate reported an improvement in symptoms associated with CS at week 4 versus no patient on placebo.

Mean reductions in cutaneous flushing episodes ranging from -0.03 to -1.7 episodes/day across telotristat etiprate 150 mg, 250 mg, and 350 mg groups were noted; on placebo patients reported mean increases at weeks 1 and 2 and mean reductions at weeks 3 and 4.

Study LX203

Introduction

The phase 2 study LX203 titled 'A Phase 2, Open-label, Multi-center, Serial Ascending-dose, Dose-finding Study to Evaluate the Safety and Tolerability of LX1606 in Subjects with Symptomatic Carcinoid Syndrome' was conducted at 11 sites in the UK and Germany between 15 June 2010 and 12 February 2014. The study report is dated 03 August 2015.

The study included adult patients of both gender with symptomatic CS and biopsy-proven metastatic carcinoid tumour with disease extent confirmed by CT, MRI, or radionuclide imaging. It consisted of a 2-week run-in phase followed by serially dose escalations from telotristat etiprate 150 mg tid every 14 days up to a maximum of 500 mg tid (150 mg, 250 mg, 350 mg, 500 mg) guided by achieving a weekly average of <4 BMs/day for each of the 2 weeks of treatment, or a reduction in average number of daily BMs ≥50% from baseline, or a positive response to the global assessment question, or a reduction in the average number of daily flushing episodes ≥50% from baseline, or dose-limiting toxicity. Once an individual optimal dose or a maximum tolerated dose was identified this was continued for a period of 4 weeks. Upon completion of the 4-week stable-dose period, eligible patients defined as achieving at least 1 of the clinical criteria described above could continue for additional 124 weeks.

Efficacy assessments included change in the number of daily BMs, description of average stool form / consistency, sensation of urgency to defecate, sensation / severity of nausea, subjective global assessment of symptoms associated with CS, description of abdominal pain or discomfort, number of cutaneous flushing episodes, and clinically meaningful symptom reduction (weekly average of <4 BMs/day for each of 2 weeks, or decrease in average daily BMs ≥50% from baseline, or positive response to global assessment question, or decrease in average daily flushing episodes ≥50% from baseline) as well as BM response rate, cutaneous flushing response rate, generalised linear analysis of number of BM and cutaneous flushing episodes, change in CgA level, use of concomitant medications for relief of symptoms associated with CSs, and investigator assessment of symptom improvement. PD assessments included 5-HT, plasma 5-HIAA, and u5-HIAA levels. Safety and PK assessments were also included.

Results

In the core phase patients on telotristat etiprate had a steady decrease in mean number of BMs/day from week 3-4 to week 9-10; the reduction in mean number of BMs/day from baseline was statistically significant for all time points ($p<0.001$). There was suggestion of a plateau in the change scores from week 9-10 to week 11-12 the time most patients had received the maximum dose of telotristat etiprate 500 mg tid.

Stool form improved from loose stool at baseline to soft stool at week 11-12 and the change from baseline in biweekly mean stool form (6-point scale) was statistically significant for all time points ($p\leq0.05$).

The mean proportion of days with sensation of urgency to defecate was numerically lower at every time point compared to the run-in period, but the difference was statistically significant only for week 7-8 ($p=0.042$ paired t-test, $p=0.047$ signed-rank test).

Patients had a reduction from baseline in sensation / severity of nausea (100-mm visual analogue scale, 4-point scale) except at week 1-2, with statistically significant improvement at week 7-8 ($p<0.05$ paired t-test and signed-rank test) and week 11-12 ($p=0.027$ paired t-test).

Abdominal pain scores and cutaneous flushing episodes were low at baseline for most patients and generally remained so.

5-HT levels remained below baseline and a reduction from baseline in mean number of BMs generally corresponded to a reduction from baseline in 5-HT level. Urinary 5-HIAA levels decreased from baseline from week 2 through week 12.

Study LX302

Introduction

The ongoing phase 3 study LX302 titled "A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)" is being conducted at 29 centres in the USA, Canada, Germany, the UK, Italy, France, Spain, Sweden, Belgium, the Netherlands, and Australia. The study started on 14 January 2014; data have been provided up to the data cut-off for the interim report 16 October 2015.

Study LX302 is an uncontrolled, open-label, long-term extension study; patients still enrolled in any telotristat etiprate phase 2 CS study (LX202, LX203) could enter and patients who participated in the phase 3 CS studies (LX301, LX303) could enter at week 48 visit without interruption in telotristat etiprate dosing. Patients were to continue at the same dose of telotristat etiprate as in their original study for 84 weeks.

Upon completion or early withdrawal, patients were required to complete a 14-day follow-up without telotristat etiprate.

The primary objective of the study was to evaluate the long-term safety and tolerability of telotristat etiprate and the secondary objective was to evaluate changes in patients' quality of life (QOL). Efficacy assessments included patient-reported QOL measures (QLQ-C30, GI.NET21) and subjective global assessment of symptoms associated with CS. PD assessments included plasma 5-HIAA levels.

Results

At the time of the data cut-off 16 October 2015, 71 patients were enrolled into the study (10 telotristat etiprate 250 mg, 56 telotristat etiprate 500 mg. The 5 other patients had completed baseline visits only and the date of first dose was not yet reported. Thus 66 patients contributed data to the provided analyses. Enrolment for this study was ongoing at the time of the initial MAA submission.

Overall domain score responses to QLQ-C30 and GI.NET21 were stable between baseline and week 24.

The OR (95% CI) for patients reporting adequate relief relative to baseline appeared generally stable between week 12 (1.6; 0.643, 4.026) and week 24 (0.8; 0.303, 2.099).

The mean change from baseline in subjective global assessment of CS symptoms on an 11-point numeric rating scale at each study visit appeared generally stable between week 12 and week 24. The mean change (SD) from baseline was 0.500 (2.439) on week 12 and 0.654 (2.365) on week 24.

Study LX303

Introduction

Phase 3 study LX303, titled 'A Phase 3, Randomized, Placebo-controlled, Multicenter, Double-blind Study to Evaluate the Safety and Efficacy of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome', was started on 11 March 2014. The data cut-off for the interim report in this application is 30 October 2015 covering the complete double-blind treatment period as well as part of the open-label extension. The trial was conducted at 31 sites in the USA, Canada, Germany, the United Kingdom, France, Spain, Sweden, Belgium, the Netherlands, Israel, and Australia.

The study design was comparable to that of the pivotal study LX301 (see above) with the exception of differences in the study population. Study LX303 allowed patients not on SSA treatment to enter the trial if they had ≥4 BMs/day or at least 1 of the following: poor stool consistency, abdominal pain, nausea, flushing, or elevated u5-HIAA. If patients were on an SSA treatment, they could enter the study with <4 BMs/day and at least 1 of the following: poor stool consistency, abdominal pain, nausea, cutaneous flushing, or elevated u5-HIAA. Patients who were previously screened for study LX301 and did not meet inclusion criteria baseline BM frequency and use of SSA therapy were eligible to enter study LX303.
In contrast to study LX301, the primary efficacy endpoint was the percent (%) change from baseline in 24-hour u5-HIAA levels at week 12 for telotristat etiprate 250 mg and telotristat etiprate 500 mg versus placebo.

The secondary efficacy endpoints were the change from baseline in the number of BMs/day averaged over the 12-week double-blind treatment period; in stool consistency as measured by the Bristol Stool Form Scale averaged across all time points; in the number of cutaneous flushing episodes; in abdominal pain averaged across all time points; in the frequency of rescue SSA used to treat CS symptoms; and in the number of daily BMs averaged over the 12-week double-blind treatment period and at each study week among patients not receiving SSA at baseline.

The primary and secondary endpoints were evaluated using the same method as study LX301. Sixty (60) patients were planned to be enrolled.

Results

Double-blind treatment

76 patients were enrolled and randomised for the double-blind treatment period (25 telotristat etiprate 250 mg and 500 mg each, and 26 placebo); all 76 patients were treated and 68 patients (89.5%) completed the double-blind treatment period [n=22 (88.0%) telotristat etiprate 250 mg and 500 mg each, n=24 (92.3%) placebo].
Of the 68 patients who completed the double-blind treatment period, 67 patients (22 telotristat etiprate 250 mg, 21 telotristat etiprate 500 mg, 24 placebo) continued into the open-label extension period. Of the 67 patients who entered the open-label extension period, 14 (20.9%) had completed the open-label extension, 11 patients (16.4%) had discontinued, and 42 patients (62.7%) were ongoing at the time of data cut-off for the interim study report.
Details of the ITT, PP, and safety populations are presented in the table below. Overall, 12 patients were excluded from the supportive efficacy analyses using the PP Population because of significant protocol deviations.

Table 43: Analysis Populations for the Double-blind Treatment Period (All Enrolled Patients)

Analysis Populations	Placebo N (%)	LX1606 250 mg N (%)	LX1606 500 mg N (%)	Total N (%)
Randomized[a]	26	25	25	76
Safety Population[a]	26 (100)	25 (100)	25 (100)	76 (100)
Intent-to-treat Population[a]	26 (100)	25 (100)	25 (100)	76 (100)
Per-protocol Population[a]	25 (96.2)	21 (84.0)	18 (72.0)	64 (84.2)

a Percentages are based on the number of patients randomized.

Demographics and baseline characteristics for the safety population were generally balanced across the 3 treatment groups. Exceptions were: a lower proportion of patients in the telotristat etiprate 500 mg group receiving SSA therapy every 4 weeks [48.0% (12/25), 64.0% (16/25), and 76.9% (20/26) telotristat etiprate 500 mg, 250 mg, and placebo, respectively], a higher proportion of patients on telotristat etiprate 250 mg (n=3, 12%) and 500 mg (n=6, 24%) not receiving any SSA therapy compared to no

patient on placebo (n=0), a lower proportion of patients on placebo (12/26; 46.2%) receiving octreotide as SSA compared to telotristat etiprate 250 mg (17/25; 68.0%) and 500 mg (16/25; 64.0%) and a higher proportion receiving lanreotide as SSA [placebo 53.8% (14/26); telotristat etiprate 250 mg 20% (5/25); telotristat etiprate 500 mg 12.0% (3/25)], and that two-thirds of patients had baseline u5-HIAA levels above the ULN.

Demographics and baseline characteristics for the open-label extension period safety population were similar to those in the double-blind treatment period.

Primary endpoint

Telotristat etiprate reduced u5-HIAA levels from baseline to week 12 for both telotristat etiprate groups compared to placebo and the result was statistically significant (p<0.001 each). Estimators (Hodges-Lehmann) for the differences in percent changes (95% CI) from baseline in u5-HIAA levels between telotristat etiprate and placebo at week 12 were -53.955% (-84.955, -25.119) for telotristat etiprate 250 mg and -89.662% (-113.104, -63.863) for telotristat etiprate 500 mg. The supplemental analyses using a mixed model with repeated measures as well as sensitivity and subgroup analyses by age, sex, baseline u5-HIAA levels, baseline mean BM frequency, daily stool consistency, average daily flushing frequency, average daily rating of abdominal pain, proportion of days with nausea, and use of a stable dose of long-acting octreotide at study entry were in line with the primary analysis.

Table 44: Analysis of Percentage Change From Baseline in Urinary 5-Hydroxyindoleacetic Acid Levels (mg/24 hours) at Week 12 During the Double-blind Treatment Period (Intent-to-treat Population)

Characteristic	Statistic	Placebo N=26	LX1606 250 mg N=25	LX1606 500 mg N=25
Baseline for patients with Baseline and Week 12 values	n	22	17	19
	Mean (SD)	84.764 (117.1379)	69.082 (60.6366)	67.637 (77.5394)
	Median	32.150	57.600	43.100
	Min, Max	3.20, 439.30	2.30, 196.20	2.80, 332.30
Percent change from Baseline	n	22	17	19
	Mean (SD)	97.721 (397.0107)	-33.164 (58.4754)	-76.466 (17.3714)
	Median	8.034	-39.931	-76.147
	Min, Max	-43.64, 1864.46	-94.74, 162.78	-98.00, -28.57
	Difference in arithmetic means (LX1606 – placebo)		-130.884	-174.186
	95% CL		-328.194, 66.425	-358.887, 10.515
Primary analysis[a]	Hodges-Lehmann estimator of treatment difference (LX1606 – placebo)		-53.955	-89.662
	95% CL		-84.955, -25.119	-113.104, -63.863
	p-value		**<0.001**	**<0.001**
Supplemental analysis[b,c]	Least squares mean	88.606	-33.711	-72.380
	95% CL	-69.757, 246.968	-177.540, 110.118	-238.163, 93.402
	Least squares mean difference		-122.317	-160.986
	95% CL		-287.171, 42.537	-316.394, -5.578
	p-value		0.14	**0.043**

Abbreviations: CL = confidence limit; Max = maximum; Min = minimum; SD = standard deviation; u5-HIAA = urinary 5-hydroxyindoleacetic acid

Note: Baseline value was defined as the last nonmissing assessment before the first dose of study drug

a The primary analysis used a blocked 2-sample Wilcoxon rank sum statistic (ie, van Elteren test) stratified by the u5-HIAA at randomization

b The supplemental analysis used a mixed model with repeated measurements. The model used the percent change from baseline in u5-HIAA levels as the dependent variable, and included treatment group, u5-HIAA at randomization, time (week 6 and week 12), and treatment-by-time interaction as fixed effects, and patient as a random effect. An

unstructured (general) covariance matrix was used to model the within-subject errors. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom

c See text preceding this table for additional details on the reliability of the supplemental analysis for this variable

Secondary endpoint

The change from baseline in BM frequency (counts/d) averaged over the double-blind treatment period for telotristat etiprate compared to placebo was statistically significant (p≤0.004 each). The change from baseline in daily BM averaged over 12 weeks was +0.1 and -0.5 in the placebo and 250 mg groups respectively. Estimators (Hodges-Lehmann) for differences between telotristat etiprate and placebo were (95% CI) -0.452 BMs/day (-0.719, -0.173) for telotristat etiprate 250 mg and -0.535 BMs/day (-0.793, -0.254) for telotristat etiprate 500 mg.

Table 45: Analysis of Bowel Movements (counts/day) During the Double-blind Treatment Period (Intent-to-treat Population)

Characteristic	Statistic	Placebo N=26	LX1606 250 mg N=25	LX1606 500 mg N=25
Baseline number of daily BMs	n	25	25	25
	Mean (SD)	2.186 (0.6706)	2.529 (1.2497)	2.786 (1.5655)
	Median	2.250	2.214	2.400
	Min, Max	1.03, 3.38	0.80, 6.64	0.81, 6.57
Change from Baseline in the number of daily BMs averaged over the Double-blind Treatment Period	n	25	25	25
	Mean (SD)	0.050 (0.3263)	-0.452 (0.6940)	-0.595 (0.7243)
	Median	0.004	-0.419	-0.533
	Min, Max	-0.68, 0.90	-2.04, 1.02	-2.98, 0.46
	Difference in arithmetic means (LX1606 – placebo)		-0.502	-0.645
	95% CL		-0.810, -0.194	-0.964, -0.325
Primary analysis[a]	Hodges-Lehmann estimator of treatment difference (LX1606 – placebo)		-0.452	-0.535
	95% CL		-0.719, -0.173	-0.793, -0.254
	p-value		**0.004**	**<0.001**
Supplemental analysis[b]	Adjusted rate (counts/day)	2.627	2.093	1.905
	95% CL	2.278, 3.029	1.846, 2.371	1.650, 2.201
	Rate ratio (LX1606:placebo)		0.797	0.725
	95% CL		0.698, 0.910	0.636, 0.827
	p-value		**<0.001**	**<0.001**

Abbreviations: BM = bowel movement; CL = confidence limit; Max = maximum; Min = minimum; SD = standard deviation; u5-HIAA = urinary 5-hydroxyindoleacetic acid

Note: Baseline value was the number of BMs/day averaged over the Run-in Period before the first dose of study drug

a The primary analysis used a blocked 2-sample Wilcoxon rank sum statistic (ie, van Elteren test) stratified by the u5-HIAA at randomization

b The supplemental analysis used a generalized linear model based on the negative binomial distribution. The model included the number of daily BMs as the dependent variable, and included treatment group and u5-HIAA at randomization as fixed effects, and the baseline number of BMs/day as a fixed covariate. The natural log value of the number of days with nonmissing diary data was used as an offset term to adjust for variable number of days

The change from baseline in stool consistency (Bristol Stool Form Scale) averaged over the double-blind treatment period for telotristat etiprate 500 mg compared to placebo was statistically significant (p=0.009), but nor for telotristat etiprate 250 mg (p=0.09). Estimator (Hodges-Lehmann) for the difference between telotristat etiprate 500 mg and placebo was (95% CI) -0.392 (-0.824, -0.124) and for telotristat etiprate 250 mg -0.203 (-0.447, 0.019).

Table 46: Analysis of Stool Consistency During the Double-blind Treatment Period (Intent-to-treat Population)

Characteristic	Statistic	Placebo N=26	LX1606 250 mg N=25	LX1606 500 mg N=25
Baseline stool consistency	n	25	25	25
	Mean (SD)	4.965 (0.9052)	5.113 (0.8410)	5.291 (0.8292)
	Median	4.879	5.350	5.462
	Min, Max	3.25, 6.19	3.37, 6.23	3.74, 6.44
Change from Baseline in stool consistency averaged across all time points during the Double-blind Treatment Period	n	25	25	25
	Mean (SD)	0.006 (0.4127)	-0.196 (0.7012)	-0.599 (0.8627)
	Median	0.000	-0.119	-0.269
	Min, Max	-0.89, 0.88	-1.34, 2.22	-2.56, 0.50
	Difference in arithmetic means (LX1606 – placebo)		-0.202	-0.605
	95% CL		-0.529, 0.125	-0.990, -0.221
Primary analysis[a]	Hodges-Lehmann estimator of treatment difference (LX1606 – placebo)		-0.203	-0.392
	95% CL		-0.447, 0.019	-0.824, -0.124
	p-value		0.09	**0.009**
Supplemental analysis[b]	Least squares mean	0.055	-0.099	-0.479
	95% CL	-0.383, 0.492	-0.479, 0.282	-0.915, -0.044
	Least squares mean difference		-0.154	-0.534
	95% CL		-0.553, 0.246	-0.927, -0.141
	p-value		0.45	**0.008**

Abbreviations: CL = confidence limit; Max = maximum; Min = minimum; SD = standard deviation; u5-HIAA = urinary 5-hydroxyindoleacetic acid

Note: Baseline value was the daily stool consistency score averaged over the Run-in Period before the first dose of study drug

a The primary analysis used a blocked 2-sample Wilcoxon rank sum statistic (ie, van Elteren test) stratified by the u5-HIAA at randomization

b The supplemental analysis used a mixed model with repeated measurements. The model used the change from baseline in the daily reported stool consistency score as the dependent variable, and included treatment group, u5-HIAA at randomization, time (Day 1 up to the earlier of the day of the last dose of double-blind study drug and Day 84), and treatment-by-time interaction as fixed effects, baseline stool consistency score as a covariate, and patient as a random effect

A compound symmetry covariance matrix was used to model the within-subject errors. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom

There were no significant differences between groups as regards the secondary endpoints changes from baseline averaged over the double-blind treatment period in cutaneous flushing, abdominal pain, or frequency of rescue SSA therapy to treat CS symptoms.

Other endpoints

The absolute reduction in u5-HIAA levels from baseline at week 12: estimates (Hodges-Lehmann) of treatment differences versus placebo were (95% CI) -29.800 mg/24 h (-78.800, -9.200) for telotristat etiprate 250 mg and -40.600 mg/24 h (-96.400, -28.700) for telotristat etiprate 500 mg.
The plasma 5-HIAA levels compared to placebo: estimators of the treatment differences versus placebo were (95% CI) -142.379 ng/mL (-242.583, -60.050) for telotristat etiprate 250 mg and -124.355 ng/mL (-201.650, -70.950) for telotristat etiprate 500 mg.

There were 40% patients (10/25) with durable response in the telotristat ethyl 250 mg group, versus 0% in the placebo group (0/26) (p=0.001).The mean proportions of days with ≥30% reduction in the number of BMs were 0.428, 0.414, and 0.154 for telotristat etiprate 250 mg, 500 mg, and placebo, respectively. The comparison of telotristat etiprate versus placebo on the proportion of days with ≥30% reduction in the number of BMs/day from baseline was statistically significant (p<0.001 each). Estimates (Hodges-Lehmann) of the differences versus placebo were (95% CI) 0.250 (0.074, 0.440) for telotristat etiprate 250 mg and 0.250 (0.060, 0.428) for telotristat etiprate 500 mg.
The worsening of BM frequency by ≥30% was more common on placebo (11 events) than in the telotristat etiprate 250 mg (7 events) and 500 mg groups (3 events). The HRs for time to occurrence compared with placebo (95% CI) were 0.53 (0.18, 1.41) and 0.25 (0.06, 0.81) for telotristat etiprate 250 mg and 500 mg, respectively.

A worsening of the EORTC QLQ-C30 was observed in the individual subscale of constipation for both telotristat etiprate groups compared to placebo; this increase was more pronounced for telotristat etiprate 500 mg.

Open-label extension

Sixty-seven (67) patients entered the ongoing open-label extension period. Reductions in u5-HIAA levels were sustained in the open-label extension period. The limited data available indicate reductions in u5-HIAA levels in patients originally assigned to placebo at weeks 18 and 24.

Reductions in BM frequency and stool consistency were also stable for patients previously assigned to telotristat etiprate 500 mg and approached similar levels to those seen for patients previously assigned to telotristat etiprate 500 mg in patients previously assigned to placebo or telotristat etiprate 250 mg.

Other results were generally comparable to those seen in the double-blind treatment phase of the trial.

Analysis performed across trials (pooled analyses and meta-analysis)

The applicant provided a comparison across studies LX301 and LX303. The study design and assessments were very similar except for the inclusion criteria as study LX 303 was designed to include patients with CS who were not eligible for the pivotal trial LX301, i.e. patients did not have to be on SSA therapy or who had <4 BMs/day (see description under Supportive Studies – Study LX303).

Disease characteristics were as follows: mean baseline u5-HIAA levels ranged from 80.968 mg/24 h to 92.645 mg/24 h in study LX301 and from 66.048 mg/24 h to 86.300 mg/24 h in study LX303. Mean baseline BM counts/day ranged from 5.200 to 6.085 in study LX301 and from 2.186 to 2.786 in study LX303. Mean stool consistency (weekly) using the Bristol Stool Form Scale ranged from 5.917 to 5.970 for study LX301 and from 4.965 to 5.291 for study LX303.
Baseline characteristics for age, gender, race, ethnicity, weight, and BMI were similar across these studies.

The results are presented in Table 47.

Table 47: Comparison of Studies LX301 and LX303 for BM and Durable Response and 5-HIAA Results during the Double-blind Treatment Period (ITT Population)

		Study LX301			Study LX303		
	Statistic	**Placebo N=45**	**LX1606 250 mg N=45**	**LX1606 500 mg N=45**	**Placebo N=26**	**LX1606 250 mg N=25**	**LX1606 500 mg N=25**
Average number of BMs (counts/day) at Baseline	Number of patients	45	45	45	25	25	25
	Mean (SD)	5.20 (1.35)	6.09 (2.07)	5.81 (1.96)	2.19 (0.67)	2.53 (1.25)	2.79 (1.57)
	Median (Min, Max)	5.06 (3.50, 9.00)	5.49 (3.52, 12.97)	5.39 (3.61, 12.46)	2.25 (1.03, 3.38)	2.21 (0.80, 6.64)	2.40 (0.81, 6.57)
Change from Baseline in the number of BMs averaged over the 12-Week DBT Period	H-L estimator of trt. dif. (LX1606-placebo) (97.5%CL)[a]	---	-0.81 (-1.26, -0.29)	-0.69 (-1.17, -0.22)	---	-0.45 (-0.72, -0.17)	-0.54 (-0.79, -0.25)
	p-value	---	**p<0.001**	**p<0.001**	---	**p=0.004**	**p<0.001**
Proportion of Patients with Durable Response	Number of patients	45	45	45	26	25	25
	Responder, n (%)	9 (20.0)	20 (44.4)	19 (42.2)	0	10 (40.0)	10 (40.0)
Baseline u5-HIAA levels (mg/24 hours)[b]	Number of patients	44	42	44	22	17	19
	Mean (SD)	80.97 (161.01)	92.65 (114.90)	89.50 (144.47)	84.76 (117.14)	69.08 (60.64)	67.64 (77.54)
	Median (Min, Max)	26.10 (0.00, 786.20)	67.00 (2.20, 637.80)	28.25 (0.00, 608.00)	32.15 (3.20, 439.30)	57.60 (2.30, 196.20)	43.10 (2.80, 332.30)
Change from Baseline in u5-HIAA levels (mg/24 hours) at Week12	H-L estimator of trt. dif. (LX1606-placebo) (97.5%CL)[a]	---	-30.10 (-56.00, -8.10)	-33.80 (-66.20, -14.60)	---	-29.80 (-78.80, -9.20)	-40.60 (-96.40, -28.70)
	p-value	---	**<0.001**	**<0.001**	---	**0.003**	**<0.001**

Baseline value was defined as the mean of the responses recorded during the Run-in Period prior to the first dose of study drug

Abbreviations: BMs = bowel movements; CL = confidence limit; DBT = Double-blind Treatment; H-L= Hodges-Lehmann; ITT = intent-to-treat; LX1606 = telotristat etiprate; Max = maximum; Min = minimum; trt. dif.: treatment difference

a 95%CL for study LX303

b Baseline data is based on all patients with data at baseline for study LX301 and on patients with data at both baseline and week 12 (derived from Listing 16.2.6.11) for study LX303

Notes: The primary analysis used a blocked 2-sample Wilcoxon rank sum statistic (ie, van Elteren test) stratified by the urinary 5-HIAA at randomisation. Patients with durable response were the responders with ⩾30% reduction in daily number of BMs for ⩾50% of the time over the Double-blind Treatment Period. The percentage was calculated based on the number of patients assessed.

To further characterise the treatment effect as regards proportions of patients achieving response, the cumulative distribution function (CDF) of responses between groups was examined with the y-axis representing the proportion of patients achieving a certain level of benefit and the x-axis the change from baseline to week 12 in average BM frequency per day (Figure 17).

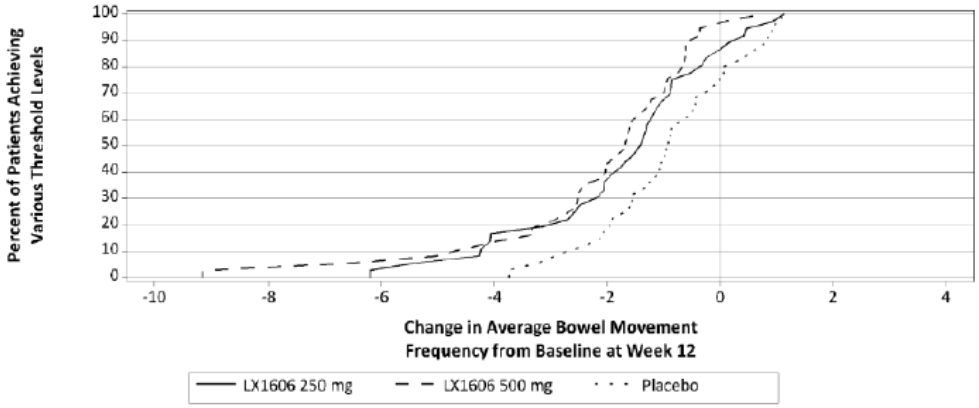


Figure 17: Study LX301: CDF of Change in Average Bowel Movement Frequency from Baseline at Week 12

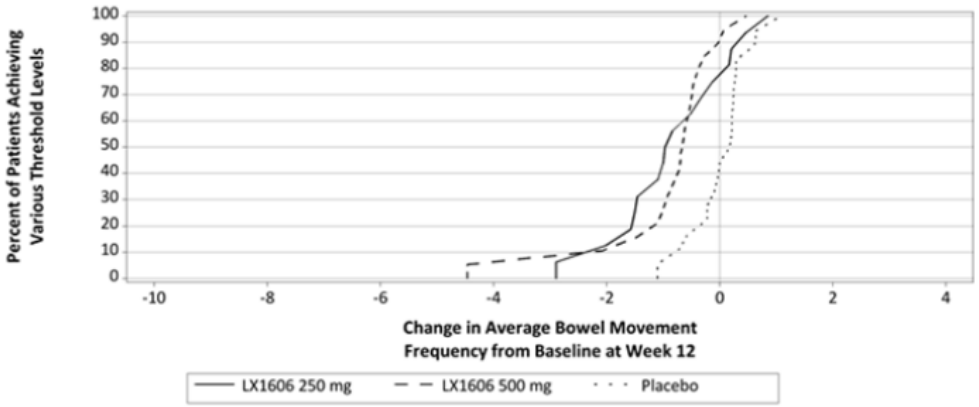


Figure 18: Study LX303: CDF of Change in Average Bowel Movement Frequency from Baseline at Week 12

Details of the results from studies LX301 and LX303 for BM frequency, u5-HIAA levels, and durable response and a summary of other key efficacy parameters are presented in the Table below.

Table 48: Other Key Efficacy Results for Studies LX301 and LX303

Study LX301 Results – DBT Period, ITT Population	Study LX303 Results – DBT Period, ITT Population
Proportion of days with >30% reduction in BM frequency Both doses of telotristat etiprate resulted in statistically significant reductions compared with placebo.	**Proportion of days with >30% reduction in BM frequency** Both doses of telotristat etiprate resulted in statistically significant reductions compared with placebo
First sustained >30% reduction in BM frequency The median time to event was 19 days for telotristat etiprate 250 mg and 27 days for telotristat etiprate 500 mg with less than one half of patients experiencing it with placebo during the DBT Period. The hazard ratios were statistically significant for both doses compared with placebo.	**First sustained >30% reduction in BM frequency** The median time to event was 34 days for telotristat etiprate 250 mg and 39 days for telotristat etiprate 500 mg with less than a half of patients experiencing it with placebo during the DBT Period. The hazard ratios were statistically significant for both doses compared with placebo.
Stool consistency Telotristat etiprate 500 mg tid (but not 250 mg tid) showed a trend toward improved stool consistency compared with placebo. Patients who experienced reductions in BM frequency generally reported improvements in stool consistency.	**Stool consistency** Telotristat etiprate 500 mg tid (but not 250 mg tid) showed statistically significant improved stool consistency compared with placebo. Patients who experienced reductions in BM frequency generally reported improvements in stool consistency.
Urgency to defecate Telotristat etiprate 500 mg tid (but not 250 mg tid) statistically significantly reduced the proportion of days with urgency to defecate in the primary statistical analysis compared with placebo. Patients who experienced reductions in BM frequency generally reported less urgency to defecate.	**Urgency to defecate** Neither dose of telotristat etiprate was statistically significantly different from placebo in the primary statistical analysis. Patients who experienced reductions in BM frequency generally reported less urgency to defecate
p5-HIAA Both doses of telotristat etiprate resulted in statistically significant reductions compared with placebo.	**p5-HIAA** Both doses of telotristat etiprate resulted in statistically significant reductions compared with placebo.
Cutaneous Flushing Neither dose of telotristat etiprate was statistically significantly different from placebo. Clinically relevant reductions were observed in telotristat etiprate treated patients compared with placebo in those with 2 or more flushing episodes/day at Baseline.	**Cutaneous Flushing** Neither dose of telotristat etiprate was statistically significantly different from placebo
Use of short-acting octreotide rescue therapy There was some evidence that telotristat etiprate 500 mg tid (but not 250 mg tid) reduced the burden of use short acting rescue therapy. There was no statistically significant difference in the primary statistical analysis. However in the supplemental statistical analyses telotristat etiprate 500 mg tid significantly reduced use of short acting rescue.	**Use of short-acting octreotide rescue therapy** No statistically significant differences were observed between the groups

Note: TE250 and TE500 = telotristat etiprate 250 mg tid and telotristat etiprate 500 mg tid respectively

LX 301: A post-hoc analysis showed that the average number of daily short-acting SSA injections used for rescue therapy over the 12-week DBT period was 0.3 and 0.7 in the telotristat ethyl 250 mg and placebo groups, respectively (see SmPC section 5.1).

Durable response was defined as a ≥30% reduction in number of BMs/day for ⩾50% of time over the DBT Period, and patients meeting these criteria were considered responders

BM = bowel movement; DBT = Double-blind Treatment Period; H-L = Hodges=Lehmann; p5-HIAA = plasma 5-hydroxyindoleacetic acid; u5-HIAA = urinary 5-hydroxyindoleacetic acid

Clinical studies in special populations

Table 49: Age Categories by Treatment Group Short-term Safety Analysis Studies LX301 and LX303 Safety Population, Double-blind Treatment

	Study 301				Study 303			
	Placebo (N=45) n(%)	250 mg tid (N=45) n(%)	500 mg tid (N=45) n(%)	All LX1606 (N=90) n(%)	Placebo (N=26) n(%)	250 mg tid (N=25) n(%)	500 mg tid (N=25) n(%)	All LX1606 (N=50) n(%)
Age Category	n (%)	n (%)	n (%)|	n (%)	n (%)	n (%)	n (%)	n (%)
< 65	25 (55.6)	26 (57.8)	22 (48.9)	48 (53.3)	12 (46.2)	14 (56.0)	15 (60.0)	29 (58.0)
>=65-<75	17 (37.8)	17 (37.8)	18 (40.0)	35 (38.9)	12 (46.2)	4 (16.0)	4 (16.0)	8 (16.0)
>=75-<85	3 (6.7)	2 (4.4)	4 (8.9)	6 (6.7)	2 (7.7)	7 (28.0)	6 (24.0)	13 (26.0)
>=85	0	0	1 (2.2)	1 (1.1)	0	0	0	0

	Overall			
	Placebo (N=71) n(%)	250 mg tid (N=70) n(%)	500 mg tid (N=70) n(%)	All LX1606 (N=140) n(%)
Age Category	n (%)	n (%)	n (%)	n (%)
< 65	37 (52.1)	40 (57.1)	37 (52.9)	77 (55.0)
>=65-<75	29 (40.8)	21 (30.0)	22 (31.4)	43 (30.7)
>=75-<85	5 (7.0)	9 (12.9)	10 (14.3)	19 (13.6)
>=85	0	0	1 (1.4)	1 (0.7)

Source: Final lock, Post-hoc Table PH-1

Table 50: Age Categories by Treatment Group Overall Telotristat Safety Analysis Studies LX202, LX203, LX301, LX302, and LX303 Safety Population

	Study 202	Study 203	Study 301	Study 303	Overall
	LX1606 (All dosages) (N=22) n(%)	LX1606 (All dosages) (N=15) n(%)	LX1606 (All dosages) (N=128) n(%)	LX1606 (All dosages) (N=74) n(%)	LX1606 (All dosages) (N=239) n(%)
Age Category	n (%)	n (%)	n (%)	n (%)	n (%)
< 65	14 (63.6)	10 (66.7)	71 (55.5)	39 (52.7)	134 (56.1)
>=65-<75	4 (18.2)	4 (26.7)	47 (36.7)	20 (27.0)	75 (31.4)
>=75-<85	4 (18.2)	1 (6.7)	9 (7.0)	15 (20.3)	29 (12.1)
>=85	0	0	1 (0.8)	0	1 (0.4)

Source: Final lock, Post-hoc Table PH-2

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Overall, efficacy data for telotristat etiprate in patients with CS have been derived from phase 2 studies LX202 and LX203, the pivotal phase 3 study LX301, and phase 3 studies LX303, and LX302.

The pivotal phase 3 trial LX301 was a randomised, placebo-controlled, parallel-group, multicentre, double-blind study in patients with CS not adequately controlled by SSA therapy. The general design of this pivotal trial LX301 is considered acceptable. After a 3 to 4 weeks run-in period, patients on stable SSA therapy were assigned to either 250 mg or 500 mg telotristat etiprate or to placebo.

Evaluation of telotristat etiprate 250 mg tid and 500 mg tid dosages for use in the phase 3 trials has been adequately justified although the dose selection is based rather on a maximal tolerated dose approach than on consistent phase II data; as dose-finding in this orphan condition is considered particularly difficult the chosen approach is acceptable.

The inclusion and exclusion criteria of trial LX301 are in general acceptable. During scientific advice the applicant was requested to exclude serotonin receptor antagonists (e.g. ondansetron) from the concomitant medications to avoid bias as well as potential safety problems, but this has not been

followed; the applicant provided further evidence that the use of serotonin receptor antagonists did not influence study results, which is agreed.

The objectives and the relevant endpoints of study LX301 are generally considered acceptable. The primary efficacy endpoint was the change from baseline in the number of daily BMs averaged over the 12-week double-blind phase of the trial. This primary endpoint might be a sensitive and objective measure of the predominant symptom of CS which can potentially be influenced by telotristat etiprate.

The randomisation was adequate. The methods used to ensure that patients and personnel involved in the study were blinded to treatment allocation are considered sufficient. It is noted that the applicant did not have a clear perception on the minimal clinically important difference for the primary endpoint. Consequently, a sample size was chosen that was able to detect the assumed treatment effect of -1.5 BMs/day with larger power than usual (96%) but that gave also larger power for detection of smaller treatment effects.

The statistical methods were generally acceptable. Endpoints were divided in primary endpoint, three secondary endpoints, and more than 20 "other endpoints" (it should be noted that a response endpoint which was recommended as a key secondary endpoint by CHMP scientific advice was explored among the other endpoints). The multiple testing strategy controlled the family-wise type 1 error for primary and secondary endpoints adequately. The large number of "other endpoints" suggests that these were planned to be analysed with an exploratory intent and results for these endpoints have to be interpreted with care taking multiplicity into account.

For the handling of missing values it was not distinguished between missing data before and after discontinuation of treatment. Nevertheless, the sensitivity analyses appear to be sufficient for assessment of the influence of missing data on the estimates of the treatment effect (also taking the actual number of missing data, missing data patterns, and results of sensitivity analysis into account). Assessing the treatment effect irrespective of rescue medication in the primary analysis probably reflects the expected effect in clinical practice and is adequate; sensitivity analyses aiming to estimate the treatment effect in absence of rescue medication were provided and are appropriate.

The protocol amendments and the protocol deviations are not considered to have affected the outcome of this trial in a negative way.

Efficacy data and additional analyses

The treatment groups were sufficiently balanced regarding demographics and baseline characteristics, except for more patients on telotristat etiprate 250 mg receiving octreotide instead of lanreotide at study entry compared to placebo and telotristat etiprate 500 mg and a higher proportion of patients on telotristat etiprate 500 mg receiving their SSA therapy every 3 weeks compared to telotristat etiprate 250 mg and placebo. The vast majority of patients were of ‘white’ ethnicity. A history of psychiatric disorders was reported by 41.5% of patients overall, similar across groups.

The primary study endpoint of change from baseline in the number of BMs/day averaged over the 12-week double-blind period in trial LX301 met the predefined criteria of statistical significance in both telotristat etiprate groups. The estimates of the treatment differences (Hodges-Lehmann) were about -0.8 (97.5% CI: -1.256, -0.290) for telotristat etiprate 250 mg and -0.7 (97.5% CI: -1.170, -0.223) for telotristat etiprate 500 mg from a baseline of about 5 to 6 average BMs/day. Supplemental and sensitivity analyses were generally in line with these findings. The pre-specified responder analysis shows that there were twice more responders in the telotristat groups (44% and 42% in the 250 mg and 500 mg groups, respectively, versus 20% in the placebo group). When the full effect of telotristat is observed (during the

last 6 weeks of the DBT period) the proportion of responders with at least 30% BM reduction was 51% (23/45) in the 250 mg versus 22% (10/45) in the placebo group (post-hoc analysis) (see SmPC section 5.1).

Post-hoc sub group analyses to evaluate the potential effect of concomitant medications (especially antidiarrhoeals and opioids) were requested to the Applicant. The responder analysis shows that in non-users of antidiarrhoeals there were 23% of responders in the placebo group (7/30) and 36% of responders in the telotristat 250 mg group (9/25); thus only 13% of patients benefited from the treatment. While in the whole population, telotristat 250 mg and telotristat 500 mg were associated with a similar responder rate of approximately 50% of patients compared to 22% of patients on placebo during the last 6 weeks of the DBT Period in Study LX301. Also in the non-users of opioids the responder rates in placebo and telotristat 250mg users were 24% (9/38) and 44% (14/32), respectively. This again indicates that opioids somewhat favour treatment effect of telotristat, although less than for antidiarrhoeals. Thus, treatment with telotristat etiprate 250 mg or 500 mg tid over 12 weeks led to a reduction of slightly less than 1 BM per day versus placebo from a background of 5 to 6 BMs per day at baseline. It is acknowledged that gastrointestinal symptoms have a substantial impact on the quality of life. Although the results did not meet the magnitude of the agreed overall reduction in the number of BMs/day of approximately 30% for a clinically important benefit, the results from the secondary endpoints support a general overall clinical benefit in symptom relief experienced in CS patients. The analysis of change in BMs by treatment week showed an effect of telotristat etiprate from week 3 onwards. Subgroup analyses of the primary efficacy endpoint change in BMs per day by age, sex, baseline u5-HIAA levels, and region were in line with the primary finding. The data from studies LX202, LX203, LX303, and LX302 are also supportive of the primary efficacy variable.

There were no significant differences between both telotristat etiprate groups and placebo as regards mean changes from baseline in stool consistency.

The effect of telotristat etiprate on cutaneous flushing and abdominal pain are relevant from a clinical perspective. However, no relevant effect of telotristat etiprate have been found in this trial.

As regards concomitant medications analgesics, antidiarrheals, intestinal anti-inflammatory / anti-infective agents, drugs for acid related disorders, and ondansetron were used by more patients in the telotristat etiprate groups compared to placebo, which appears to have introduced a bias towards an overestimation of the effect of telotristat etiprate. However, further sensitivity analyses were provided and although it is impossible to completely rule out an effect of concomitant medication on the clinical benefit observed for BMs, it is nevertheless established that in the totality of the data, there is sufficient evidence to demonstrate a clinical benefit from telotristat treatment in patients that have responded to telotristat therapy.

Demonstration of durability of effect of telotristat etiprate in the target population is considered essential. The applicant has provided analyses of the durability of the change in the frequency of BMs per day using as definition either the proportion of responders with ≥30% reduction in number of BMs/day for ≥50% of time, the proportion of days with ≥30% reduction from baseline or ≥1.5 BM reduction from baseline, or the proportion of days with a ≥1.5 reduction in BMs observed per patient. Overall, about 44%, 42%, and 20% of patients on telotristat etiprate 250 mg, 500 mg, and placebo, respectively, had a ≥30% reduction in number of BMs per day for ≥50% of time. The mean proportions of days with ≥30% reductions in BMs were about 0.4, 0.4, and 0.3 for telotristat etiprate 250 mg, 500 mg, and placebo, respectively. The mean proportions of days during which a reduction in BMs ≥1.5 BM per day was observed for each patient were 0.5, 0.5, and 0.3 for telotristat etiprate 250 mg, 500 mg, and placebo, respectively. Thus using the responder definition of ≥30% reduction in number of BMs/day for ≥50% of time for a durable response about double the number of patients on telotristat etiprate reached this criterion compared to placebo;

durability has also been shown based on the two other definitions (days with ≥30% reductions in BMs, days with reduction in BMs ≥1.5 BM per day).

In the analysis of treatment differences for mean changes in the EORTC QLQ-C30 scores for Global Health Status / QOL and the individual domain scores, effects were only seen for the individual subscales insomnia and diarrhoea. The comparison between telotristat etiprate and placebo for insomnia across all visits showed an improvement of 7.69 points for patients on placebo, while on telotristat etiprate patients experienced mean worsening of 3.33 and 4.39 points for 250 mg and 500 mg tid, respectively. Mean changes from baseline in scores of the diarrhoea subscale across all visits showed higher improvement in patients on telotristat etiprate compared to placebo. Baseline values were also different between groups with worse baseline scores for patients on telotristat etiprate compared to placebo while after 12 weeks of treatment mean scores were comparable between groups.

As regards the open-label extension phase of study LX301 interim data were provided at the time of the initial submission. About 84% of patients enrolled in the double-blind treatment phase started to participate in the open-label extension period. Reductions in the frequency of mean BMs per day and in the urinary excretion of 5-HIAA were generally maintained during the open-label extension period and patients previously on placebo showed reductions similar to those on telotristat etiprate in the double-blind period.

In the exit interview substudy, the patient's view on the benefit of treatment on CS symptoms participating patients described a high BM frequency as the most important symptom of CS; about one-third of patients in the substudy noted a reduction in BM frequency and the majority of these patients described it as meaningful. However, only a subset of patients has been included in this exit interview substudy where out of 73 eligible patients 39 consented to participate; of these only 35 patients have been interviewed. Therefore, the data is of limited value and can only be considered generally supportive.

A summary of final LX301 data (complete data of both the double-blind and open-label portions of the study) was submitted as part of the responses to D120 LoQ in February 2017. The last patient visit for the double-blind treatment period was on 29 May 2015 and the last patient visit for the open-label extension was on 17 March 2016. The final data lock was on 13 September 2016 while the date of the extraction for the interim CSR submitted in the initial application was 24 September 2015. The data provided did not indicate the need for relevant changes in the efficacy conclusions.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with telotristat in all subsets of the paediatric population in the treatment of carcinoid syndrome (see section 4.2 for information on paediatric use).

2.5.4. Conclusions on the clinical efficacy

Treatment with telotristat etiprate 250 mg and 500 mg led to a statistically significant reduction in the number of BMs per day from baseline to week 12. The effect size was slightly less than a difference of 1 BM per day versus placebo from a background of 5 to 6 BMs per day at baseline. When durability of the change in the frequency of BMs per day was defined as ≥30% reduction in number of BMs per day for ≥50% of time the proportion of patients on telotristat etiprate having a durable response was about double that on placebo (>40% versus 20%). Durability has also been shown based on the definition mean proportion of days with ≥30% reductions in BMs and mean proportion of days with a reduction in BMs ≥1.5 BM per day. Supportive data have been provided from studies LX202, LX203, LX303, and LX302 and the results are generally in line with findings in the pivotal trial. Thus overall the effects seen in the clinical

trial are sufficiently consistent, but are primarily focussed on the small change in the frequency of BMs of less than 1 BM per day based on a background of 5 to 6 BMs per day at baseline.

2.6. Clinical safety

For the purpose of the overall analysis of safety, the applicant presented the safety data as pooled safety analyses groups, which comprise the following:

- The Phase 1 safety analysis which includes:
  - The single-dose studies LX101 and LX 104 (55 subjects)
  - The multiple-dose studies LX102, LX 106, and LX 108 (88 subjects)
  - The crossover studies LX 103, LX 104, LX 107, and LX 109 (116 subjects)
- The Phase 2 and Phase 3 analyses, which comprise the following subgroups:
  - The Placebo controlled safety analyses: This includes mainly the safety data from the studies LX 301 and LX303, with limited integration of the TEAE data from 250 mg tid and 500 mg tid treatment groups from study LX202.
  - The Overall Safety Analyses, which includes all studies LX202, LX203, LX301, LX302, and LX303 with double-blind and open-label periods (239 patients).
  - The long-term safety analyses: These include all patients in the studies LX202, LX203, LX301, LX302, and LX 303 who received any dose of telotristat etiprate and were treated for at least 24 weeks (148 patients), or at least 48 weeks (74 patients).

A safety update (integrated summary of safety) was submitted as part of the Applicant's responses to D120 LoQ in February 2017. Subsequently, the CHMP requested an updated module 2.7.4 as part of the D180 LoOI, which was provided, together with an updated Module 2.5, as part of the responses to D180 LoOI in June 2017. Section 2.7 of this assessment report is based on the initial MAA dossier submitted on 22 June 2016, unless otherwise stated.

Patient exposure

For the ongoing studies LX301-303, the data extraction date was: 24th September 2015 for study LX301, 16th October 2015 for study LX302, and 30th October for study LX303. A total number of 566 subjects has been included into the trials conducted, of which were 259 healthy volunteers, 249 patients with CS, and 58 patients with ulcerative colitis.

The following tables show the summary of exposure for the overall safety population, and the two long-term safety analyses as well as the exposure for the placebo-controlled safety population divided by doses:

Table 51: Summary of Exposure for Overall and Long-Term Safety Patients (Studies LX202, LX203, LX301, and LX303)

	Overall telotristat etiprate doses for these analyses		
	Overall safety (N=239)	Long-term at least 24 weeks (N=148)	Long-term at least 48 weeks (N=74)
Mean (SD) treatment duration, weeks	41.1 (41.04)	58.6 (43.47)	85.0 (48.42)
Median treatment duration (range), weeks	30.0 (1.0, 258.3)	48.0 (24.1, 258.3)	71.8 (48.0, 258.3)
Subjects with exposure, n (%)			
<4 weeks	9 (3.8)	N/A	N/A
≥4 weeks to <8 weeks	16 (6.7)	N/A	N/A
≥8 weeks to <12 weeks	14 (5.9)	N/A	N/A
≥12 weeks to <24 weeks	52 (21.8)	N/A	N/A
≥24 weeks to <36 weeks	51 (21.3)	51 (34.5)	N/A
≥36 weeks to <48 weeks	23 (9.6)	23 (15.5)	N/A
≥48 weeks to <72 weeks	39 (16.3)	39 (26.4)	39 (52.7)
≥72 weeks to <96 weeks	17 (7.1)	17 (11.5)	17 (23.0)
≥96 weeks to <120 weeks	10 (4.2)	10 (6.8)	10 (13.5)
≥120 weeks	8 (3.3)	8 (5.4)	8 (10.8)

Source: ISS Table 6.3, ISS Table 7.3, and ISS Table 8.3

Table 52: Summary of Exposure for Placebo-controlled Safety Patients (Studies LX301 and LX303)

	Placebo (N=71)	Telotristat etiprate 250 mg tid (N=70)	Telotristat etiprate 500 mg tid* (N=70)	All telotristat etiprate (N=140)
Mean (SD) treatment duration, weeks	11.3 (2.47)	11.7 (1.93)	11.0 (2.92)	11.4 (2.49)
Median treatment duration (range), weeks	12.0 (1.4, 14.7)	12.0 (2.9, 17.9)	12.0 (1.0, 13.6)	12.0 (1.0, 17.9)
Subjects with exposure, n (%)				
<4 weeks	3 (4.2)	1 (1.4)	4 (5.7)	5 (3.6)
≥4 weeks to <8 weeks	4 (5.6)	2 (2.9)	5 (7.1)	7 (5.0)
≥8 weeks to <12 weeks	15 (21.1)	18 (25.7)	12 (17.1)	30 (21.4)
≥12 weeks	49 (69.0)	49 (70.0)	49 (70.0)	98 (70.0)

Source: ISS Table 4.3.1
* telotristat etiprate 250 mg tid for 1 week, then up-titrated to telotristat etiprate 500 mg tid

As per updated data extraction, a total number of 566 subjects has been included into the trials conducted, of which 259 were healthy volunteers, 249 patients with CS, and 58 patients with ulcerative colitis.

Table 53: Summary of Exposure for Overall and Long-Term Safety Patients (Studies LX202, LX203, LX301, and LX303)

Study Pools	Patient Group	Number of Patients Treated with Telotristat	Mean Exposure	Median Exposure
Placebo-controlled Safety	All	140	11 weeks	12 weeks
Overall Safety	All	239	51 weeks [a]	47 weeks
Long-Term Safety	24 weeks or greater	170	68 weeks	53 weeks
	48 weeks or greater	111	84 weeks	72 weeks

Data source: Module 5.3.5.3 ISS Table 6.3, Table 7.3 and Table 8.3
a. approximately 235 patient-years total.

A more detailed description is given in the following table:

Table 54: Summary of Exposure for Overall and Long-Term Safety Patients (Studies LX202, LX203, LX301, and LX303)

	Overall telotristat etiprate doses for these analyses		
	Overall safety (N=239)	Long-term at least 24 weeks (N=170)	Long-term at least 48 weeks (N=111)
Mean (SD) treatment duration, weeks	51.27 (43.916)	67.54 (42.172)	84.17 (43.573)
Median treatment duration (range), weeks	47.00 (1.0, 271.1)	53.40 (24.1, 271.1)	72.10 (48.0, 271.1)
Subjects with exposure, n (%)			
<4 weeks	8 (3.3)	N/A	N/A
≥4 weeks to <8 weeks	16 (6.7)	N/A	N/A
≥8 weeks to <12 weeks	9 (3.8)	N/A	N/A
≥12 weeks to <24 weeks	36 (15.1)	N/A	N/A
≥24 weeks to <36 weeks	24 (10.0)	24 (14.1)	N/A
≥36 weeks to <48 weeks	35 (14.6)	35 (20.6)	N/A
≥48 weeks to <72 weeks	52 (21.8)	52 (30.6)	52 (46.8)
≥72 weeks to <96 weeks	24 (10.0)	24 (14.1)	24 (21.6)
≥96 weeks to <120 weeks	23 (9.6)	23 (13.5)	23 (20.7)
≥120 weeks	12 (5.0)	12 (7.1)	12 (10.8)

Source: ISS Table 6.3, ISS Table 7.3, and ISS Table 8.3

The most important subgroup of the safety population is the placebo-controlled safety population which is shown in the following table:

Table 55: Summary of Exposure for Placebo-controlled Safety Patients (Studies LX301 and LX303)

	Placebo (N=71)	Telotristat etiprate 250 mg tid (N=70)	Telotristat etiprate 500 mg tid* (N=70)	All telotristat etiprate (N=140)
Mean (SD) treatment duration, weeks	11.24 (2.44)	11.74 (1.92)	10.97 (2.92)	11.35 (2.49)
Median treatment duration (range), weeks	12.0 (1.4, 13.1)	12.0 (2.9, 17.9)	12.0 (1.0, 13.6)	12.0 (1.0, 17.9)
Subjects with exposure, n (%)				
<4 weeks	3 (4.2)	1 (1.4)	4 (5.7)	5 (3.6)
≥4 weeks to <8 weeks	4 (5.6)	2 (2.9)	5 (7.1)	7 (5.0)
≥8 weeks to <12 weeks	15 (21.1)	17 (24.3)	12 (17.1)	29 (20.7)
≥12 weeks	49 (69.0)	50 (71.4)	49 (70.0)	99 (70.7)

Source: ISS Table 4.3.1
* telotristat etiprate 250 mg tid for 1 week, then up-titrated to telotristat etiprate 500 mg tid

Adverse events

The table below summarises TEAEs by SOC for Placebo-controlled Safety in telotristat etiprate Phase 3 trials. SOCs are sorted by descending incidence in the all telotristat etiprate group. A total of 89% of patients treated with telotristat etiprate had at least 1 TEAE (89% in the 250 mg tid group and 90% in the 500 mg tid group), as did 85% of patients in the placebo group.

Table 56: Summary of Treatment-Emergent Adverse Events by System Organ Class and Treatment Group for Placebo-Controlled Safety Patients (Studies LX301 and LX303)

	Placebo (N=71) n (%)	Telotristat etiprate 250 mg tid (N=70) n (%)	Telotristat etiprate 500 mg tid (N=70) n (%)	All telotristat etiprate (N=140) n (%)
Patients with at least 1 TEAE	60 (84.5)	62 (88.6)	63 (90.0)	125 (89.3)
SOC (sorted by descending incidence in All telotristat etiprate)				
Gastrointestinal disorders	37 (52.1)	35 (50.0)	34 (48.6)	69 (49.3)
General disorders and administration site conditions	22 (31.0)	23 (32.9)	16 (22.9)	39 (27.9)
Infections and infestations	11 (15.5)	18 (25.7)	15 (21.4)	33 (23.6)
Nervous system disorders	14 (19.7)	10 (14.3)	18 (25.7)	28 (20.0)
Metabolism and nutrition disorders	11 (15.5)	13 (18.6)	13 (18.6)	26 (18.6)
Investigations	11 (15.5)	14 (20.0)	11 (15.7)	25 (17.9)
Musculoskeletal and connective tissue disorders	9 (12.7)	7 (10.0)	17 (24.3)	24 (17.1)
Psychiatric disorders	7 (9.9)	8 (11.4)	13 (18.6)	21 (15.0)
Respiratory, thoracic and mediastinal disorders	6 (8.5)	8 (11.4)	12 (17.1)	20 (14.3)
Vascular disorders	6 (8.5)	12 (17.1)	8 (11.4)	20 (14.3)
Skin and subcutaneous tissue disorders	6 (8.5)	12 (17.1)	7 (10.0)	19 (13.6)
Renal and urinary disorders	2 (2.8)	7 (10.0)	3 (4.3)	10 (7.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (2.8)	2 (2.9)	6 (8.6)	8 (5.7)
Blood and lymphatic system disorders	2 (2.8)	4 (5.7)	2 (2.9)	6 (4.3)
Hepatobiliary disorders	0	4 (5.7)	1 (1.4)	5 (3.6)
Ear and labyrinth disorders	0	1 (1.4)	2 (2.9)	3 (2.1)
Injury, poisoning and procedural complications	1 (1.4)	1 (1.4)	2 (2.9)	3 (2.1)
Cardiac disorders	6 (8.5)	2 (2.9)	1 (1.4)	3 (2.1)
Endocrine disorders	0	0	2 (2.9)	2 (1.4)
Immune system disorders	1 (1.4)	1 (1.4)	1 (1.4)	2 (1.4)
Surgical and medical procedures	1 (1.4)	2 (2.9)	0	2 (1.4)
Eye disorders	4 (5.6)	0	0	0
Reproductive system and breast disorders	2 (2.8)	0	0	0

Source: ISS Table 4.4.2.1

Table 57: Summary of Treatment-Emergent Adverse Events by System Organ Class and Treatment Group for Placebo-Controlled Safety Patients (Studies LX301 and LX303, updated analysis)

	Placebo (N=71) n (%)	Telotristat etiprate 250 mg tid (N=70) n (%)	Telotristat etiprate 500 mg tid (N=70) n (%)	All telotristat etiprate (N=140) n (%)
Patients with at least 1 TEAE	60 (84.5)	62 (88.6)	64 (91.4)	126 (90.0)
Patients with at least 1 severe TEAE	9 (12.7)	9 (12.9)	9 (12.9)	19 (13.6.)
Patients with at least 1 study drug-related TEAE	19 (26.8)	26 (37.1)	41 (58.6)	67 (47.9)
Patients with at least 1 severe study drug-related TEAE	1 (1.4)	1 (1.4)	5 (7.1)	6 (4.3)
Patients with at least 1 SAE	12 (16.9)	8 (11.4)	11 (15.7)	19 (13.6)
Patients with a TEAE leading to death	3 (4.2)	1 (1.4)	1 (1.4)	2 (1.4)
Patients with a study drug-related TEAE leading to death	0	0	1 (1.4)	1 (0.7)
Patients with at least 1 TEAE leading to study drug discontinuation	12 (16.9)	16 (22.9)	9 (12.9)	25 (17.9)

Source: ISS Table 4.4.1

Note: Study drug discontinuation includes all TEAEs leading to temporary or permanent discontinuation of study drug or discontinuation from the study.

Table 58: Summary of Treatment-Emergent Adverse Events by System Organ Class and Treatment Group for Placebo-Controlled Safety Patients (Studies LX301 and LX303, updated analysis)

	Placebo (N=71) n (%)	Telotristat etiprate 250 mg tid (N=70) n (%)	Telotristat etiprate 500 mg tid (N=70) n (%)	All telotristat etiprate (N=140) n (%)
Patients with at least 1 TEAE	60 (84.5)	62 (88.6)	64 (91.4)	126 (90.0)
SOC (sorted by descending incidence in All telotristat etiprate)				
Gastrointestinal disorders	38 (53.5)	36 (51.4)	35 (50.0)	71 (50.7)
General disorders and administration site conditions	24 (33.8)	24 (34.3)	18 (25.7)	42 (30.0)
Infections and infestations	11 (15.5)	18 (25.7)	17 (24.3)	35 (25.0)
Nervous system disorders	16 (22.5)	10 (14.3)	18 (25.7)	28 (20.0)
Metabolism and nutrition disorders	10 (14.1)	13 (18.6)	14 (20.0)	27 (19.3)
Investigations	11 (15.5)	14 (20.0)	11 (15.7)	25 (17.9)
Musculoskeletal and connective tissue disorders	9 (12.7)	7 (10.0)	16 (22.9)	23 (16.4)
Psychiatric disorders	7 (9.9)	8 (11.4)	13 (18.6)	21 (15.0)
Respiratory, thoracic and mediastinal disorders	6 (8.5)	8 (11.4)	13 (18.6)	21 (15.0)
Vascular disorders	6 (8.5)	12 (17.1)	8 (11.4)	20 (14.3)
Skin and subcutaneous tissue disorders	7 (9.9)	12 (17.1)	7 (10.0)	19 (13.6)
Renal and urinary disorders	2 (2.8)	7 (10.0)	3 (4.3)	10 (7.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (2.8)	2 (2.9)	6 (8.6)	8 (5.7)
Blood and lymphatic system disorders	2 (2.8)	4 (5.7)	2 (2.9)	6 (4.3)
Hepatobiliary disorders	0	5 (7.1)	1 (1.4)	6 (4.3)
Ear and labyrinth disorders	0	1 (1.4)	2 (2.9)	3 (2.1)
Injury, poisoning and procedural complications	1 (1.4)	1 (1.4)	2 (2.9)	3 (2.1)
Cardiac disorders	7 (9.9)	2 (2.9)	1 (1.4)	3 (2.1)
Endocrine disorders	0	0	2 (2.9)	2 (1.4)
Immune system disorders	1 (1.4)	1 (1.4)	1 (1.4)	2 (1.4)
Surgical and medical procedures	1 (1.4)	1 (1.4)	0	1 (0.7)
Eye disorders	4 (5.6)	0	0	0
Reproductive system and breast disorders	2 (2.8)	0	0	0

Table 59 (and Table 61 updated) summarises TEAEs reported in 1% or more of patients in any telotristat etiprate treatment group for Placebo-controlled Safety in telotristat etiprate Phase 3 trials. Events are sorted by PT in descending incidence in the All telotristat etiprate group.

Table 59: Treatment-Emergent Adverse Events Reported in ≥1% Patients (in All Telotristat Etiprate Group) by Preferred Term and Treatment Group for Placebo-Controlled Safety Patients (Studies LX301 and LX303) for events occurring at least 2-times in any treatment group [Updated analysis – Data Lock Point September 2016]

	Placebo (N=71) n (%)	Telotristat etiprate 250 mg tid (N=70) n (%)	Telotristat etiprate 500 mg tid (N=70) n (%)	All telotristat etiprate (N=140) n (%)
Patients with at least 1 TEAE	60 (84.5)	62 (88.6)	63 (90.0)	125 (89.3)
Events (preferred term)				
Nausea	9 (12.7)	9 (12.9)	16 (22.9)	25 (17.9)
Abdominal pain	12 (16.9)	13 (18.6)	10 (14.3)	23 (16.4)
Fatigue	6 (8.5)	6 (8.6)	9 (12.9)	15 (10.7)
Decreased appetite	2 (2.8)	3 (4.3)	9 (12.9)	12 (8.6)
Abdominal pain upper	3 (4.2)	3 (4.3)	7 (10.0)	10 (7.1)
Headache	3 (4.2)	5 (7.1)	5 (7.1)	10 (7.1)
Gamma-glutamyl transferase increased	0	5 (7.1)	5 (7.1)	10 (7.1)
Depression	3 (4.2)	2 (2.9)	7 (10.0)	9 (6.4)
Diarrhoea	8 (11.3)	7 (10.0)	2 (2.9)	9 (6.4)
Vomiting	5 (7.0)	3 (4.3)	6 (8.6)	9 (6.4)
Flushing	4 (5.6)	6 (8.6)	3 (4.3)	9 (6.4)
Constipation	2 (2.8)	4 (5.7)	5 (7.1)	9 (6.4)
Hypokalemia	3 (4.2)	3 (4.3)	5 (7.1)	8 (5.7)
Abdominal distension	3 (4.2)	5 (7.1)	2 (2.9)	7 (5.0)
Flatulence	1 (1.4)	4 (5.7)	3 (4.3)	7 (5.0)
Urinary tract infection	2 (2.8)	5 (7.1)	2 (2.9)	7 (5.0)
Dyspnoea	2 (2.8)	3 (4.3)	4 (5.7)	7 (5.0)
Influenza	0	2 (2.9)	4 (5.7)	6 (4.3)
Dizziness	5 (7.0)	0	6 (8.6)	6 (4.3)
Pyrexia	2 (2.8)	6 (8.6)	0	6 (4.3)
Oedema peripheral	0	5 (7.1)	1 (1.4)	6 (4.3)
Nasopharyngitis	2 (2.8)	3 (4.3)	3 (4.3)	6 (4.3)
Insomnia	2 (2.8)	2 (2.9)	3 (4.3)	5 (3.6)
Cough	1 (1.4)	2 (2.9)	3 (4.3)	5 (3.6)
Oropharyngeal pain	0	3 (4.3)	2 (2.9)	5 (3.6)
ALT increased	0	2 (2.9)	3 (4.3)	5 (3.6)
Night sweats	0	3 (4.3)	2 (2.9)	5 (3.6)
Dyspepsia	5 (7.0)	3 (4.3)	1 (1.4)	4 (2.9)
Asthenia	5 (7.0)	3 (4.3)	1 (1.4)	4 (2.9)
Hypertension	1 (1.4)	1 (1.4)	3 (4.3)	4 (2.9)
Anaemia	1 (1.4)	2 (2.9)	2 (2.9)	4 (2.9)
Paraesthesia	0	1 (1.4)	2 (2.9)	3 (2.1)
Musculoskeletal chest pain	0	0	3 (4.3)	3 (2.1)
Musculoskeletal pain	1 (1.4)	0	3 (4.3)	3 (2.1)
Arthralgia	1 (1.4)	1 (1.4)	2 (2.9)	3 (2.1)
Myalgia	2 (2.8)	1 (1.4)	2 (2.9)	3 (2.1)
Neck pain	0	1 (1.4)	2 (2.9)	3 (2.1)
Pain in extremity	2 (2.8)	1 (1.4)	2 (2.9)	3 (2.1)
Pneumonia	0	0	3 (4.3)	3 (2.1)
Confusional state	0	0	3 (4.3)	3 (2.1)
Depressed mood	2 (2.8)	2 (2.9)	1 (1.4)	3 (2.1)
Epistaxis	0	0	3 (4.3)	3 (2.1)
Blood ALP increased	0	0	3 (4.3)	3 (2.1)
AST increased	0	1 (1.4)	2 (2.9)	3 (2.1)
Weight decreased	1 (1.4)	1 (1.4)	2 (2.9)	3 (2.1)
Investigation	0	2 (2.9)	1 (1.4)	3 (2.1)
Dry skin	0	2 (2.9)	1 (1.4)	3 (2.1)
Neoplasm progression	1 (1.4)	1 (1.4)	2 (2.9)	3 (2.1)
Abdominal pain lower	0	2 (2.9)	0	2 (1.4)

Disease progression	2 (2.8)	2 (2.9)	0	2 (1.4)
Hyperglycaemia	2 (2.8)	2 (2.9)	0	2 (1.4)

Table 60: Treatment-Emergent Adverse Events Reported in ⩾1% Patients (in All Telotristat Etiprate Group) by Preferred Term and Treatment Group for Placebo-Controlled Safety Patients (Studies LX301 and LX303, updated analysis Data Lock Point September 2016) for events occurring at least 2-times in any treatment group (ADR determination for preparation of SmPC section 4.8 uses data from this table.)

	Placebo (N=71) n (%)	Telotristat etiprate 250 mg tid (N=70) n (%)	Telotristat etiprate 500 mg tid (N=70) n (%)	All telotristat etiprate (N=140) n (%)
Patients with at least 1 TEAE	60 (84.5)	62 (88.6)	64 (91.4)	126 (90.0)
Events (preferred term)				
Nausea	9 (12.7)	9 (12.9)	16 (22.9)	25 (17.9)
Abdominal pain	12 (16.9)	13 (18.6)	11 (15.7)	24 (17.1)
Fatigue	6 (8.5)	7 (10.0)	9 (12.9)	16 (11.4)
Decreased appetite	2 (2.8)	3 (4.3)	9 (12.9)	12 (8.6)
Abdominal pain upper	3 (4.2)	4 (5.7)	7 (10.0)	11 (7.9)
Headache	3 (4.2)	5 (7.1)	6 (8.6)	11 (7.9)
Gamma-glutamyl transferase increased	0	5 (7.1)	5 (7.1)	10 (7.1)
Depression	3 (4.2)	2 (2.9)	8 (11.4)	10 (7.1)
Diarrhoea	8 (11.3)	7 (10.0)	2 (2.9)	9 (6.4)
Vomiting	5 (7.0)	3 (4.3)	6 (8.6)	9 (6.4)
Flushing	4 (5.6)	6 (8.6)	3 (4.3)	9 (6.4)
Constipation	3 (4.2)	4 (5.7)	5 (7.1)	9 (6.4)
Hypokalemia	3 (4.2)	3 (4.3)	5 (7.1)	8 (5.7)
Dyspnoea	2 (2.8)	3 (4.3)	5 (7.1)	8 (5.7)
Abdominal distension	3 (4.2)	5 (7.1)	2 (2.9)	7 (5.0)
Flatulence	1 (1.4)	4 (5.7)	3 (4.3)	7 (5.0)
Urinary tract infection	2 (2.8)	5 (7.1)	2 (2.9)	7 (5.0)
Oedema peripheral	1	5 (7.1)	2 (2.9)	7 (5.0)
Influenza	0	2 (2.9)	4 (5.7)	6 (4.3)
Dizziness	5 (7.0)	0	6 (8.6)	6 (4.3)
Pyrexia	2 (2.8)	6 (8.6)	0	6 (4.3)
Nasopharyngitis	2 (2.8)	3 (4.3)	3 (4.3)	6 (4.3)
Insomnia	2 (2.8)	2 (2.9)	3 (4.3)	5 (3.6)
Cough	1 (1.4)	2 (2.9)	3 (4.3)	5 (3.6)
Oropharyngeal pain	0	3 (4.3)	2 (2.9)	5 (3.6)
Night sweats	0	3 (4.3)	2 (2.9)	5 (3.6)
Dyspepsia	5 (7.0)	3 (4.3)	1 (1.4)	4 (2.9)
Asthenia	5 (7.0)	3 (4.3)	1 (1.4)	4 (2.9)
Hypertension	1 (1.4)	1 (1.4)	3 (4.3)	4 (2.9)
Anaemia	1 (1.4)	2 (2.9)	2 (2.9)	4 (2.9)
Paraesthesia	0	1 (1.4)	2 (2.9)	3 (2.1)
Musculoskeletal chest pain	0	0	3 (4.3)	3 (2.1)
Musculoskeletal pain	1 (1.4)	0	3 (4.3)	3 (2.1)
Arthralgia	1 (1.4)	1 (1.4)	2 (2.9)	3 (2.1)
Myalgia	2 (2.8)	1 (1.4)	2 (2.9)	3 (2.1)
Neck pain	0	1 (1.4)	2 (2.9)	3 (2.1)
Pain in extremity	2 (2.8)	1 (1.4)	2 (2.9)	3 (2.1)
Pneumonia	0	0	3 (4.3)	3 (2.1)
Depressed mood	2 (2.8)	2 (2.9)	1 (1.4)	3 (2.1)

Epistaxis	0	0	3 (4.3)	3 (2.1)
Blood ALP increased	0	0	3 (4.3)	3 (2.1)
AST increased	0	1 (1.4)	2 (2.9)	3 (2.1)
Weight decreased	2 (2.8)	1 (1.4)	2 (2.9)	3 (2.1)
Investigation	0	2 (2.9)	1 (1.4)	3 (2.1)
Dry skin	0	2 (2.9)	1 (1.4)	3 (2.1)
Gastroenteritis	1 (1.4)	2 (2.9)	1 (1.4)	3 (2.1)
Confusional state	0	0	2 (2.9)	2 (1.4)
Neoplasm progression	1 (1.4)	0	1 (1.4)	2 (1.4)
Abdominal pain lower	0	2 (2.9)	0	2 (1.4)
Tremor	0	1 (1.4)	1 (1.4)	2 (1.4)
Muscle spasms	1 (1.4)	0	2 (2.9)	2 (1.4)
Flank pain	1 (1.4)	1 (1.4)	1 (1.4)	2 (1.4)
Mucosal inflammation	0	1 (1.4)	1 (1.4)	2 (1.4)
Chest discomfort	1 (1.4)	2 (2.9)	0	2 (1.4)
Disease progression	2 (2.8)	2 (2.9)	0	2 (1.4)
Oral candidiasis	0	1 (1.4)	1 (1.4)	2 (1.4)
Sinusitis	0	1 (1.4)	1 (1.4)	2 (1.4)
Upper respiratory tract infection	0	1 (1.4)	1 (1.4)	2 (1.4)
Dehydration	1 (1.4)	1 (1.4)	1 (1.4)	2 (1.4)
Hyperglycaemia	2 (2.8)	2 (2.9)	0	2 (1.4)
Nervousness	0	0	2 (2.9)	2 (1.4)
Liver function test abnormal	0	1 (1.4)	1 (1.4)	2 (1.4)
Erythema	1 (1.4)	1 (1.4)	1 (1.4)	2 (1.4)
Rash	3 (4.2)	1 (1.4)	1 (1.4)	2 (1.4)
Alopecia	0	2 (2.9)	0	2 (1.4)
Haematuria	0	2 (2.9)	0	2 (1.4)
Renal failure acute	0	2 (2.9)	0	2 (1.4)
Fall	0	1 (1.4)	1 (1.4)	2 (1.4)
Palpitations	2 (2.8)	2 (2.9)	0	2 (1.4)

Source: ISS Table 4.4.2.2.

Table 61 summarises TEAEs by SOC for Overall Safety and Long-term Safety in telotristat etiprate Phase 2 and Phase 3 trials. SOCs are sorted by descending incidence in the Overall Safety telotristat etiprate group.

Table 61: Treatment-Emergent Averse Events by System Organ Class for Overall and Long-Term Safety Patients (Studies LX202, LX203, LX301, and LX303)

	Overall telotristat etiprate doses for these analyses		
	Overall safety (N=239)	Long-term at least 24 weeks (N=148)	Long-term at least 48 weeks (N=74)
Patients with at least 1 TEAE	228 (95.4)	145 (98.0)	73 (98.6)
SOC (sorted by descending incidence in Overall Safety)			
Gastrointestinal disorders	167 (69.9)	113 (76.4)	63 (85.1)
General disorders and administration site conditions	118 (49.4)	84 (56.8)	54 (73.0)
Infections and infestations	97 (40.6)	71 (48.0)	45 (60.8)
Nervous system disorders	80 (33.5)	60 (40.5)	37 (50.0)
Investigations	77 (32.2)	56 (37.8)	32 (43.2)
Musculoskeletal and connective tissue disorders	77 (32.2)	57 (38.5)	38 (51.4)
Metabolism and nutrition disorders	73 (30.5)	47 (31.8)	27 (36.5)
Psychiatric disorders	68 (28.5)	49 (33.1)	29 (39.2)
Vascular disorders	58 (24.3)	42 (28.4)	29 (39.2)
Respiratory, thoracic and mediastinal disorders	57 (23.8)	43 (29.1)	27 (36.5)
Skin and subcutaneous tissue disorders	50 (20.9)	34 (23.0)	21 (28.4)
Renal and urinary disorders	37 (15.5)	24 (16.2)	15 (20.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	36 (15.1)	27 (18.2)	20 (27.0)
Injury, poisoning and procedural complications	34 (14.2)	29 (19.6)	23 (31.1)
Cardiac disorders	25 (10.5)	20 (13.5)	13 (17.6)
Blood and lymphatic system disorders	23 (9.6)	15 (10.1)	9 (12.2)
Surgical and medical procedures	18 (7.5)	15 (10.1)	11 (14.9)
Hepatobiliary disorders	17 (7.1)	13 (8.8)	9 (12.2)
Eye disorders	16 (6.7)	14 (9.5)	11 (14.9)
Reproductive system and breast disorders	15 (6.3)	13 (8.8)	10 (13.5)
Endocrine disorders	12 (5.0)	10 (6.8)	8 (10.8)
Ear and labyrinth disorders	7 (2.9)	5 (3.4)	4 (5.4)
Immune system disorders	5 (2.1)	4 (2.7)	3 (4.1)
Social circumstances	2 (0.8)	0	0
Congenital, familial and genetic disorders	1 (0.4)	1 (0.7)	0

Source: ISS Table 6.4.1.2, ISS Table 7.4.1, and ISS Table 8.4.1

Table 62: Treatment-Emergent Averse Events by System Organ Class for Overall and Long-Term Safety Patients (Studies LX202, LX203, LX301, and LX303, updated data)

	Overall telotristat etiprate doses for these analyses		
	Overall safety (N=239)	Long-term at least 24 weeks (N=170)	Long-term at least 48 weeks (N=111)
Patients with at least 1 TEAE	233 (97.5)	168 (98.8)	110 (99.1)
SOC (sorted by descending incidence in Overall Safety)			
Gastrointestinal disorders	185 (77.4)	137 (80.6)	96 (86.5)
General disorders and administration site conditions	134 (56.1)	104 (61.2)	74 (66.7)
Infections and infestations	108 (45.2)	84 (49.4)	64 (57.7)
Nervous system disorders	94 (39.3)	76 (44.7)	58 (52.3)
Investigations	92 (38.5)	73 (42.9)	53 (47.7)
Musculoskeletal and connective tissue disorders	89 (37.2)	75 (44.1)	53 (47.7)
Metabolism and nutrition disorders	85 (35.6)	60 (35.3)	43 (38.7)
Psychiatric disorders	85 (35.6)	65 (38.2)	52 (46.8)
Vascular disorders	69 (28.9)	55 (32.4)	42 (37.8)
Respiratory, thoracic and mediastinal disorders	64 (26.8)	50 (29.4)	36 (32.4)
Skin and subcutaneous tissue disorders	59 (24.7)	44 (25.9)	31 (27.9)
Renal and urinary disorders	42 (17.6)	30 (17.6)	21 (18.9)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	39 (16.3)	32 (18.8)	22 (19.8)
Injury, poisoning and procedural complications	38 (15.9)	33 (19.4)	30 (27.0)
Cardiac disorders	36 (15.1)	32 (18.8)	20 (18.0)
Blood and lymphatic system disorders	27 (11.3)	20 (11.8)	13 (11.7)
Surgical and medical procedures	21 (8.8)	19 (11.2)	14 (12.6)
Hepatobiliary disorders	22 (9.2)	17 (10.0)	13 (11.7)
Eye disorders	19 (7.9)	17 (10.0)	13 (11.7)
Reproductive system and breast disorders	17 (7.1)	15 (8.8)	13 (11.7)
Endocrine disorders	16 (6.7)	14 (8.2)	13 (11.7)
Ear and labyrinth disorders	8 (3.3)	6 (3.5)	5 (4.5)
Immune system disorders	5 (2.1)	4 (2.4)	3 (2.7)
Social circumstances	2 (0.8)	0	0
Congenital, familial and genetic disorders	2 (0.8)	2 (1.2)	2 (1.8)

Table 63: Adverse reactions reported in clinical trials [Updated analysis – LX301/LX303 Lock (September 2016) – 12-week placebo-controlled population]

System organ class	Very common	Common
Metabolism and nutrition disorders		Decreased appetite (4.3% ; 3/70)
Nervous system disorders		Headache (7.1% ; 5/70)
Gastrointestinal disorders	Abdominal pain (25.7% ; 18/70)[a]	Abdominal distension (7.1% ; 5/70), Constipation (5.7% ; 4/70), Flatulence (5.7% ; 4/70)

Hepatobiliary disorders	Gamma-glutamyltransferase increased (11.4% ; 8/70)[b]	Alanine aminotransferase increased (ALT) (2.9% ; 2/70), Aspartate aminotransferase increased (AST) (1.4% ; 1/70), Blood alkaline phosphatase increased (ALP)[c]
General disorders and administration site conditions	Fatigue (10.0% ; 7/70)	Oedema peripheral (7.1% ; 5/70), Pyrexia (8.6% ; 6/70)

[a] Abdominal pain (including upper and lower abdominal pain)
[b] Gamma-glutamyl transferase increased (including preferred terms of gamma-glutamyl transferase increased, gamma-glutamyl transferase, and liver function test abnormal / hepatic enzyme increased for which gamma-glutamyl transferase was increased).
[c] Blood alkaline phosphatase increased was only observed at the higher dose of 500 mg (6.7% ; 3/70).

Among these adverse reactions, there were 3 patients with severe abdominal pain (2 with TEAEs of abdominal pain and 1 with a TEAE of abdominal pain upper), 1 patient with severe gamma-glutamyltransferase increased and 1 patient with severe decreased appetite. All other adverse reactions were reported as mild or moderate.

Analysis of Adverse Events of special interest

Based on the observations in non-clinical studies, Phase 1 and Phase 2 studies adverse events related to hepatic enzyme abnormalities (see laboratory findings section), depression, and GI symptoms were identified as of special interest.

Gastrointestinal Adverse Events

The most frequently reported adverse event in patients receiving telotristat was abdominal pain (25.7%; 18/70) versus placebo (19.7%; 14/71). Abdominal distension was reported in 7.1% of patients (5/70) receiving telotristta ethyl 250 mg tid, versus 4.2% in the placebo group (3/71). Flatulence was seen in 5.7% of patients (4/70) and 1.4% (1/71) in the telotristat 250 mg and placebo groups, respectively (see SmPC section 4.8). Most events were mild or moderate and did not limit study treatment.

Constipation was reported in 5.7% of patients (4/70) in the telotristat ethyl 250 mg group and in 4.2% of patients (3/71) in the placebo group. Serious constipation was observed in 3 patients treated with a higher dose (500 mg) in the overall safety population (239 patients).

Phase 1 Studies

Adverse events of special interests related to GI symptoms were integrated for Phase 1 studies in 3 groups: Single-dose Studies (LX101 and LX104), Multiple-dose Studies (LX102, LX106, and LX108), and Crossover Studies (LX103, LX105, LX107, and LX109).

Overall, a total of 71 subjects experienced 117 AESIs related to GI symptoms, 37 male and 34 female. The age of these healthy volunteers ranged from 18 to 54 years. The most frequently reported events were diarrhoea (38 events in 33 subjects), nausea (35 events in 31 subjects) and abdominal pain (14 events in 14 subjects).

In single dose studies 11 subjects experience 21 events. The most frequently reported events were diarrhoea and nausea. Other events were coded as abdominal distension, abdominal pain, abdominal tenderness, eructation and vomiting. All events occurred in higher telotristat etiprate dose groups, 2 in the 500 mg tid fasted or fed group, 4 in the 1000 mg group, and 5 in the 1500 mg tid group. All events were mild or moderate in intensity. In multiple-dose studies, 20 subjects with telotristat etiprate at various doses experienced 30 events. The most frequently reported events were nausea, constipation, and abdominal pain. Other events were coded as abdominal distension, abdominal pain, constipation,

diarrhoea, flatulence, gastrointestinal pain, infrequent bowel movements, nausea, and vomiting. All events were mild or moderate in intensity. In crossover studies 31 telotristat etiprate subjects at various doses alone or in combination experienced 45 events related to study drug. All events were mild or moderate in intensity.

Phase 2 and Phase 3 Studies

In the placebo-controlled safety population, 95 patients experienced a total of 188 AESIs related to GI symptoms, 30 (42%) in placebo group, 33 (47%) in telotristat etiprate 250 mg tid, and 32 (46%) in telotristat etiprate 500 mg tid. The 188 events were coded to 18 PTs. The most frequently reported PTs were abdominal pain and nausea.

Table 64: Summary of Treatment-Emergent Adverse Events of Special Interest Related to GI Symptoms by Treatment Group for Placebo-controlled Safety Patients (Studies LX301 and LX303)

	Placebo (N=71)		LX1606 250 mg tid (N=70)		LX1606 500 mg tid (N=70)		All LX1606 (N=140)	
	ER; #	n (%)	ER; #	n (%)	ER; #	n (%)	ER; #	n (%)
TE AESI of GI symptoms	3.78; 58	30 (42.3)	3.94; 62	33 (47.1)	4.62; 68	32 (45.7)	4.27; 130	65 (46.4)
Nausea	1.04; 16	9 (12.7)	0.76; 12	9 (12.9)	1.49; 22	16 (22.9)	1.12; 34	25 (17.9)
Abdominal pain	0.98; 15	12 (16.9)	1.02; 16	13 (18.6)	0.68; 10	10 (14.3)	0.85; 26	23 (16.4)
Vomiting	0.39; 6	5 (7.0)	0.19; 3	3 (4.3)	0.61; 9	6 (8.6)	0.39; 12	9 (6.4)
Abdominal pain upper	0.20; 3	3 (4.2)	0.25; 4	3 (4.3)	0.54; 8	7 (10.0)	0.39; 12	10 (7.1)
Constipation	0.13; 2	2 (2.8)	0.32; 5	4 (5.7)	0.48; 7	5 (7.1)	0.39; 12	9 (6.4)
Flatulence	0.07; 1	1 (1.4)	0.32; 5	4 (5.7)	0.20; 3	3 (4.3)	0.26; 8	7 (5.0)
Abdominal distension	0.20; 3	3 (4.2)	0.32; 5	5 (7.1)	0.14; 2	2 (2.9)	0.23; 7	7 (5.0)
Diarrhoea	0.52; 8	8 (11.3)	0.44; 7	7 (10.0)	0.14; 2	2 (2.9)	0.30; 9	9 (6.4)
Abdominal discomfort	0.07; 1	1 (1.4)	0.00; 0	0	0.07; 1	1 (1.4)	0.03; 1	1 (0.7)
Abdominal tenderness	0.00; 0	0	0.00; 0	0	0.07; 1	1 (1.4)	0.03; 1	1 (0.7)
Anorectal discomfort	0.00; 0	0	0.00; 0	0	0.07; 1	1 (1.4)	0.03; 1	1 (0.7)
Epigastric discomfort	0.00; 0	0	0.00; 0	0	0.07; 1	1 (1.4)	0.03; 1	1 (0.7)
Gastrointestinal pain	0.00; 0	0	0.00; 0	0	0.07; 1	1 (1.4)	0.03; 1	1 (0.7)
Abdominal pain lower	0.00; 0	0	0.13; 2	2 (2.9)	0.00; 0	0	0.07; 2	2 (1.4)
Eructation	0.13; 2	2 (2.8)	0.00; 0	0	0.00; 0	0	0.00; 0	0
Frequent bowel movements	0.00; 0	0	0.06; 1	1 (1.4)	0.00; 0	0	0.03; 1	1 (0.7)
Gastrointestinal sounds abnormal	0.07; 1	1 (1.4)	0.00; 0	0	0.00; 0	0	0.00; 0	0
Non-cardiac chest pain	0.00; 0	0	0.13; 2	1 (1.4)	0.00; 0	0	0.07; 2	1 (0.7)

Source: ISS Table 4.4.9

ER= Event rate per person-years; #= number of events

The time to onset, reported for 178 events, ranged from 1 day to approximately 3 months, and there was no apparent clustering. 15 of the 188 events were considered severe or serious by the Investigators, 5 events in the placebo group, 6 in telotristat etiprate 250 mg tid, and 4 in telotristat etiprate 500 mg tid.

In the overall safety population, 160 patients experienced a total of 552 AESIs related to GI symptoms. These 552 events include the 130 events reported for the 65 patients treated with telotristat etiprate in the placebo-controlled safety population, and the 26 events reported for the 13 patients receiving active treatment in Study LX202. The 396 AESIs related to GI symptoms reported for patients with CS while they were taking Open-Label telotristat etiprate occurred in 128 patients, 16 in Study LX202, 12 in Study LX203, 71 in Study LX301, and 29 in Study LX303.

Because telotristat etiprate reduces bowel movement frequency, TEAEs coded to constipation and fecaloma were closely monitored. In the Placebo-controlled Safety analyses, 2 (3%), 4 (6%) and 5 (7%) patients in the placebo, telotristat etiprate 250 mg tid, and telotristat etiprate 500 mg tid treatment groups experienced constipation, respectively; there was no report of fecaloma; the one case of ileus was reported in the placebo group. In the overall safety analyses, 28 (12%) patients experienced constipation and 2 (1%) patients experienced fecaloma.

Three of the patients experienced constipation that was reported as SAEs and 2 fecaloma. Additionally, 1 (0.4%) patient experienced small intestinal obstruction, and 1 (0.4%) patient each experienced ileus, intestinal obstruction and subileus (the same patient as one of the patients experiencing fecaloma), which were reported as SAEs.

The incidence of constipation tended to increase with increasing dose.

Depression

Phase 1 Studies

There were no depression-related AESIs reported for any of the Phase 1 study groups.

Phase 2 and Phase 3 Studies

No AESI related to depression was identified.

A summary of the TEAEs related to depression are presented.

Table 65: Summary of Treatment-Emergent Adverse Events of Special Interest Related to Depression by Treatment Group for Placebo-controlled Safety Patients (Studies LX301 and LX303)

	Placebo (N=71)		LX1606 250 mg tid (N=70)		LX1606 500 mg tid (N=70)		All LX1606 (N=140)	
	ER; #	n (%)	ER; #	n (%)	ER; #	n (%)	ER; #	n (%)
TE AESI of depression	0.46; 7	5 (7.0)	0.32; 5*	5* (7.1)	0.54; 8	8 (11.4)	0.43; 13	13 (9.3)
Depression	0.20; 3	3 (4.2)	0.13; 2*	2* (2.9)	0.48; 7	7 (10.0)	0.30; 9	9 (6.4)
Depressed mood	0.20; 3	2 (2.8)	0.13; 2	2 (2.9)	0.07; 1	1 (1.4)	0.10; 3	3 (2.1)
Decreased interest	0.07; 1	1 (1.4)	0.06; 1	1 (1.4)	0.00; 0	0	0.03; 1	1 (0.7)

Source: ISS Table 4.4.8

ER= Event rate per person-years; #= number of events

* Including a data entry error at the study site: patient 1201-002 had a history of anxiety and experienced no depression. When 4 patients (5.7%) are included with an AESI of depression for 250 mg tid, ER is 0.25.

In the overall safety population, TEAEs are presented for depression.

Table 66: Summary of Treatment-Emergent Adverse Events of Special Interest Related to Depression for the Overall Safety Population: All Patients with CS Treated with Telotristat etiprate Doses (N=239)

	Event rate	Events	Patients n (%)
TE AESI of depression	0.28	53*	42 (17.6)
Depression	0.14	27*	25 (10.5)
Depressed mood	0.10	18	16 (6.7)
Decreased interest	0.04	8	8 (3.3)

Source: ISS Table 6.4.7

* Including a data entry error at the study site: patient 1201-002 had a history of anxiety and experienced no depression

Table 67:Summary of Treatment-Emergent Adverse Events of Special Interest Related to Depression for the Overall Safety Population (updated analysis)

	Event rate	Events	Patients n (%)
TE AESI of depression	0.33	78	55 (23.0)
Depression	0.17	40	32 (13.4)
Depressed mood	0.10	23	19 (17.9)
Decreased interest	0.05	12	10 (4.2)
Dysthymic disorder	0.01	2	2 (0.8)
Suicidal ideation	0.00	1	1 (0.4)

CNS/Neuropsychiatric Events:

The applicant has also evaluated CNS related and neuropsychiatric events other than depression. The overall results of the analysis, both for the placebo-controlled safety population and the overall safety population are shown in the following two tables:

Table 68: Summary of Neuropsychiatric Treatment-Emergent Adverse Events by Treatment Group for Placebo-Controlled Safety Patients (Studies LX301 and LX303)

Preferred Term[a]	Placebo (N=71)	Telotristat etiprate 250 mg tid (N=70)	Telotristat etiprate 500 mg tid (N=70)	Total telotristat etiprate (N=140)
Agitation	0	1 (1.4%)	0	1 (0.7%)
Nervousness	0	0	2 (2.9%)	2 (1.4%)
Restlessness	0	1 (1.4%)	0	1 (0.7%)
Cognitive disorder	1 (1.4%)	0	0	0
Memory impairment	3 (4.2%)	0	1 (1.4%)	1 (0.7%)
Confusional state	0	0	3 (4.3%)	3 (2.1%)
Hallucinations, visual	0	1 (1.4%)	0	1 (0.7%)
Sensory disturbance	0	0	1 (1.4%)	1 (0.7%)
Headache	3 (4.2%)	5 (7.1%)	5 (7.1%)	10 (7.1%)
Insomnia	2 (2.8%)	2 (2.9%)	3 (4.3%)	5 (3.6%)
Sleep disorder	0	1 (1.4%)	0	1 (0.7%)
Dizziness	5 (7.0%)	0	6 (8.6%)	6 (4.3%)
Syncope	0	0	1 (1.4%)	1 (0.7%)
Presyncope	1 (1.4%)	1 (1.4%)	0	1 (0.7%)

Source: ISS Table 4.4.1.

Table 69: Summary of Neuropsychiatric Treatment-Emergent Adverse Events for Overall Safety Population

Preferred Term	Overall (N=239)
Anxiety	11 (4.6%)
Agitation	2 (0.8%)
Irritability	1 (0.4%)
Nervousness	2 (0.8%)
Restlessness	1 (0.4%)
Cognitive disorder	2 (0.8%)
Memory impairment	2 (0.8%)
Confusional state	6 (2.5%)
Disorientation	1 (0.4%)
Emotional disorder	1 (0.4%)
Hallucinations, visual	2 (0.8%)
Sensory disturbance	2 (0.8%)
Headache	29 (12.1%)
Insomnia	14 (5.9%)
Sleep disorder	6 (2.5%)
Dizziness	21 (8.8%)
Syncope	9 (3.8%)
Presyncope	5 (2.1%)
Incoherent	1 (0.4%)

Source: ISS Table 6.4.1.2

Of the 117 events reported in the overall safety analysis only 23 were assessed as related by the Investigator, of which 3 were for anxiety, 1 each for memory impairment, confusional state, and emotional disorder, 6 for insomnia, 2 for sleep disorder, and 9 for dizziness.

Serious adverse event / deaths / other significant events

The total number of death in all clinical trials was 19.

In the placebo-controlled safety analysis, the overall incidences of TEAEs leading to death were: 3 (4.2%) patients on placebo (unrelated to treatment), 1 (1.4%) patient on telotristat etiprate 250 mg tid (unrelated to treatment) and 1 (1.4%) patient on telotristat etiprate 500 mg tid. The patient in Study LX301, randomised to telotristat etiprate 500 mg tid, died of cardiac arrest on study Day 13. A CT scan 27 days prior to randomization showed progressive disease (worsening peritoneal carcinomatosis, increased metastatic disease at lung bases and abdominal wall, and increased metastatic lymphadenopathy in bilateral inguinal & external iliac lymph nodes).

A patient originally enrolled in Study LX203, died of acute liver failure on study Day 483 after enrolling in the extension study (Study LX302). At the time of the event, he had taken telotristat etiprate for approximately 3 years and 10 months across both studies. Approximately 1 month prior to death, the patient had experienced SAEs of (increasing) diarrhoea, increased blood creatinine, and general physical health deterioration. The patient had underlying metastatic NET with extensive liver metastasis (80% replacement) and preexisting liver fibrosis possibly due to alcohol. Laboratory results near the time of death did not suggest drug induced liver injury (DILI).

In the overall safety analysis, a total of 16 patients experienced TEAEs that resulted in death (10 males, 6 females); these 16 patients included 2 patients on active treatment in the Placebo controlled Safety analysis. Fourteen of the 16 deaths were reported as not related to study drug.

Two deaths occurred during the screening period of Study LX301; neither patient received study drug.

In the updated Overall Safety analysis, a total of 21 patients experienced TEAEs that resulted in death (15 males, 6 females); these 21 patients included 2 patients on active treatment in the Placebo controlled Safety analysis.

Table 70: Summary of All Deaths in the Clinical Development of Telotristat Etiprate and Deaths During the Screening Period

Study Period	Double-blind Treatment		Open-label Extension	Screening
	Placebo	Telotristat etiprate		
Number of deaths	3	2	14	2

Table 71: Treatment-Emergent Adverse Events Leading to Death in Studies LX202, LX203, LX301, and LX303

Patient ID	Age/Sex/Race	Preferred term	Treatment at onset of AE	Study day onset of AE	Relationship to study drug
Study LX202					
redacted	redacted	Disease progression	500 mg tid	84	Not related
redacted	redacted	Diarrhoea	500 mg tid	166	Not related
Study LX203					
redacted	redacted	Acute hepatic failure	500 mg tid	1394	Possibly related
redacted	redacted	Neoplasm progression	500 mg tid	731	Not related
Study LX301					
redacted	redacted	Carcinoid tumour	Placebo	60	Not related
redacted	redacted	Dehydration	500 mg tid	163	Not related
redacted	redacted	Sepsis	Placebo	16	Not related
redacted	redacted	Disease progression	500 mg tid	254	Not related
redacted	redacted	Disease progression	Placebo	46	Not related
redacted	redacted	Multi-organ failure	500 mg tid	297	Not related
redacted	redacted	Sepsis	500 mg tid	137	Not related
redacted	redacted	Disseminated intravascular coagulation	250 mg tid	27	Not related
redacted	redacted	Cardiac arrest	500 mg tid	13	Possibly related
redacted	redacted	Gastrointestinal hemorrhage	500 mg tid	165	Not related
redacted	redacted	Carcinoid syndrome (worsening)	500 mg tid	130	Not related

Table 72: Most Frequently Reported (⩾3 patients in Overall Safety) Treatment-Emergent Serious Adverse Events for Overall and Long-Term Safety Patients (Studies LX202, LX203, LX301, and LX303, updated analysis)

	Overall telotristat etiprate doses for these analyses		
	Overall safety (N=239)	Long-term at least 24 weeks (N=170)	Long-term at least 48 weeks (N=111)
Patients with at least 1 SAE, n (%)	94 (39.3)	68 (40.0)	48 (43.2)
SAEs (Preferred term) reported in ≥3 patients in Overall safety, n (%)			
Abdominal pain	12 (5.0)	9 (5.3)	6 (5.4)
Investigation	8 (3.3)	5 (2.9)	4 (3.6)
Diarrhoea	4 (1.7)	4 (2.4)	3 (2.7)
Radiotherapy	4 (1.7)	4 (2.4)	4 (3.6)
Syncope	5 (2.1)	3 (1.8)	2 (1.8)
General physical health deterioration	4 (1.7)	4 (2.4)	3 (2.7)
Constipation	3 (1.3)	3 (1.8)	2 (1.8)
Nausea	3 (1.3)	2 (1.2)	1 (0.9)
Vomiting	4 (1.7)	3 (1.8)	2 (1.8)
Therapeutic embolization	5 (2.1)	5 (2.9)	4 (3.6)
Neoplasm progression	1 (0.4)	1 (0.6)	1 (0.9)
Tumour pain	3 (1.3)	2 (1.2)	1 (0.9)
Disease progression	5 (2.1)	2 (1.2)	2 (1.8)
Dehydration	3 (1.3)	1 (0.6)	1 (0.9)

Laboratory findings

Elevations in ALT >3 × upper limit of normal (ULN) or ALP > 2 ULN have been reported in patients receiving therapy with telotristat, most cases being reported at a higher dose (500 mg). These have not been associated with concomitant elevations in total serum bilirubin. The increases were largely reversible on dose interruption or reduction, or recovered whilst maintaining treatment at the same dose. For clinical management of elevated hepatic enzymes, see section 4.4 of the SmPC.

Hepatic Enzyme AESIs in Placebo-Controlled Safety Population

In the Placebo-controlled Safety population, a total of 28 AESIs related to hepatic enzyme abnormalities were reported by the Investigators in 18 patients, all in the active treatment groups, 10 (14%) in telotristat etiprate 250 mg tid and 8 (11%) in telotristat etiprate 500 mg tid (Table 73). Fourteen of the patients were in Study LX301 and 4 in Study LX303.

Ten of the patients were male and 8 were female, with an age range of 45 to 74 years.

The 28 events were coded to PTs of ALT increased, AST increased, blood ALP increased, blood bilirubin increased, GGT, GGT increased, hepatic enzyme increased and liver function test abnormal. The most frequently reported PT was GGT increased (11 events in 10 patients, 5 patients each in the telotristat etiprate 250 mg tid and 500 mg tid groups), followed by ALT increased (6 events in 5 patients, 2 patients [3%] in the telotristat etiprate 250 mg tid group and 3 patients [4%] in the telotristat etiprate 500 mg tid group).

Table 73: Treatment-Emergent Adverse Events of Special Interest Related to Hepatic Enzyme Abnormality by Treatment Group for Placebo-controlled Safety Patients (Studies LX301 and LX303)

	Placebo N=71	LX1606 250 mg tid N=70	LX1606 500 mg tid N=70	All LX1606 N=140
	n (%)	n (%)	n (%)	n (%)
TE AESI of liver function	0	10 (14.3)	8 (11.4)	18 (12.9)
Gamma-glutamyl transferase increased	0	5 (7.1)	5 (7.1)	10 (7.1)
Alanine aminotransferase increased	0	2 (2.9)	3 (4.3)	5 (3.6)
Blood alkaline phosphatase increased	0	0	3 (4.3)	3 (2.1)
Aspartate aminotransferase increased	0	1 (1.4)	2 (2.9)	3 (2.1)
Liver function test abnormal	0	1 (1.4)	1 (1.4)	2 (1.4)
Blood bilirubin increased	0	1 (1.4)	0	1 (0.7)
Gamma-glutamyl transferase	0	1 (1.4)	0	1 (0.7)
Hepatic enzyme increased	0	1 (1.4)	0	1 (0.7)

Source: ISS Table 4.4.7

Twenty of the 28 events were reported as possibly, probably, or definitely related to study drug (10 events each in the telotristat etiprate 250 mg tid and 500 mg tid groups).

Three of the 28 events were considered severe by the Investigators. The remaining events were mild or moderate in intensity. None of the 28 events were reported as serious. The 3 severe events occurred in 2 patients: a patient in the telotristat etiprate 250 mg tid group experienced GGT increased, another patient in the telotristat etiprate 500 mg tid group experienced ALT and AST increased; both patients were enrolled in Study LX301.

No action was taken with study drug for 22 events; 16 resolved and 6 did not resolve. The dose of the study drug was reduced for 2 events; both resolved. Study drug was interrupted for 3 events; 2 resolved and 1 did not resolve. Study drug was discontinued for one event, GGT increased; the event also led to study withdrawal and the event did not resolve.

Hepatic Enzyme AESIs in Overall Safety Population

This section is focused on the 50 AESIs related to hepatic enzymes abnormality reported for 22 patients with CS while they were taking Open-Label telotristat etiprate..

These 50 events were coded to PTs of alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminases increased. The most frequently reported PT was gammaglutamyltransferase increased (13 events in 12 patients), followed by Blood alkaline phosphatase increased (11 events in 8 patients).

One of the 50 events (transaminases increased) was reported as an SAE. One patient in Study LX301 was randomised to telotristat etiprate 250 mg tid during the 12-week DBT Period of the study and then took 500 mg tid during the OLE period. All LTs were normal at Baseline. The patient was hospitalised 28 days after starting telotristat etiprate 500 mg tid for abdominal pain and nausea and local laboratory values at hospital showed an increase in ALT greater than 10xULN, with normal bilirubin. The treating physician suspected an idiosyncratic reaction to the study drug and interrupted the treatment. Liver tests returned

to normal. Study drug was resumed 3 weeks later at a reduced dose of 250 mg tid and finally increased to 500 mg tid 15 days later. ALT increased again but less than 3 x ULN. The ALT fluctuated from normal to high, but remained <3 x ULN. The case was considered as a hepatocellular DILI (possibly related).

Haematology

Some patient level abnormalities were observed for the haematology parameters, but the changes in mean values were minimal.

Biochemistry

Laboratory data on biochemical parameters were integrated for ALT, AST, ALP, GGT, total bilirubin, creatinine clearance, creatinine, albumin, protein, glucose, cholesterol, HDL, LDL, triglycerides, calcium, phosphate, potassium, sodium, and urate.

There were no clinically significant trends in biochemical parameters with the exception of hepatic enzyme test results and lipid levels. Mean changes in serum cholesterol, HDL, LDL and triglycerides values indicate that telotristat etiprate-treated patients' lipid levels may be slightly increased.

Urine analysis

This included the measurement of urine protein only. Mean changes were usually not clinically relevant, and the shifts observed occurred in both directions without consistent patterns. There were not clinically significant trends.

Vital signs, physical findings and other observations related to safety

For all vital sign parameters (diastolic blood pressure, pulse rate, respiratory rate, systolic blood pressure, body temperature, and weight), mean values were generally stable, and mean changes from Baseline in were relatively small. For all electrocardiogram parameters (heart rate, PR duration, QRS duration, QT duration, QT interval, and QTcF), mean changes from Baseline were relatively small. A few patients in Phase 3 studies had QTc and/or QTcF values >500 msec or >60 msec increase in QTcF values while being treated with telotristat etiprate (3 patients on 500 mg tid had QTcF changes of >60 msec, and 1 on placebo, and 1 on 500 mg tid and 2 on placebo had QTcF >500 msec).

Updated analysis: data not shown.

Safety in special populations (updated analysis)

	Overall Telotristat Safety Population (N = 239) n (%)		
MedDRA Terms	**Age <65 yrs (N=134)**	**Age ≥65 - <75 yrs (N=75)**	**Age ≥ 75 yrs (N=30)**
Event Incidence [number of events]			
Total AEs	1708	1020	322
Related AEs[a]	296	176	74
Serious AEs[a]	165	78	24
Serious Related AEs – Total[a]	19	5	2

	Overall Telotristat Safety Population (N = 239) n (%)		
MedDRA Terms	**Age <65 yrs (N=134)**	**Age ≥65 - <75 yrs (N=75)**	**Age ≥ 75 yrs (N=30)**
- Fatal[a]	2	1	0
- Hospitalization/prolong existing hospitalization[b]	18	5	2
- Life-threatening[b]	0	0	0
- Disability/incapacity[b]	0	0	0
- Other (medically significant)[b]	0	0	0
Subject Incidence [number of subjects (%)]			
AE leading to permanent discontinuation of study drug	22 (16.4%)	15 (20.0%)	6 (20.0%)
SOC Psychiatric disorders	50 (37.3%)	29 (38.7%)	6 (20.0%)
SOC Nervous system disorders	49 (36.6%)	32 (42.7%)	13 (43.3%)
SOC Injury, poisoning and procedural complications	24 (17.9%)	11 (14.7%)	3 (10.0%)
SOC Cardiac disorders	19 (14.2%)	13 (17.3%)	4 (13.3%)
SOC Vascular disorders	41 (30.6%)	18 (24.0%)	10 (33.3%)
Cerebrovascular events (including PT of Haemorragic stroke)	0	1 (1.3%)	1 (3.3%)
SOC Infections and infestations	57 (42.5%)	38 (50.7%)	13 (43.3%)
SOC Respiratory, thoracic and mediastinal disorders	33 (24.6%)	21 (28.0%)	10 (33.3%)
SOC Skin and subcutaneous tissue disorders	27 (20.1%)	19 (25.3%)	13 (43.3%)
PT Anticholinergic syndrome	0	0	0
PT Quality of life decreased	0	0	0
Sum of PT malaise, orthostatic hypotension, postural hypotension, falls, loss of consciousness, blackouts, syncope, presyncope, dizziness, ataxia, fractures[c]	23 (17.2%)	16 (21.3%)	8 (26.7%)

Source: Updated ISS (April 2016 data extract) Post-hoc Table S-6.3 unless stated otherwise.
[a] Source: LX202/LX203/LX301/LX302/LX303 CSR SAE listings

[b] Source: LX202/LX203/LX301/LX302/LX303 CSR SAE narratives
[c]Fractures include the following PTs: Hand/Forearm/Femur/Ankle/Foot/Radius/Upper limb fractures.

Renal impairment

In the overall safety analysis, similar incidences of TEAEs occurred for each renal impairment subgroup for all SOCs, with the largest difference being in Investigations, where the severe renal impairment group had a higher incidence (56%) compared to those with mild (36%) and moderate (26%) impairment. However, there were only 9 patients in the severe renal impairment group.

Table 74: Summary of Patients with Treatment Emergent Adverse Events for Overall Safety Patients by Renal Impairment Category (Studies LX202, LX203, LX301, LX302 and LX303)

	Mild (CrCl 60-<90 mL/min) N=62	Moderate (CrCl 30-<60 mL/min) N=27	Severe (CrCl <30 mL/min) N=9
Patients with at least 1 TEAE[a]	61 (98.4)	27 (100.0)	9 (100.0)

a Patients treated with telotristat etiprate.
Source: ISS Post-hoc Table 10

Hepatic impairment

Patients with hepatic impairment were identified using the hepatic failure, fibrosis, cirrhosis and other liver damage-related conditions SMQ. A total of 42 patients in the Phase 2 and Phase 3 studies were identified as having hepatic disease or impairment with an exposure of 32.9 patient-years.

In the overall safety analysis, of the patients with hepatic impairment using the criteria above, 39 patients (93%) had at least 1 TEAE. This incidence is similar to that of the overal population (95%).

Safety related to drug-drug interactions and other interactions

Safety related to drug-drug interactions has not been evaluated based on data from the phase 2/3 trials, but for the phase I DDI studies only. At request, the applicant has additionally analysed the phase 2/3 data for DDIs with the concomitant intake of CNS medication, cardiovascular medication, and potentially hepatotoxic medication, which did not give clear hints for the increase of adverse events with co-administration of these compounds (data not shown).

Discontinuation due to adverse events

The following tables show the incidence of premature discontinuation due to AEs and also include temporary interruptions of the intake of the study drug as discontinuations.

Table 75: Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by System Organ Class and Treatment Group

	Placebo (N=71) n (%)	Telotristat etiprate 250 mg tid (N=70) n (%)	Telotristat etiprate 500 mg tid (N=70) n (%)	All telotristat etiprate (N=140) n (%)
Patients with at least 1 TEAE leading to discontinuation of study drug	12 (16.9)	15 (21.4)	9 (12.9)	24 (17.1)
SOC (sorted by descending incidence in all telotristat etiprate group)				
Gastrointestinal disorders	5 (7.0)	7 (10.0)	5 (7.1)	12 (8.6)
General disorders and administration site conditions	1 (1.4)	3 (4.3)	2 (2.9)	5 (3.6)
Investigations	1 (1.4)	3 (4.3)	1 (1.4)	4 (2.9)
Psychiatric disorders	0	2 (2.9)	0	2 (1.4)
Infections and infestations	1 (1.4)	2 (2.9)	0	2 (1.4)
Skin and subcutaneous tissue disorders	0	1 (1.4)	1 (1.4)	2 (1.4)
Cardiac disorders	1 (1.4)	0	1 (1.4)	1 (0.7)
Hepatobiliary disorders	0	1 (1.4)	0	1 (0.7)
Metabolism and nutrition disorders	0	1 (1.4)	0	1 (0.7)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (2.8)	1 (1.4)	0	1 (0.7)
Renal and urinary disorders	0	1 (1.4)	0	1 (0.7)
Respiratory, thoracic, and mediastinal disorders	1 (1.4)	1 (1.4)	0	1 (0.7)
Vascular disorders	1 (1.4)	1 (1.4)	0	1 (0.7)
Blood and lymphatic system disorders	1 (1.4)	0	0	0

Source: ISS Table 4.4.6.1.

Table 76: Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by Preferred Term (for >1 Patient) and Treatment Group for Placebo-controlled Safety Patients (Studies LX301 and LX303)

	Placebo (N=71) n (%)	Telotristat etiprate 250 mg tid (N=70) n (%)	Telotristat etiprate 500 mg tid (N=70) n (%)	All telotristat etiprate (N=140) n (%)
Patients with at least 1 TEAE leading to discontinuation of study drug	12 (16.9)	15 (21.4)	9 (12.9)	24 (17.1)
PT (sorted by descending incidence in all telotristat etiprate group)				
Abdominal pain	2 (2.8)	4 (5.7)	2 (2.9)	6 (4.3)
Gamma-glutamyl transferase increased	0	2 (2.9)	1 (1.4)	3 (2.1)
Abdominal pain upper	0	1 (1.4)	1 (1.4)	2 (1.4)
Constipation	0	1 (1.4)	1 (1.4)	2 (1.4)
Dyspepsia	1 (1.4)	1 (1.4)	1 (1.4)	2 (1.4)
Diarrhoea	0	2 (2.9)	0	2 (1.4)
Nausea	1 (1.4)	2 (2.9)	0	2 (1.4)
Fatigue	0	1 (1.4)	1 (1.4)	2 (1.4)

Source: ISS Table 4.4.6.1.

The following table shows AEs leading to discontinuation for the uncontrolled study phases.

Table 77: Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by Preferred Term (for >1 Patient) for Overall Safety Patients (Studies LX202, LX203, LX301, and LX303)

	Overall (N=239) n (%)
Patients with at least 1 TEAE leading to discontinuation of study drug	79 (33.1)
PT (sorted by descending incidence in overall safety)	
Abdominal pain	12 (5.0)
Nausea	8 (3.3)
Diarrhoea	5 (2.1)
Fatigue	5 (2.1)
Gamma-glutamyltransferase increased	5 (2.1)
Asthenia	4 (1.7)
Vomiting	4 (1.7)
Abdominal distension	3 (1.3)
Constipation	3 (1.3)
Disease progression	3 (1.3)
General physical health deterioration	3 (1.3)
Depression	3 (1.3)
Decreased appetite	3 (1.3)
Dehydration	3 (1.3)
Syncope	3 (1.3)
Abdominal pain upper	2 (0.8)
Dyspepsia	2 (0.8)
Haematemesis	2 (0.8)
Pyrexia	2 (0.8)
Blood alkaline phosphatase increased	2 (0.8)
Body temperature increased	2 (0.8)
Anxiety	2 (0.8)
Hallucination, visual	2 (0.8)
Carcinoid tumour of the small bowel	2 (0.8)
Haematuria	2 (0.8)
Flushing	2 (0.8)
Carcinoid syndrome	2 (0.8)
Dyspnoea	2 (0.8)

Source: ISS Table 6.4.5.
Note: Study drug discontinuation includes all TEAEs leading to temporary or permanent discontinuation of study drug or discontinuation from the study.

Post marketing experience

The applicant did not submit post marketing data as telotristat etiprate had not been approved for marketing.

2.6.1. Discussion on clinical safety

The safety of telotristat was based on the treatment of a total of 239 patients with carcinoid syndrome, 58 patients with ulcerative colitis, and 259 subjects receiving the compound in early drug development. In total, 170 CS-patients have been exposed for at least 24 weeks, and 111 have been exposed for at least 48 weeks.

While the number of patients included into the development programme reflects the low incidence and prevalence of the disease (and the orphan status of the product), the number of patients included into the safety analysis is considered to be too small to detect rare events.

The most commonly reported adverse reactions in patients treated with telotristat were abdominal pain (26%), gamma-glutamyl transferase increased (11%) and fatigue (10%). They were generally of mild or moderate intensity. The most frequently reported adverse reaction leading to discontinuation of

telotristat was abdominal pain in 7.1% of patients (5/70). Two of these ADRs (abdominal pain and increased GGT) were also the most frequent reasons for discontinuations during the trials.

In the evaluation of the double-blind data, the most common AEs occurred in the SOCs gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, nervous system disorders, metabolism and nutrition disorders, investigations, musculoskeletal and connective tissue disorders, and psychiatric disorders, whereas the most common single AEs (PT) occurred for nausea, abdominal pain, fatigue, decreased appetite, abdominal pain upper, depression, and diarrhoea.

The most frequently observed treatment related events occurring at higher frequencies in any of the active treatment groups were: Nausea, abdominal pain, constipation, fatigue, decreased appetite, GGT increased, vomiting, abdominal distension, and flatulence. Based on this evaluation, the conclusion that the compound mainly has adverse effects in the gastrointestinal tract appears to be justified.

The double-blind treatment with the compound was not associated with a higher incidence of death in the patient population included. In total 21/239 patients died during the duration of the trials reflecting the disease burden of the patients included.

The incidence of serious adverse events was generally low, and was overall lower in the active treatment groups compared to placebo and the assessment of the causative association of single SAEs was generally hampered by the overall low incidence (as a consequence of the underlying low patient numbers).

The treatment with telotristat etiprate did generally not have a relevant influence on laboratory findings from haematology or biochemistry, or on vital signs and physical findings. However, increases (compared to placebo where no increase or even a decrease was noted) of lipid levels (cholesterol, triglycerides) and of hepatic enzymes were noted during the treatment with the compound. Whereas the changes in lipid parameters are considered not clinically relevant, the increase in hepatic enzymes has also led to an increased reporting of elevated liver enzymes as TEAEs. Most of these increases were mild to moderate in magnitude, only a few had higher increases and these were partially associated with disease progression in patients with pre-existing liver metastases, and/or their treatment. Hence, hepatic enzyme increase has been included as an important identified risk in the RMP and warning in section 4.4 of the SmPC and has been described in SmPC 4.8. For the double-blind as well as the extension treatment phases, despite several cases with high elevations of transaminases and/or ALP and also single cases of relevant bilirubin increases were found, no case complying with the Hy's law criteria was detected. During the long-term extension phases, the number of patients experiencing such elevations appeared to be increased, most likely to the disease progression in patients with liver metastases.

The applicant has additionally evaluated so-called adverse events of special interest (AESIs) with regards to depression related events, neuropsychiatric events, liver injury events, and gastrointestinal events.

The two CNS-related categories were evaluated due to the theoretical potential of a compound inhibiting serotonin metabolism on mood-related and cognitive CNS processes. No clear conclusion was possible with regards to the depression related events and the neuropsychiatric events, where no clear conclusion on relatedness could be drawn. Overall, it can, however, be preliminarily concluded, especially for the low dose proposed for licensing, that adverse events with regard to mood and neuropsychiatric effects may be caused by the treatment . Therefore, depression and other depression-related events are included in the RMP as important potential risks and a warning included in section 4.4 of the SmPC.

From the separate evaluation of GI events it has been shown that the overall rate of GI associated AEs is higher in the active treatment groups than in the placebo group during the double-blind treatment period, confirming that the adverse event profile is mainly restricted to events in the GI tract.

The causation of complications of constipation, such as faecaloma and ileus remains largely unresolved due to the small numbers involved into the studies but remains a potential concern. Therefore, constipation due to decreased GI motility has been identified as an important identified risk and faecaloma and intestinal obstruction have been included as important potential risks in the RMP. A warning about constipation included in the SmPC section 4.4.

Women of childbearing potential should be advised to use adequate contraception during treatment with telotristat.

It is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Xermelo contains anhydrous lactose as an excipient. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product

Telotristat has a minor influence on the ability to drive and use machines. Fatigue may occur following administration of telotristat (see SmPC section 4.7).

There is limited clinical experience with telotristat overdose in humans. Gastro-intestinal disorders including nausea, diarrhoea, abdominal pain and vomiting have been reported in healthy subjects taking a single dose of 1,500 mg in a phase 1 study. Treatment of an overdose should include general symptomatic management.(See section 4.9)

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety database is considered limited based on the low number of patients included as well as the limited exposure. However, the data shows a relatively benign overall adverse event/adverse drug reaction profile which is mainly restricted to symptoms of the gastrointestinal tract, such as nausea, abdominal pain, constipation, abdominal distension and flatulence. These events were mostly mild to moderate in intensity. No serious adverse reactions were identified, however, the safety database is too small to make any definitive conclusions. Long term safety will be collected and evaluated in the ongoing studies LX301, LX302 and LX303.

2.7. Risk Management Plan

Safety concerns

Table 78 - Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Constipation due to decreased GI motility • Hepatic enzyme increased
Important potential risks	• Depression and other depression-related events

Summary of safety concerns	
	• Faecaloma and intestinal obstruction
Missing information	• Use in pregnancy • Use in lactation • Use in severe hepatic impairment • Use in severe renal impairment • Use in non-White patients • Long term safety

Pharmacovigilance plan

Table 79: Summary of planned additional PhV activities from RMP

Study/activity, category	Objectives	Safety concern addressed	Status	Date for submission of interim or final reports
Study 301: A Phase III, Randomised, Placebo-controlled, Parallel-group, Multicentre, Double-blind Study to Evaluate the Efficacy and Safety of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome Not Adequately Controlled by Somatostatin Analog (SSA) Therapy Category 3	Primary objective: to confirm that at least one or more dose groups of telotristat compared to placebo is effective in reducing the number of daily bowel movements from Baseline averaged over the 12-week double-blind portion of the trial in patients not adequately controlled by current SSA therapy. Includes a 36-week open-label Extension Period in which all patients received telotristat etiprate 500 mg tid.	Long term safety	Database lock 13 September 2016; CSR under preparation	Final CSR: Post approval Q4 2017
Study 302: A Multicentre, Long Term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606) Category 3	To evaluate the long term safety and tolerability of orally administered telotristat etiprate Patients received telotristat 250 mg tid and 500 mg tid.	Long term safety	Ongoing	Final CSR: Q4 2018 (estimated)
Study 303: A Phase III, Randomised, Placebo-controlled,	Primary objective: to evaluate the effect of telotristat versus placebo	Long term safety	Database lock 14 September	Final CSR: Post approval Q4

Multicentre, Double-blind, Study to Evaluate the Safety and Efficacy of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome Category 3	over the double-blind portion of the study on the incidence of TEAEs, and percent change from Baseline in 24-hour u5-HIAA levels at Week 12. Includes a 36-week open-label Extension Period in which all patients received telotristat etiprate 500 mg tid.		2016; CSR under preparation	2017

*Category 1 are imposed activities considered key to the benefit risk of the product.

Category 2 are specific obligations

Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 80: Proposal from applicant for risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Constipation due to decreased GI motility	SmPC Section 4.4: Telotristat reduces bowel movement frequency. Prescribers should monitor signs of constipation and should re-evaluate the use of telotristat and concomitant therapies if constipation develops.PIL: The PIL includes similar text (or equivalent lay terms) in 'Other medicines and Xermelo' and 'Warnings and precautions'. Patients are advised to report symptoms of constipation. SmPC Section 4.8: Constipation is listed as a common ADR. PIL: The PIL includes the same terms (or equivalent lay terms) in 'Possible side effects'.	None proposed
Hepatic enzyme increased	SmPC Section 4.4: Prescribers should monitor hepatic enzymes prior and during treatment, especially if signs suggestive of liver dysfunction occur. They should discontinue treatment if liver injury is suspected.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	PIL:The PIL includes similar text (or equivalent lay terms) in 'Warnings and precautions' and 'Possible side effects'. Patients are advised to look out for side effects suggestive of liver dysfunction. Section 4.8 ALT increased, AST increased and blood ALP increased are listed as common ADRs, and GGT increased as a very common ADR.	
Important potential risks		
Depression and other depression-related events	SmPC Section 4.4: Prescribers should advise patients to report any symptoms of depression, depressed mood and decreased interest. PIL:The PIL includes similar text (or equivalent lay terms) in 'Warnings and precautions'.	None proposed
Faecaloma and intestinal obstruction	SmPC Section 4.4: Prescribers should monitor signs of constipation and should re-evaluate the use of telotristat and concomitant therapies if constipation develops. PIL: The PIL includes similar text (or equivalent lay terms) in 'Other medicines and Xermelo' and 'Warnings and precautions'. Patients are advised to report symptoms of constipation. SmPC Section 4.8: Constipation is listed as a common ADR. PIL: The PIL includes the same terms (or equivalent lay terms) in 'Possible side effects'.	None proposed
Missing information		
Use in pregnancy	SmPC Section 4.6: Women of childbearing potential Women of childbearing potential should be advised to use adequate contraception during treatment with telotristat. Pregnancy Xermelo is not recommended during pregnancy and in women of childbearing potential not using contraception. PIL: The PIL includes similar text (or equivalent lay terms) in 'Pregnancy and breast-feeding'	None proposed
Use in lactation	SmPC Section 4.6 Patients should not breast-feed during telotristat treatment. PIL: The PIL includes similar text (or equivalent lay terms) in 'Pregnancy and breast-feeding'.	None proposed
Use in severe hepatic impairment	SmPC Section 4.2:	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Dose adjustment in patients with mild/moderate hepatic impairment may be considered according to tolerability in these patients. As no data are available in patients with severe hepatic impairment, the use of telotristat is not recommended. PIL: The PIL includes the following text in 'Warnings and precautions': Patients should talk to their physicians if they have severe liver problems.	
Use in severe renal impairment	SmPC Section 4.2: No specific study has been performed in patients with renal impairment. Patients with mild or moderate renal impairment It is advised to treat patients with mild or moderate renal impairment with caution. No specific dose recommendations are available for patients with mild or moderate renal impairment. The use of telotristat is not recommended in patients with severe renal impairment and in patients with end-stage renal disease requiring dialysis PIL: The PIL includes the following text in 'Warnings and precautions': Patients should talk to their physicians if they have kidney problems	None proposed
Use in Non-White patients	None proposed	None proposed
Long term safety	None proposed	None proposed

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s) at the moment.

There are no safety concerns that need additional risk minimisation measures. Routine pharmacovigilance measures are sufficient at the moment.

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle

with the international birth date (IBD). The IBD is 28.02.2017.The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of telotristat ethyl with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Xermelo (telotristat ethyl) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Telotristat etiprate has been developed as an adjunct to somatostatin analogue (SSA) therapy for the long-term treatment of carcinoid syndrome (CS) to improve symptom control in adult patients with metastatic neuroendocrine tumours (NETs).

CS consists of symptoms of facial flushing, diarrhoea, and episodic abdominal pain. It is caused by kinins and serotonin secreted from NETs that arise from neuroendocrine cells found in almost all organs of the body, most commonly the gastrointestinal tract. Only 30 to 40% of NETs cause clinical syndromes; ileal neuroendocrine tumours most commonly cause CS. Over 95% of patients with CS have metastatic disease. Hormones secreted by the primary tumour are metabolised by the liver and so do not cause symptoms, but symptoms may develop with liver metastases, as these release hormones that bypass the enterohepatic circulation and enter the systemic circulation.

Telotristat etiprate, which inhibits tryptophan hydroxylase (TPH), the rate limiting enzyme in the biosynthesis of serotonin, is expected to relieve CS symptoms.

3.1.2. Available therapies and unmet medical need

Radical resection of NET is the initial approach and may be curative. At later stages, cytoreductive surgery including tumour resection and radiofrequency ablation may be used in an effort to control clinical symptoms and enhance patient survival. However, most of the therapeutic options currently available for the treatment of NETs address control of symptoms.

SSAs (octreotide and lanreotide) are authorised for the control of symptoms of the condition in the Community. Both compounds are only approved for the relief of symptoms and not for their capability to regress tumour growth. In addition, ketanserin, ondansetron, methysergide, and cyproheptadine reduce effects of serotonin or act as serotonin antagonists. Methysergide maleate is approved in some countries for diarrhoea caused by CS.

There are also authorised products for the treatment of diarrhoea, abdominal cramp, and flushing.

However, there is an unmet medical need in patients with CS when tachyphylaxis on SSA therapy develops, or hepatic tumour load increases. Options are to increase the dose of long acting SSA, to use rescue short acting octreotide injections, and to use antidiarrheal therapies to try to reduce symptoms of CS.

3.1.3. Main clinical studies

The pivotal phase 3 trial, Study LX301, was a randomised, placebo-controlled, parallel-group, multicentre, double-blind study in patients with CS not adequately controlled by SSA therapy investigating oral doses of 250 mg tid and 500 mg tid of telotristat etiprate versus placebo.

Patients were required to have histopathologically confirmed, well-differentiated, metastatic NET with extent documented by CT, MRI, or radionuclide imaging, documented history of CS, and experiencing an average of ≥4 BMs/day during run-in.

The primary objective was to compare both groups of telotristat etiprate with placebo on reducing the number of BMs per day from baseline averaged over the 12-week double-blind treatment period in patients not adequately controlled by SSA therapy. The main secondary objectives were the effects of telotristat etiprate versus placebo on change in u5-HIAA levels, in the daily number of cutaneous flushing episodes, and abdominal pain.

The ITT and safety populations analysed consisted of 45 patients per group after exclusion of 1 patient in the telotristat etiprate 500 mg group who was randomised twice.

In a phase 3 study of similar design, Study LX303, a total of 76 patients were evaluated for efficacy. All patients had well-differentiated metastatic neuroendocrine tumour with CS. Most patients had fewer than 4 BM per day, and all except 9 were treated by SSA therapy.

The primary endpoint was the percent change from baseline in u5-HIAA at week 12. The mean change from baseline is daily BM averaged over 12 weeks was assessed as a secondary endpoint.

3.2. Favourable effects

The number of BMs per day was statistically significantly reduced. The primary study endpoint in trial LX301, change from baseline averaged over the 12-week double-blind treatment period in the number of BMs per day, met the predefined criteria in both telotristat etiprate groups (250 mg, 500 mg). The estimates of the treatment differences (Hodges-Lehmann) were about -0.8 BMs/day (97.5% CI: -1.256, -0.290) for telotristat etiprate 250 mg and -0.7 BMs/day (97.5% CI: -1.170, -0.223) for telotristat etiprate 500 mg from a baseline of about 5 to 6 BMs/day. Supplemental and sensitivity analyses were generally in line with these findings.

The mechanistically important biomarker urinary 5-HIAA (secondary endpoint) indicated a clear effect. The estimates of the treatment differences of telotristat etiprate versus placebo (Hodges-Lehmann) for the change from baseline in urinary 5-HIAA levels at week 12 were about -30 mg per 24 hours (97.5% CI: -56.000, -8.100) for telotristat etiprate 250 mg and about -34 (97.5% CI: -66.200, -14.600) for 500 mg.

Based on the criterion of a ≥30% reduction in number of BMs per day for ≥50% of time, durability of effect of telotristat etiprate on BMs per day in the target population has been shown, with a reduction in about 42%, 44%, and 20% of patients on telotristat etiprate 500 mg, 250 mg, and placebo, respectively.

In line with findings on change in BMs per day, patients on telotristat etiprate had a smaller proportion of days with urgency to defecate compared to placebo; mean proportions of days with urgency to defecate were about 0.60, 0.67, and 0.75 for telotristat etiprate 500 mg, 250 mg, and placebo, respectively.

In the assessment of the patient's view on the benefit of treatment on CS symptoms (exit interview substudy) interviewed patients described a high BM frequency as the most important symptom of CS. About one-third of patients in the substudy noted a reduction in BM frequency and the majority of these patients described it as meaningful.

Reductions in the frequency of mean BMs per day and in the urinary excretion of 5-HIAA were generally maintained during the open-label extension period and patients previously on placebo showed reductions similar to those on telotristat etiprate in the double-blind period.

3.3. Uncertainties and limitations about favourable effects

Post-hoc sub group analyses to evaluate the potential effect of concomitant medications (especially antidiarrhoeals and opioids) were requested to the Applicant. The concomitant medication appears to favour the treatment effect reported but the BM reduction figures do not show any large and consistent differences between users and non-users of concomitant medication. The responder analysis shows that in non-users of antidiarrhoeals there were 23% of responders in the placebo group and 36% of responders in the telotristat 250 mg group; thus only 13% of patients benefited from the treatment. Results from a pooled analysis of data from the phase III studies LX301 and LX303 are in accordance with the previously reported data, i.e. responder rates between patients who used antidiarrhoeals or opioids were in the similar extent which was reported for study LX301 in the previous response document. In patients who used antidiarrhoeals or opioids there was an absolute difference between telotristat 250 mg and placebo that was higher than in patients who did not use these concomitant medications, but a higher effect of telotristat 250 mg compared to placebo was demonstrated in both groups irrespective of the use of these concomitant medications.

Although the treatment effect is considered lower than expected, nevertheless some patients do benefit from the symptomatic treatment. Based on the subgroup analyses, no particular patient population could be ascertained that would identify responder patients vs non-responder patients to the treatment. Hence,

a statement was included in the SmPC section 4.2 that available data suggest that clinical response is usually achieved within 12 weeks of treatment and it is recommended to reassess the benefit of continued therapy in a patient not responding within this time period.

3.4. Unfavourable effects

The most frequent adverse reactions were related to the gastrointestinal tract, which affects about 50% of the treated population. Symptoms representing these unfavourable effect include abdominal pain and distension, including flatulence and constipation, which occur from about 5% (constipation), up to slightly more than 20% of the patient population (abdominal pain abdominal distension, flatulence) within three months of treatment.

Further unfavourable effects occurring at high frequency include headaches (7.1% ; 5/70)but the overall incidence of these events was not or only slightly increased by treatment with telotristat etiprate.

Abnormalities in liver enzymes (11.4% (8/70) for GGT in the 12-week placebo-controlled safety population; more than 10% in long-term, up to 5% for transaminases) were usually not symptomatic and not associated with increases in bilirubin.

3.5. Uncertainties and limitations about unfavourable effects

Due to its mechanism of action, telotristat etiprate has the potential to cause CNS effects, including effects on mood and causation of depressive symptoms. There is currently no sign that telotristat etiprate may have an effect on depressive or other neuropsychiatric symptoms. No differences in occurrence rates in comparison to placebo were identified although a couple of cases with mild depressive symptoms and single cases with even major depressive disorder could be identified. After analysis of the cases with positive de-challenge, only one case remains to be suspicious of a causal association. Based on this number a final conclusion is not possible, but the 1 case in 239 patients could indicate a relevant association which might only become evident with higher numbers of patients being exposed. Therefore, depression and other depression-related events are included in the RMP as important potential risks.

Although the overall evaluation of the liver enzyme abnormalities has shown that the changes are transient and usually not accompanied by a concomitant increase in bilirubin, no final conclusion on hepatic safety can be drawn. Although no case of severe DILI complying with Hy's law has been detected, the observed increases might indicate a potential for liver injury with the compound which might become apparent with higher number of patients exposed only. Therefore, hepatic enzyme increase has been included as an important identified risk in the RMP.

3.6. Effects Table

Table 81 - Effects Table for Xermelo as an adjunct to somatostatin analogue therapy for the long-term treatment of CS to improve symptom control in adult patients with metastatic NETs Updated safety analysis (Final lock LX301/LX303 - Data lock points: 13 and 14 September 2016 – Placebo-controlled population)

Effect	Short Description	Unit	Treatment		Control	Uncertainties/ Strength of evidence	References
Favourable Effects							
			TE 250 mg	TE 500 mg	Placebo		
Change BM frequency	Primary endpoint: Change frequency BMs/d (n) from base averaged over 12-week period vs placebo	n BMs/d Base (SD) Mean change (SD) HL est diff p 97.5 CI	45 6.085 (2.0703) -1.434 (1.3646) -0.813 <0.001 -1.256, -0.290	45 5.805 (1.9624) -1.455 (1.3098) -0.689 <0.001 -1.170, -0.223	45 5.200 (1.3500) -0.623 (0.8275)	Statistically significant; effect size small (considerably below recommendation in scientific advice); clinical relevance of effect size currently unclear	
Unfavourable Effects							
Abdominal pain (including PTs of abdominal pain upper and abdominal pain lower)	Adverse event	%	25.7% (18/70)		19.7%	Difference to placebo low, symptom of underlying disease; strong evidence	
Constipation Faecaloma	Adverse event	% n	5.7(4/70)% 2 - observed in the overall safety population (n=239) in patients treated with twice the recommended dose (500 mg tid)		4.2% (3/71) N/A	Clear difference to placebo, strong evidence, in accordance with MoA; Faecaloma only in open-label extension study	
Liver enzymes increased	Adverse events; mean values during trials;	%	GGT increased: 11.4% (8/70) – includes PTs of GGT increased, GGT and liver function test abnormal / hepatic enzyme increased for which GGT was increased)		0	Strong evidence, no uncertainty, clinical relevance unclear Occurrence of more severe liver injury unclear	

Abbreviations: vs: versus; BM: bowel movement; d: day; te: telotristat etiprate; GGT: gammaglutamyl transferase; HL: Hodges-Lehmann; base: baseline; SD: standard deviation; est: estimator; diff: difference; CI: confidence interval; p: p-value; h: hour; n: number;

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

CS refers to an array of symptoms that occurs secondary to NETs; it is a serious condition impacting daily functioning of patients.

The clinical benefit of telotristat etiprate has been demonstrated by a decrease in BM of approximately 1 BM/day, although the net effect size of BM is low. In exit interviews study participants described a high BM frequency as the most important symptom of CS which impacted their daily life. There is no clinically relevant effect of telotristat on other symptoms of CS.

The adverse event profile of the compound shows an AE profile that is overall mild and manageable and mainly affecting the gastrointestinal tract. Overall, the unfavourable GI ADRs appear to be transient and benign in nature, in their vast majority non-serious, and do not lead to a discontinuation of the treatment. Although the safety database is considered still small with few treated patients, there are currently no major concerns with the changes in liver enzymes observed as well as the potential effects on the CNS.

3.7.2. Balance of benefits and risks

A clinical benefit of telotristat etiprate in adult patients with carcinoid syndrome who are inadequately controlled by SSA therapy has been demonstrated and outweighs the safety risks which are considered mild and manageable with the recommendations and warnings in the SmPC.

3.7.3. Additional considerations on the benefit-risk balance

Further analyses of the available data together with relevant literature did not identify a subgroup of patients that might benefit most from a treatment with telotristat etiprate. Thus, the recommendation in SmPC section 4.2 has been included to inform the healthcare professional to continue treatment only in those patients who are assessed as responders after 12 weeks of treatment.

3.8. Conclusions

The overall B/R of Xermelo is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Xermelo is favourable in the following indication:

Xermelo is indicated for the treatment of carcinoid syndrome diarrhoea in combination with somatostatin analogue (SSA) therapy in adults inadequately controlled by SSA therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that telotristat is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.