STUDY PROTOCOL

A PHASE I, OPEN-LABEL STUDY TO COMPARE THE PHARMACOKINETICS OF TELOTRISTAT ETHYL AND ITS METABOLITE IN SUBJECTS WITH IMPAIRED RENAL FUNCTION TO HEALTHY SUBJECTS WITH NORMAL RENAL FUNCTION AFTER A SINGLE DOSE OF TELOTRISTAT ETIPRATE

Study Number D-FR-01017-002

Protocol Version 2.0 dated 20 December 2017

EUDRACT Number 2017-003948-20

IND Serial Number: Not applicable

Sponsor

Ipsen Pharma SAS

65 quai Georges Gorse

92100 Boulogne-Billancourt, France

Serious Adverse Event Reporting

Fax: PPD

Email: PPD

Emergency Contact

PPD, EU Qualified Person for Pharmacovigilance, Ipsen Biopharm Ltd

102 Park Drive, Milton Park, Abingdon, OX14 4RY, United Kingdom

Phone: PPD

Mobile: PPD

The person listed above is the designated by the sponsor as the first point of contact for emergency situations.

Sponsor Authorised Protocol Approver

Name, Title: PPD
Address: Ipsen Innovation, 5 avenue du Canada, 91940 Les Ulis, France
Phone: PPD
Mobile: PPD
Email: PPD

Sponsor Medical Monitor

Qualified physician designated by the sponsor who is responsible for all study-site related medical decisions (if other than investigator).

Name, Title: PPD, Oncology and Endocrinology
Address: Global Drug Development, R&D, IPSEN Biopharm,
102 Park Drive, Milton Park, Oxford, OX14 4RY, UK
Phone: PPD
Mobile: PPD
Email: PPD

Coordinating Investigator

Name, Title: Dr Atef Halabi, MD., PhD
Address: PPD
Phone: PPD
Email: PPD

Project Management and Monitoring Office

Address: Aepodia France SARL, 3 avenue du Canada, 91940 Les Ulis, France
Phone: +33 (0)1 60 92 70 90
Fax: +32 10 39 20 99

AGREEMENT – SIGNATURE PAGE

Protocol Title

A PHASE I, OPEN-LABEL STUDY TO COMPARE THE PHARMACOKINETICS OF TELOTRISTAT ETHYL AND ITS METABOLITE IN SUBJECTS WITH IMPAIRED RENAL FUNCTION TO HEALTHY SUBJECTS WITH NORMAL RENAL FUNCTION AFTER A SINGLE DOSE OF TELOTRISTAT ETIPRATE

By signing below, I hereby confirm that I have read, discussed and understood the above mentioned version of the protocol and the background information concerning the study drug. I attest that I will carry out the study according to this protocol.

I also agree that the work will be performed according to Good Clinical Practice (GCP) guidelines, the ethical principles, as referenced in Section 13, and all currently applicable laws and regulations of the country(ies) where the study will be conducted.

Investigator		**Sponsor**	
Name	_____	Name	PPD
Date	_____	Date	December 21 2017
Signature	_____	Signature	PPD

SYNOPSIS

Sponsor name	Ipsen Pharma SAS
Name of finished product	Telotristat etiprate
Name of active ingredient	Telotristat ethyl
Title of the study	A PHASE I, OPEN-LABEL STUDY TO COMPARE THE PHARMACOKINETICS OF TELOTRISTAT ETHYL AND ITS METABOLITE IN SUBJECTS WITH IMPAIRED RENAL FUNCTION TO HEALTHY SUBJECTS WITH NORMAL RENAL FUNCTION AFTER A SINGLE DOSE OF TELOTRISTAT ETIPRATE
Sponsor study number	D-FR-01017-002
EUDRACT number	2017-003948-20
IND serial number	Not applicable
Phase of development Type of study	Phase I Interventional (pharmacokinetics, safety) study
Number of planned clinical units	4
Objectives	**Primary objective** • To compare the pharmacokinetics (PK) of telotristat ethyl and its active metabolite (telotristat) following a single oral dose of 250 mg telotristat ethyl in subjects with renal impaired function versus the PK in healthy subjects with normal renal function. **Secondary objectives** • To compare the safety and tolerability of a single oral dose of 250 mg telotristat ethyl in subjects with renal impaired function versus healthy subjects with normal renal function. • To assess the effect of impaired renal function on protein binding of telotristat ethyl and its active metabolite (telotristat). • To evaluate the PK of the inactive metabolite LP-951757 following a single oral dose of 250 mg telotristat ethyl in subjects with renally impaired function and healthy subjects with normal renal function.
Study design	This study will be an open-label single dose staged study with Part B contingent upon the results of Part A. Part A will include two groups, a test group and a control group. The test group will include subjects with a GFR as low as possible i.e. < 20 mL/min, but not requiring dialysis (subjects with severely impaired renal function). If inclusion of such subjects is not possible, subjects with severely decreased renal function and a GFR between 15 and 29 ml/min (both inclusive) may be included. The test group will be compared to a control group of demographically-matched healthy subjects with normal renal function (i.e. with a GFR

	equal or above 90 mL/min). The PK and protein binding analysis of telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757 will be assessed in eight subjects with severely decreased renal function and compared to those in eight demographically-matched subjects with normal renal function (GFR ≥ 90 mL/min) following single oral dose of 250 mg telotristat ethyl. If results of Part A show a substantial effect (set as 2-fold increase in total and unbound of either the maximal plasma concentration (C_{max}) or plasma exposure (AUC) of the active metabolite (telotristat)), the PK and protein binding analysis of telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757 will also be assessed in eight subjects with a mildly (GFR between 60 and 89 mL/min, both inclusive) and eight subjects with a moderately (GFR between 30 and 59 mL/min, both inclusive) decreased renal function (Part B) following single oral dose of 250 mg telotristat ethyl. Safety and tolerability of the single oral dose of 250 mg telotristat ethyl will also be evaluated. Renal function will be classified based on estimated GFR as determined by the Modification of Diet in Renal Disease (MDRD) formula. After a maximum 28-day screening period (56 days for subjects with mildly and moderately impaired renal function), eligible subjects will begin their stay at the clinical unit on Day-1 (admission day). Subjects will receive a single oral dose of telotristat etiprate (as one tablet containing 250 mg telotristat ethyl) on Day 1. Following safety assessments, subjects will be discharged from the clinical unit either on Day 2 or Day 4. In the first option (discharge on Day 2), subjects will return to the clinical unit for outpatient visits on Day 3 and Day 4 for PK blood sampling and supply of urine collected at home. In the second option (involving a stay up to Day 4), subjects will have safety assessments performed on Day 2 and will be discharged upon completion of PK blood samplings and urine collection on Day 4. All subjects will return to the clinical unit for an end of study (EOS) visit no less than seven days after dose administration (between Day 8 and Day 15).
Planned number of subjects	A total of 16 (Part A) with up to 32 subjects (for Part A and B) subjects are planned to be included in the study: • Part A: Total of 16 subjects – eight subjects (aiming at least three males and three females) with severely impaired renal function, and eight healthy subjects demographically-matched for gender, age (± 10 years) and body mass index (BMI ± 20%). • Part B: Total of 16 subjects – eight subjects (aiming at least three males and three females) in each additional renal function group, i.e. mildly impaired renal function group and moderately impaired group.
Main eligibility criteria	Subjects included in the study will be adult subjects at least 18 years old, either with (i) impaired renal function stable for more than 3 months prior to dosing with a documented history of underlying renal insufficiency or (ii) healthy subjects with normal renal function. Subjects with impaired renal function must be on a stable medication regimen for at least one month prior to dosing, and stable and appropriately managed relative to any other chronic diseases. There will be one subject with normal renal function matched to each subject with severely impaired renal function.

Treatment: Route, strength, regimen	Telotristat etiprate will be supplied in a white-coated, debossed, oval tablet containing telotristat etiprate, equivalent to 250 mg telotristat ethyl. Telotristat etiprate will be given to subjects as a single oral 250-mg tablet dose.
Reference treatment: Route, strength, regimen	Not Applicable
Criteria for evaluation (endpoints)	**Safety** Safety and tolerability of telotristat etiprate will be assessed by a review of adverse events (AEs), changes in routine clinical laboratory parameters (haematology, blood biochemistry, coagulation, and urinalysis), supine vital signs, 12-lead electrocardiogram (ECG) measurements, and clinically significant changes noted in physical examination findings. **Pharmacokinetics** The following PK parameters will be determined using non compartmental analysis for total telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757 (where possible): Maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (t_{max}), area under the plasma concentration-time curve (AUC) from time 0 to infinity (AUC_{inf}), AUC from 0 to time t corresponding to the last quantifiable concentration ($AUC_{0\text{-}tlast}$), apparent terminal elimination half-life ($t_{1/2}$), apparent first order terminal elimination rate constant (λ_z), apparent total clearance from plasma (CL/F), apparent volume of distribution (V_z/F), unbound plasma fraction (f_u). The amount of unchanged telotristat ethyl and its active metabolite (telotristat) excreted in urine (A_e) will also be determined (where possible). The ratio active metabolite (telotristat)/telotristat ethyl and the ratio active metabolite (telotristat)/[telotristat ethyl + active metabolite (telotristat)] will also be determined for C_{max} and AUC. PK parameters may also be expressed in terms of unbound concentrations (e.g. C_{maxu}, AUC_u, CL_u/F), if applicable. **Protein binding** The percentages of drug bound and drug unbound will be determined (where possible) for telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757.
Statistical methodology	**Sample size** The sample size (eight subjects per group) is selected to provide information on PK and protein binding following a single oral dose of telotristat ethyl. Based on previous data from subjects treated with a single dose of 250 mg (53% coefficient of variation), eight subjects per group will provide 84% power to detect a 2-fold difference in AUC_{inf} between the renal impaired group and the control group with normal renal function. Safety and tolerability will be evaluated as secondary parameters. The conduct of Part B of the study is contingent upon the results of Part A.

	PK analysis Arithmetic means, coefficients of variation (CV), standard deviation (SD), median, minimum, and maximum values, and number of observations will be calculated for each renal function group. Geometric mean and geometric CV will be provided for all PK parameters except t_{max}. Median, minimum, maximum, and number of observations will be calculated for t_{max}. An analysis of variance (ANOVA) will be performed separately for the groups with a renal impaired function, on the natural log-transformed telotristat ethyl and its active metabolite (telotristat) C_{max}, $AUC_{0\text{-}tlast}$, and AUC_{inf}. The repeated-measures ANOVA, which takes into account the fact that the measures are correlated, will be performed using a linear mixed effects model, with renal function group as a fixed term. An estimate and 90% confidence interval (CI) for the geometric least squares mean (LSM) ratios for each renal impaired group (test) versus the control group with normal renal function (reference) will be provided for C_{max}, $AUC_{0\text{-}tlast}$, and AUC_{inf}. Ratios of LSM will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln transformed C_{max}, $AUC_{0\text{-}tlast}$, and AUC_{inf}. These ratios will be expressed as a percentage relative to the reference group. The 90% CIs will be obtained for the difference between the LSM (test minus reference) resulting from the analyses of the ln transformed C_{max}, $AUC_{0\text{-}tlast}$, and AUC_{inf}. The t_{max} will be analysed using nonparametric analysis (Walsh averages and appropriate quantile of the Wilcoxon signed rank test statistic). The median difference between the test and reference groups and the corresponding 90% CI for the difference will be calculated. **Safety analysis** Safety analyses will be descriptive only. No statistical test will be performed for safety analyses. Summaries will be prepared by renal function group and, as needed, by timepoint. Study drug treatment-emergent AE (TEAE) summaries will include the overall incidence (by system organ class and preferred term), events by maximum intensity, events by relationship to study drug, events leading to discontinuation of study drug, and serious AEs (SAEs). Vital signs (blood pressure and heart rate (HR)), ECG and laboratory parameters (haematology, blood biochemistry, coagulation, and urinalysis) will be summarised descriptively at each timepoint. Actual and change from baseline data will be calculated and summarised where data are available. The investigator's interpretation of 12-lead ECGs will be listed.

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RATIONALE FOR PROTOCOL VERSION 2.0

The protocol has been amended after the review by Belgium Competent Authority in the framework of the Voluntary Harmonised Procedure procedure VHP1189.
In addition, some inconsistencies in the protocol have been corrected.

All modifications are presented in the Attachment 4.

PROTOCOL HISTORY

Protocol version	Rationale for amendment
V1.0, 08NOV2017	NA – initial version
V2.0, 20DEC2017, Amendment #1	To update after the review by Belgium Competent Authority (reference member state) in the framework of the Voluntary Harmonised Procedure procedure

LIST OF DEFINITIONS AND ABBREVIATIONS

DEFINITIONS	Wording Definition
Audit	Systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analysed, and accurately reported according to the protocol, sponsor's standard operating procedures, good clinical practices, and the applicable regulatory requirement(s).
Complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all the study-related requirements, good clinical practices requirements and the applicable regulatory requirements.
End of Study	Date of the last visit or last scheduled procedure shown in the study schedule for the last active subject in the study.
Enrol / Randomise	Act of assigning a subject to a treatment. Subjects who are enroled in the study are those who have been assigned to a treatment.
Enter / Consent	Act of obtaining informed consent for participation in a clinical study from subjects deemed- or potentially eligible to participate in the clinical study. Subjects entered into a study are those who sign the informed consent document directly or through their legally acceptable representatives.
Ethics Committee	Board or committee (institutional, regional, or national) composed of medical professional and non-medical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical study are protected.
Investigator	Physician responsible for the conduct of a clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
Preliminary (interim) analysis	Any analysis intended at any time prior to the formal completion of a study.
Screen	Act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves [invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws)]. For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
Subject	Individual who is or becomes a participant in clinical research, either as a recipient of the test article or as a control. A subject may be ether a healthy human or a patient.

ABBREVIATION	Wording Definition
AADC	Aromatic L-amino acid decarboxylase
βHCG	Beta human chorionic gonadotrophin
λ_z	Terminal elimination rate constant
A_e	Amount of unchanged drug excreted in urine
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the (plasma concentration vs. time) curve
$AUC_{0\text{-tlast}}$	Area under the plasma concentration time- curve from time 0 to time t corresponding to the last quantifiable concentration
AUC_{inf}	Area under the (plasma concentration vs. time) curve from time 0 to infinity
AUC_t	Area under the serum concentration time curve from time 0 to last quantifiable timepoint
AUC_{tau}	Area under the (plasma concentration vs. time) curve during dosing interval
AUC_u	Area under the (plasma concentration vs. time) curve unbound
BMI	Body mass index
bpm	Beats per minute
CA	Competent Authority
CFR	Code of Federal Regulations (United States of America)
CI	Confidence interval
CL/F	Apparent total clearance (from plasma)
CLu/F	Apparent total clearance (from plasma) unbound
CL_R	Renal clearance
C_{max}	Observed maximal (peak) concentration
C_{maxu}	Observed maximal (peak) concentration unbound
CRF	Case report form
CRO	Contract research organisation
CRP	C-reactive protein
CRU	Clinical research unit
CS	Clinically significant
CSR	Clinical study report

ABBREVIATION	Wording Definition
CV	Coefficient of variation
DBP	Diastolic blood pressure
DRC	Data review committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ED	Early discontinuation
EMA	European Medicines Agency
EOS	End of study
EU	European Union
F	Bioavailability
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
f_u	Unbound plasma fraction
GCP	Good clinical practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GMP	Good manufacturing practices
HbA1C	Glycosylated haemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethic Committee
IMP	Investigational medicinal product
IND	Investigational new drug
INR	International normalised ratio
IRB	Independent Review Board
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LSM	Least square mean
MCH	Mean cell haemoglobin

ABBREVIATION	Wording Definition
MCHC	Mean cell haemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of diet renal disease
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
NET	Neuroendocrine tumour
PK	Pharmacokinetic(s)
PTT	Partial thromboplastin time
RBC	Red blood cell(s)
RNA	Ribonucleic acid
SAE	Serious adverse events
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SSA	Somatostatin analogue
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TEAE	Treatment emergent adverse event
TFLs	Tables, figures, and listings
t_{max}	Time to maximum plasma concentration
TPH	Tryptophan hydroxylase
USA	United States of Amercia
VS	Vital signs
V_z/F	Apparent volume of distribution
WBC	White blood cell(s)
WHO	World Health Organisation

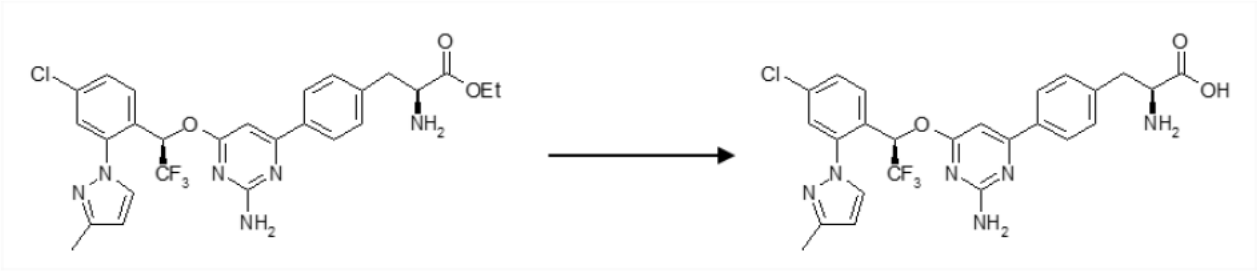
1 BACKGROUND INFORMATION

1.1 Introduction

Well-differentiated neuroendocrine tumour (NET), formerly known as carcinoid tumour, is a relatively rare tumour type that arises from cells of the neuroendocrine system (1) (2). NETs are generally slow-growing and patients may live for several years after diagnosis despite the lack of a highly effective tumour-directed therapy. Carcinoid syndrome is generally associated with metastatic NETs and occurs when well-differentiated NETs secrete large amounts of serotonin (5-HT) and other vasoactive products into the systemic circulation. Classically, symptoms associated with carcinoid syndrome include cutaneous flushing, diarrhoea, wheezing, abdominal pain, and valvular heart disease (3). It is a severe debilitating chronic condition, which highly impacts patients' daily life. Diarrhoea and flushing are prominent issues for patients (4), with diarrhoea being reported as the most debilitating symptom. As patients have distant metastases at diagnosis with inoperable disease, treatment goals are to suppress tumour growth, prolonging progression-free survival, and in these patients with carcinoid syndrome, to control the debilitating symptoms.

The standard of care for patients with carcinoid syndrome is symptom management using somatostatin analogues (SSAs), which are available in both short- and long-acting release formulations. Octreotide and lanreotide are effective for both tumour and symptoms control. However, not all patients achieve complete control of their symptoms (5) (6) (7) and the efficacy of SSAs for symptoms control can also diminish with time (8) (9) (10).

Telotristat etiprate is an orally administered small molecule. Telotristat etiprate is the hippurate salt form of an ethylester prodrug (telotristat ethyl). Telotristat etiprate in solution (and in the gastrointestinal tract) dissociates to form telotristat ethyl (free base) and hippuric acid. In vivo, telotristat ethyl is rapidly converted through the activity of carboxylesterase 1 and 2 (CES1 and CES2) to its active metabolite (telotristat) (Figure 1) primarily in the liver and intestine. Telotristat etiprate was specifically designed as a prodrug to enhance the oral bioavailability of the active metabolite (telotristat) without crossing the blood-brain barrier.



Telotristat ethyl (prodrug) Telotristat (active metabolite)

Figure 1 Hydrolysis of telotristat ethyl to telotristat

Both the prodrug (telotristat ethyl) and its active metabolite (telotristat) are inhibitors of L-tryptophan hydroxylases (TPH1 and TPH2, the rate limiting steps in 5-HT biosynthesis, Figure 2). Through inhibition of peripheral TPH1, telotristat ethyl and its active metabolite (telotristat) reduce the production of 5-HT by NET cells, thus alleviating symptoms associated with carcinoid syndrome.

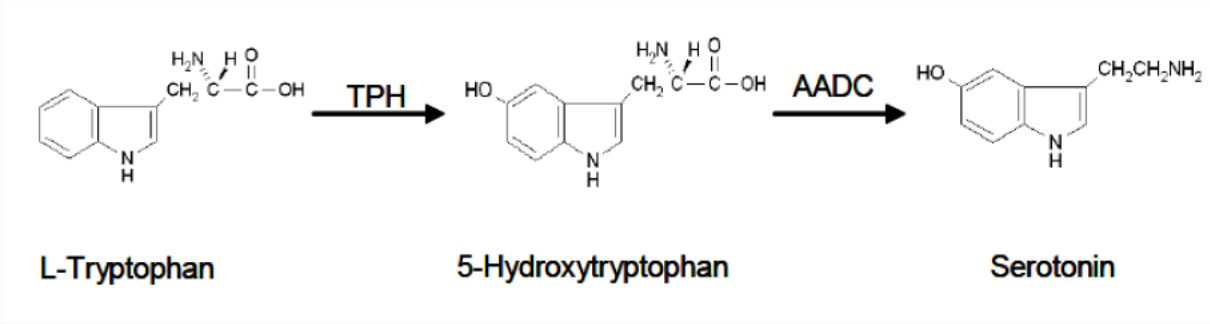


Figure 2 Synthesis of serotonin (5-HT) from L-tryptophan

The European Commission granted a marketing authorisation in September 2017 for Telotristat etiprate (Xermelo®) 250 mg film-coated tablets for the treatment of carcinoid syndrome diarrhoea in combination with SSA therapy in adults inadequately controlled by SSA therapy. Telotristat etiprate (Xermelo®) is also indicated for the treatment of carcinoid syndrome diarrhoea in combination with SSA therapy in adults inadequately controlled by SSA therapy in the USA (February 2017).

The recommended dosage of telotristat etiprate in adult patients is 250 mg three times daily.

1.2 Name and Description of the Investigational Medicinal Product

The investigational medicinal product (IMP) telotristat etiprate is an ethyl ester (hippurate salt) specifically designed as a prodrug to have enhanced oral bioavailability over its active metabolite.

Telotristat etiprate is converted to the active ingredient telotristat ethyl which undergoes hydrolysis in the liver to its active metabolite (S)-2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl) propanoic acid (telotristat).

1.3 Non-Clinical Data

The pharmacological, pharmacokinetic (PK) and toxicological properties of telotristat etiprate have been studied in relevant non-clinical systems with the objective to create the basis for a safe introduction of the compound to clinical studies.

Relevant non-clinical safety data are presented in the corresponding section of the summary of product characteristics (SmPC).

1.4 Clinical Data

Xermelo® (telotristat etiprate) has a marketing authorisation for the treatment of carcinoid syndrome diarrhoea in combination with SSA therapy in adults inadequately controlled by SSA therapy. Marketing authorisation was based on the results of clinical trials (11) (12) (13) during which over 230 subjects with carcinoid syndrome were treated with telotristat etiprate.

From a PK perspective, telotristat ethyl and its active metabolite (telotristat) have been characterised in healthy volunteers and subjects with carcinoid syndrome. Following oral administration of telotristat etiprate, telotristat ethyl is rapidly absorbed and extensively converted to its active metabolite (telotristat), with some conversion of telotristat to an inactive

metabolite LP-951757 [redacted]. Plasma concentrations of telotristat ethyl are significantly lower (approximately 100-fold lower) than those of its active metabolite (telotristat) in both healthy subjects and subjects with carcinoid syndrome at all dose levels investigated during clinical development.

Both telotristat ethyl and its active metabolite (telotristat) are highly bound to human plasma proteins (>99%). During previous investigations on clinical samples from healthy volunteers, the unbound fraction of the telotristat ethyl was below the limit of quantification and could not be assessed, while the unbound fraction of the active metabolite (telotristat) was estimated to be 0.356% (14). The estimated apparent total volume of distribution for telotristat is 296 L in healthy subjects and 231 L in subjects with carcinoid syndrome, which may be suggestive of tissue distribution.

In a [^{14}C]-telotristat etiprate mass balance study in healthy subjects (15), reported values of cumulative excretion showed that approximately 93% of the administered dose of total radioactivity was recovered in the urine and faeces by the end of sample collection (240 h), with the majority (92.78%) of the dose being recovered from faeces and <1% recovered from the urine.

Renal function has been tested in a population PK analysis, and assessed as a continuous covariate using creatinine clearance (16) (17). Plasma concentration data were obtained from four phase I studies (18) (19) (20) (21) and one phase III study (12) including its open-label extension period. A total of 3314 plasma concentration data were collected from 242 individuals (135 healthy subjects and 107 subjects) and pooled for the analysis. The covariate analysis did not identify renal function as a significant predictor of variability in the population PK model. The range of renal function was mostly normal (glomerular filtration rate [GFR] ≥90 mL/min, 68.2%) followed by mild renal impairment (GFR between 60 and 89 mL/min, both inclusive, 21.9%), moderate renal impairment (GFR between 30 and 59 mL/min, both inclusive, 7.4%) and severe renal impairment (GFR below 30 mL/min, 2.1%). Most of the subjects in phase I studies had normal renal function. In the phase III study, 37 subjects had normal renal function, 46 subjects had mild, 18 subjects had moderate, and five subjects had severe renal impairment. Figure 3 shows an overlap of distribution of the active metabolite (telotristat) exposure in subjects with carcinoid syndrome with various degrees of impaired renal function. The PK of the active metabolite (telotristat) was not shown to be influenced by creatinine clearance: subjects with normal, mild, and moderate renal impairment had comparable exposures. No conclusion could be drawn on the severely impaired group since the number of subjects was too low (n=5).

Clinical pharmacokinetics and safety are also presented in the corresponding sections of the SmPC.

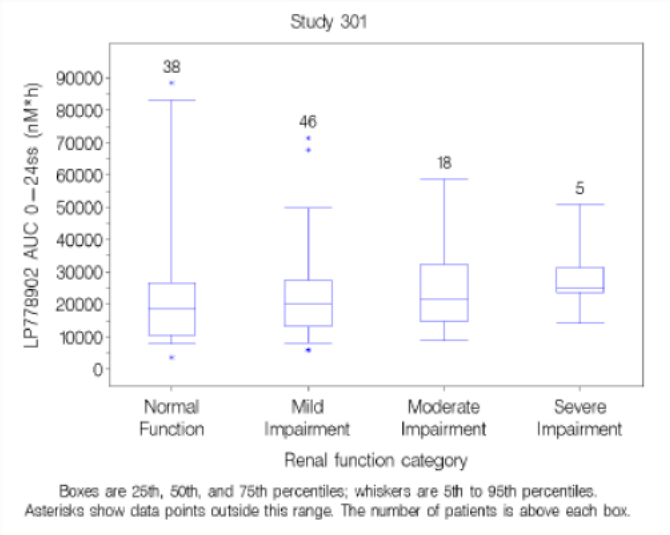


Figure 3 Relationship between telotristat exposure in patients with carcinoid syndrome and categorised PK covariate of interest (renal function)

1.5 Rationale for the Study

This study is run as a post-authorisation measure following European (EU) approval. The rationale for this study is to assess the influence of renal impairment on the PK (including protein binding analysis) of telotristat ethyl and its active metabolite (telotristat) to further allow recommendations for dose adjustment (if necessary) in patients with renal impaired function. Any effect on the overall safety profile of telotristat etiprate will also be assessed.

1.6 Dosage Selection

The recommended dosage of telotristat etiprate for the treatment of carcinoid syndrome diarrhoea in combination with SSA therapy in adults inadequately controlled by SSA therapy is a single dose telotristat etiprate equivalent to 250 mg telotristat ethyl three times daily (t.i.d.).

Based on previous studies with telotristat etiprate and available PK, safety and tolerability data in healthy volunteers, a single dose telotristat etiprate equivalent to 250 mg telotristat ethyl is considered to be safe for this population and also a reasonable dose to investigate in subjects with renal impaired function.

Data from a multiple dose study in healthy subjects (19) showed that C_{max} and AUC_{tau} values are comparable on Day 1 and Day 14 following dosing at 500 mg t.i.d.. In addition, PK has been shown to be linear between 250 mg and 500 mg. As telotristat ethyl and its active metabolite (telotristat) exhibit dose-linear and time-independent PK, and steady-state can be predicted from single dose data, a single dose study is considered as sufficient.

1.7 Population to be Studied

A total of 16 (up to 32) subjects are planned to be included in the study. This study has a staged approach such that the recruitment of subjects for Part B of the study is contingent upon the results of Part A, as follows:

- Part A: Total of 16 subjects - eight subjects (aiming for at least three males and three females) with severely impaired renal function (i.e. with GFR as low as possible i.e. < 20 mL/min) but not requiring dialysis. If inclusion of such subjects is not possible, subjects

with severely decreased renal function (GFR between 15 and 29 mL/min, both inclusive), and eight healthy subjects demographically-matched for gender, age (± 10 years) and body mass index (BMI ± 20%).

Healthy subjects will be included based on the characteristics of the severe renal impairment subject population according to a one-to-one matching procedure. For this purpose, individual recruitment of healthy subjects will start after each completed subject with severely impaired renal function.

- Part B: Total of 16 subjects - eight subjects (aiming for at least three males and three females) in each additional renal function group, i.e. mildly impaired renal function group and moderately impaired one.

The renal function of the specific population with renal impairment will be assessed based on estimated GFR as determined by the Modification of Diet in Renal Disease (MDRD) formula as presented below:

GFR (mL/min/1.73 m²) = $175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African/American})$

S_{cr}: serum creatinine (mg/dL) - GFR reported normalised to 1.73 m² body surface area

Or

GFR (mL/min/1.73 m²) = $175 \times (S_{cr} \times 0.0113)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African/American})$

S_{cr}: serum creatinine (µmol/L) - GFR reported normalised to 1.73 m² body surface area

Measured GFR using an exogenous substance are not readily available in routine clinical practice, and thus may not be an optimal endpoint for dosing recommendation. Besides, measuring GFR using exogenous marker is subject to diurnal variations of GFR and may not be more reliable than estimated GFR from prediction equations (e.g. MDRD and Cockcroft-Gault method).

Table 1 Renal function groups

Description	GFR (mL/min)
Normal renal function	≥ 90
Mildly decreased renal function	60 - < 90
Moderately decreased renal function	30 - < 60
Severely decreased renal function	< 30 not requiring dialysis
End stage renal disease	< 15 requiring dialysis

1.8 Known and Potential Risks to Human Subjects

The most commonly reported adverse reactions in subjects with carcinoid syndrome treated with telotristat etiprate were abdominal pain, gamma-glutamyl transferase increased and fatigue. They were generally of mild and moderate intensity. In the clinical program supporting EU and United States (U.S.) approvals, the most frequently reported adverse reaction leading to discontinuation of treatment was abdominal pain in 7.1% subjects.

As part of the clinical development programme, safety of telotristat etiprate was also assessed in male and female healthy subjects. In a single ascending dose study (18), telotristat etiprate

was well tolerated in healthy subjects at single doses up to 500 mg, with gastrointestinal (GI)-related adverse events (AEs) (diarrhoea, nausea, abdominal distension, constipation) reported at the 1000 mg and 1500 mg dose. There were no clinically significant laboratory or electrocardiogram (ECG) abnormalities.

This study is considered to present a limited and acceptable risk profile to the protocol specified populations.

As renal excretion is a minor elimination pathway for telotristat etiprate (less than 1% of the administered dose recovered from the urine), a staged clinical trial design is proposed for assessing the effects of impaired renal function on the PK of telotristat ethyl and its active metabolite (telotristat) (a potential design mentioned in the European Medicines Agency (EMA) (22) and Food and Drug Administration (FDA) (23) guidelines for non-renally eliminated drugs).

2 STUDY OBJECTIVES

2.1 Primary Objective

To compare the pharmacokinetics (PK) of telotristat ethyl and its active metabolite (telotristat) following a single oral dose of 250 mg telotristat ethyl in subjects with renal impaired function versus healthy subjects with normal renal function.

2.2 Secondary Objectives

To compare the safety and tolerability of a single oral dose of 250 mg telotristat ethyl in subjects with renal impaired function versus healthy subjects with normal renal function.

To assess the effect of renal impaired function on protein binding of telotristat ethyl and its active metabolite (telotristat).

To evaluate the PK of the inactive metabolite LP-951757 following a single oral dose of 250 mg telotristat ethyl in subjects with renal impaired function and healthy subjects with normal renal function.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This will be an open-label single dose staged study starting with a Part A. Part A will include two groups, a test group and a control group. The test group will include eight subjects with a GFR as low as possible (i.e. < 20 mL/min), but not requiring dialysis. If inclusion of such subjects is not possible, subjects with severely decreased renal function (i.e. with a GFR between 15 and 29 mL/min, both inclusive) may be included. The test group will be compared to a control group of eight demographically-matched healthy subjects with normal renal function (i.e. with a GFR equal or above 90 mL/min) (Table 1).

The PK and protein binding of telotristat ethyl and its active metabolite (telotristat) following administration of a single oral dose of 250 mg telotristat ethyl will be evaluated. If the results from Part A of the study show a substantial effect (set as 2-fold increase in either the maximal plasma concentration (C_{max}) or plasma exposure (AUC) of the active metabolite (telotristat), PK and protein binding analysis of telotristat ethyl and its active metabolite (telotristat) will also be assessed in Part B in eight subjects with a mildly and eight with a moderately decreased renal function (see Table 1 for renal function groups definition) following administration of a single oral dose of 250 mg telotristat ethyl. Safety and tolerability of the single oral dose of 250 mg telotristat ethyl will also be evaluated.

After a maximum 28-day screening period (56 days for subjects with mildly and moderately impaired renal function), eligible subjects will begin their stay at the clinical unit on Day-1 (admission day). Subjects will receive a single oral dose of telotristat etiprate (as one tablet containing 250 mg telotristat ethyl) on Day 1. Following safety assessments, subjects will be discharged from the clinical unit either on Day 2 or Day 4. In the first option (discharge on Day 2), subjects will return to the clinical unit for outpatient visits on Day 3 and Day 4 for PK blood sampling and supply of urine collected at home. In the second option (involving a stay up to Day 4), subjects will have safety assessments performed on Day 2 and will be discharged upon completion of PK blood samplings and urine collection on Day 4. All subjects will return to the clinical unit for an end of study (EOS) visit no less than seven days after dose administration (between Day 8 and Day 15).

Blood samples will be collected for the determination of plasma concentrations of telotristat ethyl, its active metabolite (telotristat) and its inactive metabolite LP-951757 predose and at regular timepoints up to 72 hours post-dose. Blood samples will also be collected for protein binding assessment of telotristat ethyl and its active metabolite (telotristat) at defined timepoints post-dose.

Urine samples will be collected for the determination of telotristat ethyl and its active metabolite (telotristat) concentrations on regular intervals predose and up to 72 hours post-dose.

Physical examinations will be carried out at screening, upon admission, prior to discharge and at the EOS/early withdrawal visit.

Blood pressures (diastolic and systolic), heart rate and electrocardiograms (ECGs) will be recorded at screening, upon admission, on Day 2 for subjects remaining at the clinical unit for 4 days, prior to discharge and at the EOS/early withdrawal visit.

Clinical laboratory evaluations (haematology, blood biochemistry, and urinalysis) will be performed at screening, upon admission, on Day 2 for subjects remaining confined for 4 days, prior to discharge and at the EOS/early withdrawal visit. Coagulation will be evaluated at screening, upon admission and at the EOS/early withdrawal visit.

Adverse events and concomitant medications (drug, dose, frequency, route of administration) will be monitored from the time a subject gives informed consent and throughout the study.

3.1.1 Data Review Committee

A decision to dose subjects with a mildly and moderately impaired renal function will be taken during a data review committee (DRC) meeting after completion of the eight subjects with a severely impaired renal function and eight demographically-matched subjects with normal renal function.

Further details for the operation of the DRC (data to be reviewed, minimum list of attendees) are defined in a stand-alone document (DRC charter).

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint of the study is the assessment of plasma exposure of telotristat ethyl and its active metabolite (telotristat), measured in subjects with impaired renal function and healthy control subjects with normal renal function.

3.2.2 Secondary Endpoints

Secondary endpoints will be assessed throughout the study in subjects with impaired renal function and healthy control subjects with normal renal function:

- by evaluating AEs, change from baseline in clinical laboratory test results, vital signs, ECGs measurements, and concomitant medication usage,
- by the determination of the percentages of drug bound and drug unbound determined (where possible) for telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757,
- by the determination of the amount excreted in urine (where possible) for telotristat ethyl, and its active metabolite (telotristat).

3.3 Study Duration

This study will consist of a maximum 28-day screening period (56 days for subjects with mildly and moderately impaired renal function), one day dosing, and a maximum of 15-day follow-up period. Subjects are expected to participate in this study for a minimum of 10 days and maximum of 71 days for the mild and moderate subjects.

The overall study is anticipated to last approximately 12 months.

The study will be considered to have started when the first subject has provided informed consent and will be considered to have ended after the last subject has completed the EOS/early discontinuation visit.

3.4 Randomisation and Blinding

Not applicable.

3.5 Study Treatment

3.5.1 Dosage Form and Strength

Telotristat etiprate will be supplied in a film-coated tablet formulation (Xermelo® 250 mg).

The active substance is telotristat ethyl. Each tablet of Xermelo® contains telotristat etiprate equivalent to 250 mg telotristat ethyl.

The tablets are white to off-white, film-coated and oval shaped, with 'T-E' debossed on one side and '250' debossed on the other.

3.5.2 Supplies, Packaging and Labelling

The IMP will be supplied by Beaufour Ipsen Industrie, rue Ethé Virton, 28100 Dreux, France, with lot number, expiry date, certificate of analysis and statement of compliance with Good Manufacturing Practice (GMP). Primary and Secondary packaging will be translated according to applicable regulations requirements and national laws in force.

3.5.3 Storage

The investigator, or an approved representative (e.g. pharmacist), will ensure that the IMP is stored in a secured area.

Boxes and blisters containing the tablets can be stored without any special storage conditions.

3.5.4 Preparation and Dispensing

The investigator or an approved representative (e.g. pharmacist) will ensure that the IMP is dispensed by qualified trained staff.

3.5.5 Accountability Procedures

The investigator should ensure adequate records (allocation, disposition, shipment, dispensing and returned drugs) are maintained in an IMP accountability log.

Unused IMP will be destroyed preferably locally as per site procedure or if not possible to destroy locally, returned to the sponsor for destruction.

3.5.6 Product Complaints

Sponsor collects product complaints on study drugs used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

The investigator is responsible for handling the following aspects of the product complaint process in accordance with the instructions in pharmacy manual provided for this study:

- Recording a complete description of the product complaint reported and any associated AEs,
- Using the study-specific complaint form provided for this purpose,
- Faxing or sending by e-mail the completed product complaint form within 24 hours.

If the investigator is asked to return the product for investigation after written request of the sponsor, they should return a copy of the product complaint form with the product.

3.6 Stopping Rules and Discontinuation Criteria

A specific site or a given cohort can be discontinued or the complete study terminated prematurely at any time if the sponsor judges it necessary for any reason. In that case, all scheduled procedures and assessment for subjects who are still in the study will be performed.

Some possible reasons for the closure of a study site may include:

- Failure of the investigator staff to comply with the protocol or with the good clinical practices (GCP) guidelines,
- Safety concerns,
- Inadequate subject's recruitment.

During the conduct of the study, serious adverse events (SAEs) will be reviewed as they are reported from the study site to identify safety concerns. The study may be terminated by the sponsor at any time.

In case of premature discontinuation of a site or the complete study, the sponsor will notify the impacted investigator(s) in writing, depending on the reason(s) of the discontinuation.

3.7 Source Data Recorded on the Case Report Form

The source documents must, as a minimum, contain a statement that the subject is included in a clinical study, the date that informed consent was obtained prior to participation in the study, the identity of the study, diagnosis and eligibility criteria, visit dates (with subject status), IMP administration, and any AEs and associated concomitant medications.

Definitions for source data and source documents are given below:

- Source data: All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- Source documents: Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x rays, subject files, and records kept at the pharmacy, at the laboratories and at medicotechnical departments involved in the clinical study).

No source data will be directly recorded on the case report form (CRF) during the present study.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects must fulfil all of the following criteria to be considered eligible for enrolment in the study:

All subjects

(1) Provision of written informed consent prior to any study related procedure.

(2) Men and women enroling in the study must be at least 18 years of age at the time of giving informed consent.

(3) BMI between 18 and 37 kg/m^2 (both inclusive).

(4) Body weight between 50 kg and 120 kg (both inclusive).

(5) Women of childbearing potential must agree to use an adequate double-barrier method of contraception during the study and for 30 days after discharge. Adequate methods of contraception for subject or partner include vasectomised partner (at least six months prior to dosing); intrauterine device; condom with spermicidal gel, foam, cream, film, or suppository; diaphragm with spermicidal gel, foam, cream, film, or suppository; or cervical cap with spermicidal gel, foam, cream, film, or suppository. Women of childbearing potential are defined as those who have not undergone surgical sterilisation, or those who are not considered postmenopausal. Postmenopausal is defined as absence of menstruation for at least two years. If necessary, follicle-stimulating hormone (FSH) results >50 IU/L at screening are confirmatory in the absence of a clear postmenopausal history.

(6) Men must agree to use an adequate, double barrier method of contraception during the study and for 30 days after discharge.

(7) Must be willing and able to comply with study restrictions and to remain at the clinical unit for the required period during the study and willing to return to the clinical unit for a follow-up safety evaluation (EOS visit).

Additionally, for subjects with renal impaired function

(8) Vital signs (after 5 minutes resting in a supine position) must be within the following ranges:

  (a) Systolic blood pressure, 90 to 155 mmHg

  (b) Diastolic blood pressure, 50 to 100 mmHg

  (c) Heart rate, 45 to 100 bpm.

  Subjects with vital signs outside the mentioned ranges may be eligible for the study if in the investigator's judgement the results are not clinically significant, based on the age and renal impairment status of the subject, and will not impact study conduct.

(9) Clinical diagnosis of renal impaired function that has been stable for more than 3 months prior to dosing- with a documented history of underlying renal insufficiency, and no significant change in disease status from screening to Day-1, as indicated by no worsening of clinical and/or laboratory signs of renal impairment as determined by the investigator.

(10) Renal impaired function classified as mild, moderate, or severe (see Table 1, Section 1.7).

(11) Under stable medication regimen, i.e. not starting new therapy(ies) or significant changing dosage(s) within at least 1 month prior to dosing, as determined by the investigator.

(12) Stable and appropriately managed relative to chronic diseases (e.g. diabetes, hypertension) as determined by medical history, physical examination, ECGs, and clinical laboratory tests.

(13) Abnormal laboratory values must be clinically acceptable, as judged by the investigator.

Additionally, for healthy subjects with normal renal function

(14) Vital signs (after 5 minutes resting in a supine position) must be within normal ranges. Subjects with vital signs outside the normal ranges may be eligible for the study if in the investigator's judgement the results are not clinically significant, based on the age of the subject, and will not impact study conduct.

(15) Each subject will be demographically-matched to one of the subjects with severely impaired renal function for gender, age (± 10 years), BMI (± 20%). There will be one subject with normal renal function matched to each subject with severely impaired renal function.

(16) Clinical laboratory test results must be strictly within the normal laboratory reference ranges for urea, creatinine, protein, and albumin. For other parameters, they should be deemed as not clinically significant by the investigator. A single test repeat at the discretion of the investigator is allowed during the screening period to determine eligibility.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be considered eligible for enrolment in the study.

All subjects

(1) Existence of any surgical or medical condition that, in the judgment of the investigator, might interfere with the absorption, distribution, metabolism, or excretion of telotristat etiprate (including bariatric surgery, or any other gastrointestinal surgery, excepting appendectomy and hernia repair, which are acceptable).

(2) History of any major surgery within six months or anticipated surgery prior to Day-1.

(3) Receipt of any investigational agent or study drug within 30 days or 10 half-lives, whichever is longer, prior to Day-1.

(4) Participation in a clinical trial within 30 days after a single-dose study, within 90 days after a multiple-dose study before screening or more than four times in the previous year.

(5) Donation or loss of more than 250 mL of blood or blood product within three months prior to screening.

(6) History of any serious adverse reaction or hypersensitivity to any inactive component of the drug product (i.e. microcrystalline cellulose, croscarmellose sodium [disintegrant], talc, silicon dioxide, and magnesium stearate [non-bovine]), unless the reaction is deemed irrelevant to the study by the investigator.

(7) Patients with hereditary problems of galactose intolerance (lactase deficiency or glucose-galactose malabsorption).

(8) History of any active infection within 30 days prior to Day-1, if deemed clinically significant by the investigator.

(9) Positive hepatitis panel results (including hepatitis B surface antigen and hepatitis virus C ribonucleic acid).

(10) Positive results for human immunodeficiency virus, or who has received diagnosis for acquired immunodeficiency syndrome.

(11) Positive urine screen for drugs of abuse (not including cotinine).

(12) Consumption of alcohol within 48 hours prior to Day-1 (as confirmed by alcohol breath screen) and for the duration of the confinement period.

(13) Smoking more than ten cigarettes per day or equivalent (e.g. e-vapor cigarette, pipe, cigar, chewing tobacco, nicotine patch, nicotine gum); unable or unwilling to refrain from smoking and tobacco use for two hours prior to dosing and four hours after dose administration.

(14) Consumption of caffeine- and/or xanthine-containing products (e.g. cola, coffee, tea, chocolate) on Day-1 until 24 hours postdose.

(15) Consumption of grapefruit, Seville oranges, and grapefruit- or Seville orange-containing products within 72 hours prior to Day-1 and for the duration of the confinement period.

(16) Use of any medication (prescription or over-the-counter), Chinese herbal medications or herbal tea, energy drinks, herbal products (e.g. St. John's wort, garlic), or supplements/supra therapeutic doses of vitamins within 14 days prior to Day-1 and up to Day 4 after dosing, apart from those approved by the investigator.

(17) Need for special dietary restrictions, unless restrictions are approved by the investigator.

(18) Women who are breastfeeding or are planning to become pregnant during the study.

(19) Positive pregnancy test (women only).

(20) Inability or difficulty swallowing tablets.

(21) Poor vein access as defined by the investigator (or designee).

(22) Unable or unwilling to cooperate with the investigator for any reason.

(23) Sponsor employee or clinical unit personnel directly affiliated with the study, and their immediate relatives (defined as a spouse, parent, child or sibling, whether biological or legally adopted).

Additionally, for renal impaired subjects

(24) Clinically significant physical (e.g. oedema in heavy subjects with renal impaired function), laboratory, or ECG findings (apart from those parameters which are related to impaired renal function or underlying disease e.g. diabetes, hypertension) that, in the opinion of the investigator, may interfere with any aspect of the study conduct or interpretation of the results.

(25) Glycated haemoglobin A1c $\geq$ 9%.

(26) Change in any clinical laboratory value from screening to Day -1 that is considered by the investigator to be clinically significant.

(27) Subjects with a life expectancy less than 3 months.

Additionally, for healthy subjects with normal renal function

(28) Clinically significant illness or disease including cardiac, pulmonary, hepato-biliary, gastrointestinal, or endocrinology, or cancer within the last 5 years (except localised or in situ non-melanoma skin cancer), as determined by medical history, physical examination, laboratory tests, and 12-lead ECGs.

(29) Clinically significant physical, laboratory, or ECG findings that, in the opinion of the investigator, may interfere with any aspect of the study conduct or interpretation of the results.

(30) History of renal disease.

(31) History of alcohol or drug abuse within 2 years prior to screening.

4.3 Withdrawal of Subjects

In accordance with the declaration of Helsinki and the applicable country's acceptance, each subject is free to withdraw from the study at any time, for any reason (e.g. lost to follow-up, withdrawal of consent, AE).

The investigator can withdraw a subject from the study at any time for any reason (e.g. protocol deviation, noncompliance with the protocol conditions, lack of cooperation, in the event of concurrent illness, AE, or other reasons concerning the health or well-being of the subject).

The reason for and date of withdrawal from the study must be recorded in the CRF.

If withdrawal is based on subject's decision every attempt will be made to determine:

- The reason for withdrawal,
- Whether the subject also decides to withdraw his consent for the sponsor to collect and use the data collected up to the withdrawal point.

Data collected prior to subject withdrawal may be kept in study records and shared with for further analyses unless the subject formally specifies his decision to withdraw consent for using data already collected.

If the reason for withdrawal is an AE or a clinically significant laboratory test abnormality, monitoring will continue until the event has resolved or stabilised, until the subject is referred to the care of a local health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made. The specific AE(s) or test result(s) must be recorded in the CRF.

Should a subject drop out or be withdrawn from the study after study drug administration and before normal study completion, all efforts will be made to complete the follow-up end-of-study assessments and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made whenever possible.

Any subject who drops out or is discontinued from the study before normal study completion may be replaced at the discretion of the sponsor. Replacement subjects will receive the same schedule and treatment as the subject they replace.

All cases of discontinuation will be discussed between the investigator and the sponsor.

5 STUDY CONDUCT

5.1 Study Schedule of Assessments

The schedule of procedures and assessments during the study is summarised and presented in Section 18.1.

The total volume of blood drawn for each subject and all evaluations throughout this study is detailed and presented in Section 18.2.

5.2 Study Visits and Procedures

5.2.1 Informed Consent

After a subject has received explanations and responses to his potential questions about the study by the investigator (or designee) and has been given reasonable time to think about it, a signed and dated informed consent form will be obtained prior to any study procedures.

5.2.2 Screening

After informed consent is obtained, screened subjects will be allocated a study-specific subject number which must comply with formatting specifications provided by the sponsor.

All screened subjects must be identifiable throughout the study. The investigator will maintain a list of all subjects screened with subject numbers and names to enable records to be found at a later date if required. Records up to the time of premature termination or normal study completion should be completed. In the event that a subject is screen failure or does not receive study treatment, the primary reason will be recorded.

The subjects with severely impaired renal function and the healthy subjects will attend the clinical unit for an outpatient visit to enter the screening period within 28 days prior to dosing on Day 1.

Once four subjects with severely impaired renal function and the four matching healthy subjects will be dosed, screening of reserve subjects with mildly and moderately impaired renal function may be initiated. The screening period will be extended to 56 days for these two groups. Screened subjects with mildly and moderately impaired renal function will however not be dosed before decision by the DRC and completion of the eight subjects with severely impaired renal function and the eight healthy subjects with normal renal function.

During the screening visit, screening tests and assessments will be performed to check compliance with inclusion/exclusion criteria and study requirements in order to confirm subjects' eligibility prior to enrolment.

The screening procedures detailed in Section 18.1 will be performed during outpatient visits.

Detailed clinical laboratory tests are listed in Section 18.3.

Subjects will not be allowed to be screened more than once, except reserve subjects who might be re-screened only once.

5.2.3 Admission at the Clinical Unit

Subjects will be admitted at the clinical unit on Day-1 of the study (start of the confinement period at the clinical unit).

Upon admission, compliance with inclusion/exclusion criteria will be confirmed, before assessment and collection of baseline parameters as listed in Section 18.1 and detailed in Section 18.3 for clinical laboratory parameters.

5.2.4 Dosing and Follow-up after Dosing

Subjects will be dosed on Day 1 in the morning.

They will then be followed postdose for safety assessments and sampled for PK evaluation (blood and urine), as presented in the study schedule of assessments Section 18.1. A detailed list of clinical laboratory test is also presented in Section 18.3.

In accordance with the investigator decision, subjects will have the option either to stay at the clinical unit up to Day 4 postdose or be discharged on Day 2 postdose. In this latter case, subjects will be requested to come back to the clinical unit for outpatient visits on Day 3 and Day 4 for blood sampling and supply of urines collected at home.

Subjects staying at the clinical unit up to Day 4, will be examined on Day 2 as listed in the study schedule of assessments Section 18.1. The list of expected clinical laboratory tests is detailed in Section 18.3.

5.2.5 Discharge

Discharge may happen on Day 2 or Day 4. The safety procedures to be conducted before discharge are detailed in the study schedule of assessment Section 18.1. The list of expected clinical laboratory tests is detailed in Section 18.3.

5.2.6 Early Discontinuation or End of Study Visit

Subjects will be discontinued from the study after completion of an EOS visit for follow-up safety assessments, which will happen between Day 8 to Day 15 after dosing, or earlier in case of early discontinuation.

Subjects who participate in the study in compliance with the protocol for at least eight days following study drug administration will be considered to have completed the study.

For subjects who complete the study, or for those who withdraw prematurely from the study, final safety procedures are listed in Section 18.1. Detailed clinical laboratory tests are also provided Section 18.3.

5.3 Lifestyle Restrictions

Besides restrictions already presented in the exclusion criteria, subjects will be requested to avoid the following from 48 hours prior to Day -1 and until discharge from the study or early discontinuation:

- Strenuous physical activity,
- Poppy-seeds consumption.

5.4 Priority Order on Study Procedures

When several assessments have to be performed at the same timepoint, they must be done in the following order:

- Blood samples for PK assessments,
- Blood samples for protein binding,
- Vital signs,
- 12 lead-ECG,
- Clinical laboratory samples.

6 TREATMENT OF SUBJECTS

6.1 Study Drug

Study drug administration will occur under medical supervision.

A single dose of 250 mg telotristat ethyl will be given under fed conditions (i.e. between 15 minutes before and 1 hour after the meal or snack).

6.2 Concomitant Medications

Unless otherwise specified (i.e. in the inclusion/exclusion criteria), concomitant medications are to be avoided during the study unless required to treat an AE or an ongoing medical problem.

Subjects with renal impaired function must be stable (dosage, regimen) as defined in the inclusion criteria. Any change in concomitant medication use, whether drug, dose, frequency or route, will be documented.

Any morning dose of H_2 receptor antagonists, proton pump inhibitors, or any known carboxyesterase inhibitor intake will be postponed to 4 hours postdose.

Any prior or concomitant medication given to a subject 30 days prior to dosing and during the study will be indicated in the CRF. Dose and trade name will be indicated.

6.3 Subject Compliance Monitoring

The investigator will be responsible for monitoring subject compliance.

Monitoring procedures will be described in a stand-alone document.

The investigator is responsible for the validity of all data collected at the site.

The sponsor is responsible for monitoring these data to verify that the rights and well-being of subjects are protected, study data are accurate (complete and verifiable to source data), and that the study is conducted in compliance with the protocol, GCP, and regulatory requirements.

Sponsor assigned study monitor will conduct regular site visits. The investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the CRF, and assist with the monitor's activities, if requested.

Adequate time and space for monitoring visits should be made available by the investigator.

The CRF is expected to be completed an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The study monitor will use functions of the electronic data capture (EDC) system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a subject name is revealed on a document required by the sponsor (e.g. laboratory print outs) the name must be blacked out permanently by the site personnel, leaving the date of birth visible, and annotated with the subject number as identification.

7 SAFETY ASSESSMENTS

The following safety parameters will be collected and reviewed during the study at specific timepoints as described in the study schedule of assessments in Section 18.1.

- Adverse events,
- Concomitant medications,
- Medical and surgical history,
- Physical examination (including height, body weight, body temperature),
- Vital signs (including pulse, and diastolic and systolic blood pressures),
- 12-lead ECG,
- Clinical laboratory tests including haematology, blood biochemistry, coagulation and urinalysis.

Further routine medical assessments or any additional safety procedures may be performed during the study, if warranted and agreed upon between the sponsor and the investigator, or when clinically indicated.

The investigator will be responsible for a clinical assessment of the study participants during the whole participation of the subjects in the study, from informed consent up to discharge from the study, and for setting up of a discharge plan if needed.

Every effort should be made to ensure that all safety evaluations are completed by the same individual who made the initial baseline determination.

The sponsor global patient safety physician will monitor safety data throughout the course of the study.

Any clinically significant finding that result in a diagnosis should be recorded as an AE from the time informed consent is given.

7.1 Adverse Events

Adverse events will be monitored from the time that a subject gives informed consent and throughout the study, and will be elicited by direct, nonleading questioning or by spontaneous reports.

7.1.1 Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition, whether or not considered causally related to the study drug. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, ECG).

An AE can include an undesirable medical condition occurring at any time, even if no study drug has been administered.

This definition includes events occurring from the time of the subject giving informed consent until the EOS/Early Discontinuation (ED).

7.1.2 Adverse Events Categorisation, Recording, and Follow-up

For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. study drug administration, study procedure or other illness). The investigator is required to assess causality and record that assessment in the CRF.

Adverse events will be classified by the investigator as mild, moderate or severe according to the following criteria:

- **Mild:** Symptoms do not alter the subject's normal functioning,
- **Moderate:** Symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the subject,
- **Severe:** Symptoms definitely hazardous to well-being, significant impairment of function or incapacitation.

The relationship of an AE to IMP administration will be classified by the investigator according to the following:

- **Related**: Reports including good reasons and sufficient information (e.g. plausible time sequence, dose-response relationship, pharmacology) to assume a causal relationship with study drug administration in the sense that it is plausible, conceivable or likely,
- **Not related**: Reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with IMP administration.

7.1.2.1 Assessment of Expectedness

The expectedness of an AE shall be determined by the sponsor according to the Summary of Product Characteristics (SmPC) in Europe (Marketing authorisation number EU/1/17/1224/001 and EU/1/17/1224/002).

7.1.2.2 Follow-Up of Adverse Events

Any AEs already recorded and designated as "continuing" should be reviewed at each subsequent assessment.

If an AE is still present at the end of the study, reasonable follow-up clinical monitoring should be managed by the investigator or any appropriate physician until the event or its sequelae resolves or stabilises at an acceptable level, as judged by the investigator. The frequency of follow-up evaluation is left to the investigator's discretion.

7.1.2.3 Reporting of Adverse Events

Any AE considered related to study drug administration that the investigator becomes aware of after completion of the EoS/ED visit must be reported to the sponsor and will be recorded in the corresponding database, adverse events in the clinical database, serious adverse events in the safety database.

7.1.3 Serious Adverse Event Assessment and Reporting to Sponsor

The investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets criteria for classification as a Serious AE (SAE) requiring immediate notification to the global patient safety department of the sponsor.

An SAE is any AE that:

- Results in death,
- Is life-threatening, that is any event that places the subject at immediate risk of death from the event as it occurs. It does not include an event that, had it occurred in a more severe form, might have caused death,
- Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons,

- Hospitalisation is defined as any in-patient admission (even if less than 24 hours). For chronic or long term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit,
- Prolongation of hospitalisation is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the investigator or treating physician. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the sponsor,
- Preplanned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above,

- Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions,
- Results in congenital anomaly/birth defect in the offspring of a subject who received the study drug,
- Is an important medical event that may not result in death, be life-threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

All SAEs, regardless of treatment group or suspected relationship to study drug, must be reported immediately (**within 24 hours** of the investigator's knowledge of the event) using the fax number or the e-mail address specified on the front page of the current document, up to 30 days after last administration.

Any appropriate means of notification may be used. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.

The following information is the minimum that must be provided to the sponsor:

- Study number,
- CRU/Investigational site identification,
- Subject number,
- AE,
- Investigator's name and contact details.

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment if it was not provided with the initial report.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

7.1.4 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the approved SmPC in Europe (Marketing authorisation number EU/1/17/1224/001 and EU/1/17/1224/002) and that the investigator identifies as related to the study drug or study procedure.

7.1.5 Pregnancy

Beta-human chorionic gonadotrophin (βHCG) will be assessed in all women as specified in the schedule of assessments Section 18.1.

Information regarding pregnancies occurring during the study up to 30 days after discharge of the study must be collected and reported to the sponsor as an SAE. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy.

The investigator must instruct all women to inform him immediately should they become pregnant. The investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy.

Investigators must instruct all men to inform them immediately should his sexual partner become pregnant during the study.

If the investigator becomes aware of a pregnancy occurring in the partner of a subject participating in the study, this should be reported to the sponsor. After the partner has given signed written consent, the investigator should counsel the woman, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject's partner should continue until conclusion of the pregnancy, which may involve follow-up after the subject's involvement in the study has ended.

7.1.6 Deaths

All AEs resulting in death either during the study period or within 30 days after the last dose must be reported as a SAE.

The convention for recording death is as follows:

- AE term: Lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction),
- Outcome: Fatal.

The only exception is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the AE term may be "death" or "sudden death".

7.1.7 Reporting to Competent Authorities, IECs/IRBs and other Investigators

The sponsor will ensure that processes are in place for submission of reports of SUSARs occurring during the study to the Competent Authorities (CAs), Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) and other investigators or clinicians who may be administering the study drug.

Reporting will be done in accordance with the applicable regulatory requirements.

The sponsor must report all SUSARs to European Medicines Agency's (EMA) EudraVigilance database within 15 days. Fatal and life-threatening SUSARs should be reported within seven calendar days, with another eight days for completion of the report.

The sponsor can prepare additional reports for other authorities (e.g. FDA).

7.2 Specific Safety Assessments

The investigator is responsible to monitor subjects' safety at any time during the study.

For each assessment performed, the investigator must document his review of the result(s) in the source document(s). In case of abnormal result or value(s) falling outside of predefined normal ranges, the investigator should specify whether the finding is considered as "clinically significant" (CS) or "not clinically significant" (NCS).

Any finding, whether judged CS or NCS may lead to retest at the discretion of the investigator.

7.2.1 Physical examinations

Physical examinations (including height, body weight and body temperature) will be conducted as presented in the schedule of assessments in Section 18.1.

Any changes from baseline in physical examination findings judged to be clinically significant by the investigator will be recorded as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

7.2.2 Vital signs

Vital signs (VS), including systolic and diastolic blood pressure (SBP and DBP), heart rate , will be assessed as presented in the schedule of assessments in Section 18.1.

Assessments of SBP, DBP and heart rate will be performed with an automated device so that measurements are independent of the observer. These parameters will be recorded after at least five minutes rest in supine position.

7.2.3 Electrocardiograms

Twelve-lead computerised standard ECGs, with paper printout, will be obtained while subject is in resting supine position for at least five minutes and until four regular consecutive complexes are available, at timepoints presented in the schedule of assessments in Section 18.1.

For each timepoint, computerised standard ECGs will be recorded so that the following parameter can be automatically calculated and reported on the ECG paper printout:

- Sinus rhythm,
- RR interval duration or heart rate,
- PR interval duration,
- QRS interval duration,
- QT interval duration,
- QT interval corrected by the Fridericia's methodology.

Automated ECG interval data will be interpreted by a qualified physician at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, for immediate subject management. The qualified physician will document his review and interpretation (including evaluation of clinical significance in case of abnormality) on every ECG printout.

The paper printouts will be kept in the source documents at site. Only the interpretation and abnormalities will be reported in the CRF for integration with other clinical study data. These paper ECGs may be subject to further review, if appropriate.

Clinically significant changes, in the judgement of the investigator, in the abovementioned parameters will be recorded as AEs.

7.2.4 Clinical laboratory tests

Blood and urine samples collection will be performed for standard clinical laboratory tests, including biochemistry, haematology, coagulation and urinalysis panels, as well as specific tests such as urine drug screening, breath ethanol tests and pregnancy tests for women of childbearing potential, at timepoints indicated in the schedule of assessments in Section 18.1.

Full details related to the samples processing, labelling, storage, shipment and destruction procedures will be documented in a stand-alone document (i.e. laboratory manual).

The results of laboratory tests performed during the screening phase including Day-1 must be obtained before dosing on Day 1.

The investigator will review each safety laboratory test results, document the review, and record any clinically significant changes as AEs.

All clinically significant out of normal range laboratory tests occurring during the study may be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the investigator or until the abnormality is explained by an appropriate diagnosis that do not require further follow-up.

7.2.4.1 Blood Analyses

Parameters to be assessed are listed in Section 18.3.

7.2.4.2 Urinalysis

Freshly voided urine samples (at least 10 mL) will be collected to perform a dipstick assessment of the parameters listed in Section 18.3. In case of abnormal result on the dipstick, a confirmatory analysis or additional assessments might be requested to the local laboratory, at the discretion of the investigator.

Microscopy will be performed, if indicated, but results will not be collected in the CRF. If in the opinion of the investigator there are any clinically significant abnormalities in microscopy, they will be recorded as an AE in the CRF.

7.2.4.3 Pregnancy Test

Beta-human chorionic gonadotrophin (βHCG) will be assessed in all female subjects as specified in the schedule of assessments in section 18. It may be repeated at any time during the study according to investigator's judgement.

7.2.4.4 Drug of Abuse / Alcohol testing

Urine drug screen and breath alcohol testing will be performed as specified in section 18 and at any time at the discretion of the investigator.

8 PHARMACOKINETIC ASSESSMENTS

Detailed procedures for the collection, processing, labelling, storage, shipment and destruction of the samples will be provided in stand-alone documents (laboratory manual, PK sample management plan).

Pharmacokinetic blood samples will be collected predose (time 0) and up to 72 hours postdose. Sampling timepoints are presented in the study schedule of assessments in Section 18.1.

Urine samples will be collected predose , and up to 72 hours postdose. Collection intervals are presented in the study schedule of assessment in Section 18.1.

Plasma and urine concentrations of telotristat ethyl and its active metabolite (telotristat) will be determined by validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods.

The following PK parameters for total telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757, will be determined (where possible):

- C_{max} Maximum plasma concentration
- AUC_{inf} Area under the concentration-time curve (AUC) from 0 to infinity
- $AUC_{0\text{-}tlast}$ AUC from 0 to the last quantifiable concentration
- t_{max} Time to maximum plasma concentration
- $t_{1/2}$ Apparent terminal elimination half life
- λ_z Apparent first order terminal elimination rate constant
- CL/F Apparent total clearance from plasma
- V_z/F Apparent volume of distribution
- f_u Unbound plasma fraction

The amount of unchanged telotristat ethyl and its active metabolite (telotristat) excreted in urine (A_e) will also be determined (where possible).

The ratio active metabolite (telotristat)/telotristat ethyl and the ratio active metabolite (telotristat)/[telotristat ethyl + active metabolite (telotristat)] will also be determined for C_{max} and AUC.

The mean fraction f_u will be used to derive the following PK parameters for unbound telotristat ethyl and its active metabolite (telotristat):

- C_{max} Maximum plasma concentration
- AUC_{inf} Area under the concentration-time curve (AUC) from 0 to infinity
- $AUC_{0\text{-}tlast}$ AUC from 0 to the last quantifiable concentration
- CL/F Apparent total clearance from plasma
- V_z/F Apparent volume of distribution

Protein binding

Blood samples will be collected for protein binding of telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757 at various timepoints postdose. Sampling timepoints for protein binding assessment are presented in the study schedule of assessments in Section 18.1.

Plasma protein binding will be assessed using equilibrium dialysis followed by LC-MS/MS for determination of unbound drug concentrations.

The parameter f_u unbound plasma fraction will be determined (where possible) for telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757. PK parameters may also be expressed in terms of unbound concentrations (e.g. C_{maxu}, AUC_u, CL_u/F), if applicable.

9 PHARMACODYNAMIC/EFFICACY ASSESSMENTS

Not applicable.

10 EXPLORATORY ASSESSMENTS

Not applicable.

11 STATISTICAL ANALYSES

11.1 Analyses Populations

The following populations will be used for statistical analyses:

- Screened population: All subjects screened (i.e. who signed the informed consent),
- Safety population: All subjects who received the single oral dose of study drug,
- Pharmacokinetics valid population: All subjects who received the single oral dose and have no major protocol deviations affecting the PK variables and for whom the renal function group is assessable and who have a sufficient number of plasma concentrations to estimate the main PK parameters.

11.2 Sample Size Calculation

No prospective calculations of statistical power are made. The sample size (eight subjects per group) is selected to provide information on PK following single oral dose of telotristat etiprate. Safety and tolerability will be evaluated as secondary parameters.

These number of subjects per group are mentioned in the FDA and EMA guidelines. Based on previous data from subjects treated with a single dose of 250 mg (53% coefficient of variation), eight subjects per group will provide 84% power to detect a 2-fold difference in AUC_{inf} between the renal impaired group and the control group with normal renal function.

Subjects who withdraw from the study or do not complete the study may be replaced as deemed necessary after agreement between the sponsor or its representative and investigator.

11.3 Significance Testing and Estimations

A 90% confidence interval (CI) will be calculated for the geometric least square mean ratios from analysis of variance (ANOVA) on the log transformed C_{max}, AUC_{inf} and $AUC_{0\text{-}tlast}$ to illustrate the difference between renal impaired group versus the control group with normal renal function.

Moreover, 90% CI of the median difference for t_{max} will be produced.

The statistical analysis of safety is only descriptive therefore no formal statistical significance testing will be performed.

11.4 Statistical Methods

Statistical analyses will be performed by an external contract research organisation (CRO), managed by the sponsor's biometry department.

A statistical analysis plan (SAP) will describe the planned statistical analysis in detail. Tables, figures, and listings (TFLs) templates will be developed as a separate document.

An overview of the main analysis strategy is provided in the following sections.

Any deviation from the original SAP will be described and justified in the final report.

11.4.1 Demographic Characteristics

Descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency counts of demographic (age, height, weight and body mass index) will be presented overall for the safety population.

Baseline data (medical history, concomitant disease (predose AEs and ongoing medical history, prior medications and therapies, baseline symptoms, etc) will be presented by renal function group and overall for the safety population.

11.4.2 Subject Disposition and Withdrawals

The numbers and percentages of subjects screened and included in each of the PK and safety populations will be tabulated. The reasons for subject exclusions from PK populations will also be tabulated. Primary reasons for discontinuation of study treatment will be tabulated.

11.4.3 Safety Evaluation

Summaries will be presented by renal function group and, as needed, by timepoint.

All AEs will be coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Study drug treatment-emergent AE (TEAE) summaries will include the overall incidence (by system organ class and preferred term), events by maximum intensity, events by relationship to study drug, events leading to discontinuation of study drug, and SAEs.

Physical examination findings, vital signs, ECG recordings and clinical laboratory parameters (biochemistry, haematology, coagulation and urinalysis) will be summarised descriptively at each timepoint. Actual and change from baseline data will be calculated and summarised where data are available. The investigator's interpretation of 12-lead ECGs will be listed. In addition, a listing will be presented of all values for a subject with at least a clinically significant abnormal laboratory value.

Concomitant medications will be coded by using the latest version of the World Health Organisation (WHO) drug dictionary and will be summarised by renal function group and by overall with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

11.4.4 Pharmacokinetic Evaluation

Arithmetic means, coefficients of variation (CV), standard deviation (SD), median, minimum and maximum values, and number of observations will be calculated for each renal function group. Geometric mean and geometric CV will be provided for all PK parameters except t_{max}. Median, minimum, maximum, and number of observations will be calculated for t_{max}.

An analysis of variance (ANOVA) will be performed separately for the groups with a renal impaired function, on the natural log-transformed telotristat ethyl and the active metabolite (telotristat) C_{max}, $AUC_{0\text{-}tlast}$, and AUC_{inf}. The repeated-measures ANOVA, which takes into account the fact that the measures are correlated, will be performed using a linear mixed effects model, with renal function group as a fixed term. An estimate and 90% CI for the geometric least squares mean (LSM) ratios for each renal impaired group (test) versus the control group with normal renal function (reference) will be provided for C_{max}, $AUC_{0\text{-}tlast}$, and AUC_{inf}.

Ratios of LSM will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the log-transformed C_{max}, $AUC_{0\text{-}tlast}$, and AUC_{inf}. These ratios will be expressed as a percentage relative to the reference group (rest [mild, moderate, or severe renal impaired groups] versus reference [control group with normal renal function]). The 90% CIs will be obtained for the difference between the LSM (test minus reference) resulting from the analyses of the log-transformed C_{max}, $AUC_{0\text{-}tlast}$, and AUC_{inf}.

The t_{max} will be analysed using nonparametric analysis (Walsh averages and appropriate quantile of the Wilcoxon signed rank test statistic). The median difference between the test and reference groups and the corresponding 90% CI for the difference will be calculated.

Protein binding

The following parameter will be determined (where possible) for telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757: f_u unbound plasma fraction.

PK parameters may also be expressed in terms of unbound concentrations (e.g. C_{maxu}, AUCu, CLu/F), if applicable.

11.4.5 Interim Analyses

There will be an interim analysis of PK and safety data following the completion of subjects with severely impaired renal function and demographically-matched healthy subjects with normal renal function (Part A) to determine whether subjects with mildly, and moderately impaired renal function (Part B) will be enroled in the study.

The decision to dose eight subjects with mildly impaired renal function and eight subjects with moderately impaired renal function will be based on the PK evaluation of the Part A subjects and the observation of a 2-fold increase in total and unbound fraction of either the maximal plasma concentration (C_{max}) or plasma exposure (AUC) of the active metabolite telotristat.

Decision will not be based on the PK evaluation of the telotristat ethyl since it is rapidly converted to its active metabolite, but also because its PK profile might not be fully characterised because of anticipated low (or below limit of quantification) plasma concentrations.

This 2-fold increase in total and unbound fraction of either the C_{max} or AUC of the active metabolite (telotristat) in subjects with severely impaired renal function as compared to healthy subjects with normal renal function is a clinically relevant increase and considered as a conservative approach for further PK investigations in subjects with mildly and moderately impaired renal function.

Indeed, in a previous study in healthy subjects (20), 250 mg telotristat etiprate given as a tablet led to a mean maximal plasma concentration (C_{max}) of 449 ng/mL (corresponding to 1.60 ng/mL unbound C_{max} based on an f_u of 0.356%) and a mean plasma exposure (AUC_{inf}) of 1305 h.ng/mL of the active metabolite (telotristat) (corresponding to 4.65 h.ng/mL unbound AUC based on an f_u of 0.356%) (see Table 2 below).

A 2-fold increase in total and unbound fraction of either the mean C_{max} or AUC of the active metabolite (telotristat) would lead to approximately 900 ng/mL (corresponding to 6.40 ng/mL unbound C_{max} based on a 2-fold increase f_u of 0.712%) and 2600 h.ng/mL (corresponding to 18.51 h.ng/mL unbound AUC based on a 2-fold increase f_u of 0.712%) respectively. This mean plasma concentration is close to the one reported following a single oral dose of 1500 mg of telotristat etiprate (given to healthy subjects as six 250-mg tablets) from a previous study (21), while the exposure is below:

- Mean C_{max} of 1818 ng/mL (corresponding to 6.47 ng/mL unbound C_{max}),
- Mean AUC_{inf} of 12634 h.ng/mL (corresponding to 44.98 h.ng/mL unbound AUC).

In this study, 1500 mg single dose level was safe and well tolerated by the subjects.

Table 2 Pharmacokinetic parameters of the active metabolite (telotristat) following single dose of 250 mg telotristat ethyl

Parameter	Treatment A: 250 mg LX1606-Capsule				Treatment B: 250 mg LX1606-Tablet			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	22	3.73	0.94	25.09	22	1.23	0.69	55.84
C_{max} (ng/mL)	22	340	152	44.53	22	449	251	55.92
AUC_{last} (hr*ng/mL)	22	1297	525.9	40.55	22	1285	692.2	53.87
AUC_{inf} (hr*ng/mL)	21	1355	501.1	36.97	22	1305	699.7	53.62
AUC_{Extrap} (%)	21	2.60	6.42	246.58	22	1.67	0.55	32.98
λ_z (hr^{-1})	21	0.2253	0.0816	36.20	22	0.2140	0.0980	45.81
$T_{1/2}$ (hr)	21	3.59	2.06	57.44	22	3.90	1.57	40.13
T_{last} (hr)	22	22.09	5.03	22.78	22	20.18	5.72	28.35
C_{last} (ng/mL)	22	5.82	9.18	157.66	22	3.67	1.26	34.40

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Collection

In compliance with GCP, source data, e.g. medical records/medical notes, should be clearly marked and permit easy identification of a subject's participation in the specified clinical study.

Source data identification and location, whether standalone documents or direct CRF records, will be specified in a stand-alone document signed by the investigator(s).

The investigator must record all data relating to protocol procedures, study drug administration, laboratory data, safety and PK data on the source documents and report requested data on electronic CRFs (eCRF) provided for the study (see Section 12.2).

To ensure accurate, complete, and reliable data, the sponsor or its representative will provide instructional material to the study site(s), as appropriate. Training session will be given during a start-up/initiation meeting for instructions on the completion/data entry of any source data documents and CRF.

The investigators or their designees must verify that all data entries in the CRF are accurate and consistent with Source data records. If certain information is not available for a particular timepoint and/or subject, specific instructions should be followed, e.g. to document that the procedure was either not done or not applicable.

12.2 Data Reporting

Electronic data capture will be utilised for collecting subject data. The study site is required to have a computer and internet connection available for study site entry of clinical data. All entries in the CRF will be made under the electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the CRF.

For subjects who signed an informed consent form (ICF), underwent procedures at screening visit but were screen failed, a minimum of data will be collected: ICF signature date, demographic data, reason for failure, any AE according to the study protocol definition and related concomitant medication.

For participants who successfully met screening criteria but failed to be enroled while all assessments were performed and results obtained, all data for the screening visit should be timeliness collected in the CRF. For the inclusion visit only the date of the visit, the reason of failure and any AE which occurred since the screening visit and related concomitant medication should be collected.

12.1 Data Management

Details of all data management procedures, from the initial planning to the archiving of final datasets/documents following database freeze/lock will be documented in appropriate stand-alone data management and validation plan(s).

Data management will be conducted by a CRO approved by the sponsor. All data management procedures will be completed in accordance with the sponsor and the contracted CRO standard operating procedures (SOPs). Prior to data becoming available for processing at the assigned data management CRO, they will be monitored. Data documentation removed from the CRU will be tracked by the CRO and the monitor.

The sponsor will ensure that an appropriate CRF is developed to capture the data accurately and that suitable queries are raised to resolve any missing or inconsistent data. The investigator will receive the data from the clinical study in an electronic format (PDF files), which will be an exact copy of the CRF, and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted data management CRO. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The CRO will also ensure, via SAE reconciliation, that SAE data collected in the CRF are consistent with SAE data held in the sponsor's global patient safety department (and vice versa).

The coding of AE, medical history, surgical procedures and concomitant medication terms will be performed by the sponsor's Central Group. Concomitant medications will be coded using the latest version of the WHO Drug Dictionary and AEs/medical history terms will be coded using the latest version of MedDRA.

12.2 Record Keeping

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes.

During the prestudy and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

Study documents should be retained until at least two years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least two years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by applicable regulatory requirements or by an agreement with the sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the study site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

If the principal investigator relocates or retires, or otherwise withdraws responsibility for maintenance and retention of study documents, the sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

13 REGULATORY AND ETHICAL CONSIDERATIONS

13.1 Regulatory Considerations

The study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH Guidelines related to GCP. Any episode of noncompliance will be documented. The electronic data capture (EDC) system will comply with the Food and Drug Administration (FDA), 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

In addition, the study will adhere to all applicable international and local regulatory requirements.

All or some of the obligations of the sponsor will be assigned to a clinical research unit (CRU) or a CRO.

An identification code assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other trial-related data .

13.2 Ethical Review Considerations

The following documents should be submitted to the relevant ethics committee(s) (EC) for review and approval to conduct the study (this list may not be exhaustive):

- Protocol/amendment(s) approved by the sponsor,
- Currently applicable Investigator' Brochure or package labelling,
- Relevant investigator's curriculum vitae,
- Subject information and informed consent document(s) and form(s),
- Subject emergency study contact cards,
- Recruitment procedures/materials (advertisements), if any.

The ECs will review all submission documents as required, and a written favourable opinion for the conduct of the study should be made available to the investigator before initiating the study. This document must be dated and clearly identify the version numbers and dates of the documents submitted/reviewed and should include a statement from the EC that they comply with GCP requirements.

The study may begin at the investigative sites only after receiving this dated and signed documentation of the EC approval or favourable opinion.

During the study, any update to the following documents will be sent to the EC either for information, or for review and approval, depending on how substantial the modifications are: (1) SmPC; (2) reports of SAEs; (3) all protocol amendments and revised informed consent(s), if any.

At the end of the study, the EC will be notified about the study completion.

13.3 Subject Information Sheet and Consent

The investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering, orally and/or in writing, to any questions the subject may have throughout the study and sharing any new information that may be relevant to the subject's willingness to continue his or her participation in the study in a timely manner.

The subject information sheet and consent document will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered

into the study, and to document that the subject is satisfied with his understanding of the study and desires to participate.

The investigator is ultimately responsible for ensuring that the EC-approved informed consent is appropriately signed and dated by each subject prior to the performance of any study procedures. Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations.

13.4 Data Protection

The data will be processed in accordance with Regulation (EU) 2016/679 (24) of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) for the European countries and for countries outside of Europe in accordance with the local regulatory requirement.

13.5 Final Report Signature

The investigator coordinating/principal or designee will be proposed to review and sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusion of the report.

14 INSURANCE AND FINANCE

14.1 Insurance

The Sponsor declares that it has taken out a product liability insurance covering all subjects screened and enroled in this study in respect to risks involved in the study.

14.2 Financial Agreement

Since this study is to be performed in partnership with a CRO, separate financial agreements between the sponsor and the CRO on one side, and the CRO and the CRU on the other side, will be signed prior to initiating the study, outlining overall sponsor and investigators responsibilities in relation to the study.

15 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the sponsor or its representatives will provide instructional material to the study sites, as appropriate. A training session during the study initiation visit will be done prior to screening start to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRF, and all study procedures.

15.1 Protocol Amendments and Protocol Deviations and Exceptions

15.1.1 Protocol Amendments

In the event that an amendment to this protocol is required, it will be classified into one of the following three categories:

- Non-substantial amendments are those that are not considered 'substantial' (e.g. administrative changes) and as such only need to be notified to the IECs or regulatory authorities for information purposes.
- Substantial amendments are those considered 'substantial' to the conduct of the clinical study where they are likely to have a significant impact on:
  - the safety or physical or mental integrity of the subjects;
  - the scientific value of the study;
  - the conduct or management of the study; or
  - the quality or safety of the study drug used in the study.

  Substantial amendments must be submitted to and approved by the IECs and relevant regulatory authorities, according to local regulations, prior to implementing changes.
- Urgent amendments are those that require urgent safety measures to protect the study subjects from immediate hazard and as such may be implemented immediately by the sponsor with subsequent IECs and regulatory authority notification, forthwith.

The principal investigator and the sponsor will sign the protocol amendment.

15.1.2 Protocol Deviations and Exceptions

Protocol deviations are defined and classified as either major or minor for a given study. Major deviations (or a combination of minor becoming major) may or may not impact on the analysis population. All minor and major protocol deviations will be identified and recorded by CRU personnel and should be traceable.

Major Protocol Deviation Definition

Any changes in the study design, study conduct and/or procedures that are not in accordance with the protocol and any study materials originally approved by the IEC and which may affect the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

Minor Protocol Deviation Definition

Any changes in the study design, study conduct and/or procedures that are not in accordance with the protocol and any study materials originally approved by the IEC but that do not have an important impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

As a matter of policy, the sponsor will not grant exceptions to protocol-specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered

ethically, medically, and scientifically justified for a particular subject, prior approval from the sponsor is required before the subject will be allowed to enter the study.

If investigative clinical unit personnel learn that a subject who did not meet the protocol eligibility criteria was entered in a study (eligibility criteria deviation), they must immediately inform the sponsor. Such subjects will be discontinued from the study, except in exceptional circumstances, following review and written approval by the sponsor.

15.1.3 Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (e.g. when new staff become involved).

The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the clinical unit authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

15.2 Monitoring

The investigator is responsible for the validity of all data collected at the site.

The sponsor is responsible for monitoring these data to verify that the rights and well-being of subjects are protected, study data are accurate (complete and verifiable to source data), and that the study is conducted in compliance with the protocol, GCP, and regulatory requirements.

Before first subject inclusion, the sponsor assigned study monitor will provide a monitoring plan indicating the monitoring procedures and at which occasions during the study monitoring visits will be performed. Sponsor assigned study monitor will conduct regular site visits.

Periodic visits will be made to the study site throughout the study at mutually agreeable times. Any appropriate communication tools will be set up to ensure the sponsor and/or its representative is/are available for consultation, so they can stay in contact with the study site personnel.

Adequate time and space for monitoring visits should be made available by the investigator.

The investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the CRF, and assist with the monitor's activities, if requested.

Quality of the paper-based or electronic data will be reviewed to detect errors in data collection and, if necessary, to verify the quality of the data.

The CRF is expected to be completed an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The study monitor will use functions of the EDC system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a subject name is revealed on a document required by the sponsor (e.g. laboratory print outs) the name must be blacked out permanently by the site personnel, leaving the date of birth visible, and annotated with the study subject number as identification.

15.3 Investigator's Regulatory Obligations

All clinical work under this protocol will be conducted according to GCP rules. This includes that the study may be audited at any time by a quality assurance personnel designated by the sponsor, or by regulatory bodies. The investigator must adhere to the GCP principles in addition to any applicable local regulations.

If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable EC with direct access to any original source documents.

The investigator should demonstrate due diligence in recruitment and screening of potential study subjects. The enrolment rate should be sufficient to complete the study as agreed with the sponsor. The sponsor should be notified of any projected delays, which may impact the completion of the study.

15.3.1 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised quality assurance personnel may carry out inspections and audits.

15.3.2 Data Quality Assurance

Monitored CRF, transferred from the CRU/Investigator site to the assigned data management group, will be reviewed (secondary monitoring) for completeness, consistency, and protocol compliance.

Reasons should be given in the relevant CRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the CRF.

16 PUBLICATION POLICY

The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor.

The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators or a steering committee. The sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or authors' institution) after receipt of the proposed publication by the sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the sponsor's request for delay to the proposed publication should the sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

17 REFERENCES

(1) Turaga KK, Kvols LK. Recent progress in the understanding, diagnosis, and treatment of gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin 2011;61(2):113–32.

(2) 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(18):3063-72.

(3) Kulke MH and Mayer RJ. Carcinoid Tumors. NEJM 1999;340(11):858-68.

(4) Beaumont JL, Cella D, Phan AT et al. Comparison of health-related quality of life in subjects with neuroendocrine tumors with quality of life in the general US population. Pancreas 2012;41(3):461-6.

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(6) Rubin J, Ajani J, Schirmer W, et al. Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. J Clin Oncol 1999;17(2):600.

(7) Ruszniewski P, Ish-Shalom S, Wymenga M, et al. Rapid and sustained relief from the symptoms of carcinoid syndrome: Results from an open 6-month study of the 28-day prolonged-release formulation of Lanreotide. Neuroendocrinology 2004;80(4):244–51.

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(10) 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(2):225-9.

(11) Study LX1606-202. A phase II, multicentre, 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. Report issued August 18, 2015.

(12) Study LX1606-301. A phase III, randomised, placebo-controlled, parallel group, multicentre, double-blind study to evaluate the efficacy and safety of telotristat etiprate in patients with carcinoid syndrome not adequately controlled by somatostatin analogue therapy. Report issued February 16, 2016.

(13) Study LX1606-303. A phase III, randomized, placebo-controlled, multicenter, double-blind study to evaluate the safety and efficacy of telotristat etiprate (LX1606) in patients with carcinoid syndrome. Report issued March 03, 2016.

(14) Study D-FR-0117-001. A phase I open-label study to evalutate the single dose pharmacokinetics of telotristat etiprate in male and female subjects with mild, moderate and severe hepatic impairment and matched subjects with normal hepatic function. Report issued December 09, 2016.

(15) Study LX1606-104. A phase I, open label , non randomised, single dose study to evaluate the absorption, metabolism, and excretion of [^{14}C] telotristat etiprate, following oral administration, in healthy male subjects. Report issued March 26, 2014.

(16) Modeling and simulation of telotristat ethyl and LP-778902 to support the telotristat etiprate development program in patients with carcinoid syndrome. Report issued February 26, 2016.

(17) Addendum 2 to a modeling and simulation-based strategy to support the telotristat etiprate development program in patients with carcinoid syndrome. Report issued May 12, 2017.

(18) Study LX1606-101. A phase I, randomised, double-blind, placebo-controlled, ascending single dose study to determine the safety and tolerability of orally administered telotristat etiprate in healthy subjects. Report issued September 26, 2008.

(19) Study LX1606-102. A phase I, randomised, double-blind, placebo-controlled, ascending multiple dose study to determine the safety and tolerability of orally administered telotristat etiprate in healthy subjects. Report issued February 17, 2009.

(20) Study LX1606-103. A phase I, randomised, open label, 2-way crossover study of two oral formulations of telotristat etiprate in healthy subjects. Report issued June 27, 2012.

(21) Study LX1606-105. A phase I, randomised, double-blind, placebo-controlled, positive controlled, 3-period, 6-sequence, crossover study to define the electrocardiogram effects of a single dose of telotristat etiprate 1500 mg compared with placebo and open label moxifloxacin in healthy subjects: a thorough QT study. Report issued February 19, 2015.

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(24) Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

18 ATTACHMENTS

18.1 Attachment 1 – Study Schedule of Assessments

Study Procedures	Screening Day -28 to Day -2 [a]	Admission Day -1	Day 1 (predose)	Day 1 (postdose)	Day 2 (optional discharge)	Day 3	Discharge Day 4	EOS Day 8 up to Day 15 Early discontinuation
Informed consent	X							
Confinement		X [b]						
Inclusion/exclusion criteria	X	X						
Demography	X							
Medical and medication history	X	X [c]						
Alcohol breath test	X	X						
Urine drug of abuse screen	X	X						
Serology [d]	X							
Pregnancy test [e]	X [f]	X [g]						X [g]
FSH (if applicable)	X [h]							
Height	X							
Body weight	X	X						X

Abbreviations: EOS = End of study; FSH = Follicle stimulating hormone; HBsAg = Hepatitis B surface antigen; HIV = Human immunodeficiency virus; HCV = Hepatitis C virus; RNA = Ribonucleic Acid

a Except for reserve subjects with midly and moderately impaired renal function, screening period extended to Day-56 to Day-2.
b Might be up to Day 2 or Day 4.
c Assessment of baseline symptoms and review of changes in medication since screening.
d Serology includes HBsAg, HIV antibodies, and HCV RNA.
e Women of child bearing potential only.
f Serum pregnancy test.
g Urine pregnancy test.
h Optional test to confirm postmenopausal status in female subjects

Study Procedures	Screening Day -28 to Day -2 [i]	Admission Day -1	Day 1 (predose)	Day 1 (postdose)	Day 2 (optional discharge)	Day 3	Discharge Day 4	EOS Day 8 up to Day 15 Early discontinuation
Physical examinations	X	X			X [j]		X	X
Body temperature		X						
Clinical laboratory [k]	X [l]	X [l]			X		X	X
ECG	X	X			X [m]		X	X
Vital signs (supine)	X	X			X [m]		X	X
Renal function assessment	X	X						
Study drug administration			X [n]					
Blood sampling (PK)			X	X [o]				
Blood sampling (protein binding)				X[p]				
Urine collection		X [q]		X [r]				
Adverse events	X [s]							
Concomitant medications	X [s]							

Abbreviations: ECG = Electrocardiogramm; EOS = End of study; HbA1c = Glycated haemoglobin; PK = Pharmacokinetics

i Except for reserve subjects with midly and moderately impaired renal function, screening period extended to Day-56 to Day-2.
j Physical examination in case of discharge on Day 2.
k Haematology, blood biochemistry, coagulation (only at screening, upon admission and EOS), and urinalysis.
l Including HbA1c for subjects for renal impaired function (only at screening and upon admission).
m Approximately 24 hours postdose.
n Under fed conditions.
o Blood sampling at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours postdose.
p Blood sampling at 0.5, 1, 2 and 3 hours postdose.
q Two 4-hour intervals of predose urine collection.
r 0-4h, 4-8h, 8-12h, 12-24h, 24-48h, 48-72h postdose urine collection intervals.
s From the time a subject gives informed consent and throughout the study.

18.2 Attachment 2 – Blood Sampling Summary

This table summarises the maximum number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories and bio-analytical assays) during the study.

Fewer venipunctures and blood draws may actually occur if needed for safety purposes, but this will not require a protocol amendment.

The maximum volume of blood drawn for all evaluations throughout this study is around 140 mL for each subject as detailed in the table below.

Purpose	Maximum Blood volume per sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Safety			
Clinical laboratory tests: Haematology	4	5	20
Clinical laboratory tests: Biochemistry	8.5	5	42.5
Clinical laboratory tests: Coagulation	3	3	15
Clinical laboratory tests: Serology	8.5	1	8.5
Provision for repeat tests (local lab)	-	-	20
Pharmacokinetics (PK)			
telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757	2	11	22
Protein binding			
telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757	4	4	16
Total over maximum 2.5 months		**Approximately 144 mL**	

18.3 Clinical Laboratory Tests

18.3.1 Haematology

Haematology	Screening Day-28 to Day -2*	Day -1	Day 2 + Discharge	ED / EOS
Erythrocyte count (RBC)	X	X	X	X
Haematocrit	X	X	X	X
Haemoglobin	X	X	X	X
Mean cell haemoglobin (MCH)	X	X	X	X
Mean cell haemoglobin concentration (MCHC)	X	X	X	X
Mean cell volume (MCV)	X	X	X	X
Leukocyte count (WBC)	X	X	X	X
Absolute counts of:				
• Neutrophils	X	X	X	X
• Lymphocytes	X	X	X	X
• Monocytes	X	X	X	X
• Eosinophils	X	X	X	X
• Basophils	X	X	X	X
Platelets	X	X	X	X

*except for mild and moderate renal impaired function subjects, the screening period is extended from Day -56 to Day -2.

18.3.2 Clinical chemistry

Clinical Chemistry	Screening Day-28 to Day -2*	Day -1	Day 2 + Discharge	ED / EOS
Alanine aminotransferase (ALT)	X	X	X	X
Aspartate aminotransferase (AST)	X	X	X	X
Alkaline phosphatase (ALP)	X	X	X	X
Gamma-glutamyl transferase (GGT)	X	X	X	X
Conjugated bilirubin	X	X	X	X
Total bilirubin	X	X	X	X
Total protein	X	X	X	X
Albumin	X	X	X	X
Creatinine	X	X	X	X
Urea	X	X	X	X
Glucose (fasting)	X	X	X	X
Glycated haemoglobin (A1C) (for renal impaired only)	X	X		
Amylase	X	X	X	X

Clinical Chemistry	Screening Day-28 to Day -2*	Day -1	Day 2 + Discharge	ED / EOS
Bicarbonate	X	X	X	X
C reactive protein (CRP)	X	X	X	X
Calcium	X	X	X	X
Chloride	X	X	X	X
Inorganic phosphate	X	X	X	X
Potassium	X	X	X	X
Sodium	X	X	X	X
Total cholesterol	X	X	X	X
Triglycerides (TG)	X	X	X	X

18.3.3 Coagulation

Coagulation	Screening Day-28 to Day -2*	Day -1	Day 2 + Discharge	ED / EOS
Activated partial thromboplastin time (aPTT)	X	X		X
INR	X	X		X

18.3.4 Endocrine

Endocrine	Screening Day-28 to Day -2*	Day -1	Day 2 + Discharge	ED / EOS
FSH	X			

18.3.5 Serology

Serology	Screening Day-28 to Day -2*	Day -1	Day 2 + Discharge	ED / EOS
Hepatitis B surface antigen	X			
Hepatitis C (HCV ribonucleic acid)	X			
Human immunodeficiency virus (HIV)	X			

*except for mild and moderate renal impaired function subjects, the screening period is extended from Day -56 to Day -2.

18.3.6 Urinalysis (dipstick)

Urinalysis	Screening Day-28 to Day -2*	Day -1	Day 2 + Discharge	ED / EOS
Bilirubin	X	X	X	X
Blood	X	X	X	X
Leukocyte	X	X	X	X

Urinalysis	Screening Day-28 to Day -2*	Day -1	Day 2 + Discharge	ED / EOS
Nitrit	X	X	X	X
Glucose	X	X	X	X
Ketones	X	X	X	X
Specific gravity	X	X	X	X
pH	X	X	X	X
Protein	X	X	X	X
Urobilinogen	X	X	X	X

Microscopy to be performed, only in case of positive findings in leukocyte, blood, protein and nitrit.

18.3.7 Urinalysis electrolytes

Urinalysis	Screening Day-28 to Day -2*	Day -1	Day 2 + Discharge	ED / EOS
Potassium	X	X	X	X
Sodium	X	X	X	X
Chloride	X	X	X	X
Bicarbonates	X	X	X	X
Urea	X	X	X	X
Creatinine	X	X	X	X

*except for mild and moderate renal impaired function subjects, the screening period is extended from Day -56 to Day -2.

18.3.1 Specific parameters

Specific Parameters	Screening Day-28 to Day -2*	Day -1	Day 2 + Discharge	ED / EOS
Ethanol testing breath test	X	X		
Urine drug screen, including at least amphetamines, methamphetamines, benzodiazepines, cocaine, opiates, THC and barbiturates	X	X		
Pregnancy test (women of childbearing potential)	Serum test	Urine test		Urine test

*except for mild and moderate renal impaired function subjects, the screening period is extended from Day -56 to Day -2.

18.4 Attachment 4 – Protocol version 2 Summary

All additions have been identified by the use of underline and all deletions by ~~strikethroughs~~.

Cover Page, Emergency Contact

PPD Deputy EU Qualified Person for Pharmacovigilance ~~Sr VP Global Patient Safety~~, Ipsen Biopharm Ltd

102 Park Drive, Milton Park, Abingdon, OX14 4RY, United Kingdom

Phone: PPD

Mobile: PPD

The person listed above is the ~~qualified physician~~ designated by the sponsor as the first point of contact for emergency situations.

3.1 Overall Study Design and Plan

Blood samples will be collected for the determination of plasma concentrations of telotristat ethyl, its active metabolite (telotristat) and its inactive metabolite LP-951757 predose and at regular timepoints up to 72 hours post-dose. Blood samples will also be collected for protein binding assessment of telotristat ethyl and its active metabolite (telotristat) ~~predose and~~ at defined timepoints post-dose.

3.2.2 Secondary Endpoints

Secondary endpoints will be assessed throughout the study in subjects with impaired renal function and healthy control subjects with normal renal function:

- by evaluating AEs, change from baseline in clinical laboratory test results, vital signs, ECGs measurements, and concomitant medication usage,
- by the determination of the percentages of drug bound and drug unbound determined (where possible) for telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757,
- by the determination of the amount excreted in urine (where possible) for telotristat ethyl, and its active metabolite (telotristat) ~~and the inactive metabolite LP-951757~~.

18.5 Exclusion Criteria

Subjects who meet any of the following criteria will not be considered eligible for enrolment in the study.

All subjects

(1) Existence of any surgical or medical condition that, in the judgment of the investigator, might interfere with the absorption, distribution, metabolism, or excretion of telotristat etiprate (including bariatric surgery, or any other gastrointestinal surgery, excepting appendectomy and hernia repair, which are acceptable).

(2) History of any major surgery within six months or anticipated surgery prior to Day-1.

(3) Receipt of any investigational agent or study drug within 30 days or 10 half-lives, whichever is longer, prior to Day-1.

(4) Participation in a clinical trial within 30 days after a single-dose study, within 90 days after a multiple-dose study before screening or more than four times in the previous year.

(5) Donation or loss of more than 250 mL of blood or blood product within three months prior to screening.

(6) History of any serious adverse reaction or hypersensitivity to any inactive component of the drug product (i.e. microcrystalline cellulose, croscarmellose sodium [disintegrant], talc, silicon dioxide, and magnesium stearate [non-bovine]), unless the reaction is deemed irrelevant to the study by the investigator.

(7) Patients with hereditary problems of galactose intolerance (lactase deficiency or glucose-galactose malabsorption).

6.1 Study Drug

Study drug administration will occur under medical supervision.

A ~~Treatment,~~ single dose of 250 mg telotristat ethyl ~~,~~ will be given under fed conditions (i.e. between 15 minutes before and 1 hour after the meal or snack).

13.1 Regulatory Considerations

The study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH Guidelines related to GCP. Any episode of noncompliance will be documented. The electronic data capture (EDC) system will comply with the Food and Drug Administration (FDA), 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

In addition, the study will adhere to all applicable international and local regulatory requirements.

All or some of the obligations of the sponsor will be assigned to a clinical research unit (CRU) or a CRO.

An identification code assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other trial-related data ~~(see~~.

13.4 Data Protection

The data will be processed in accordance with Regulation (EU) 2016/679 (24) of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) for the European countries and for countries outside of Europe in accordance with the local regulatory requirement.

17. Reference

Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

18.1 Attachment 1 – Study Schedule of Assessments

Except for reserve subjects with midly and moderately impaired renal function, screening period extended to Day-56 to Day-2.

j Physical examination in case of discharge on Day 2.
k Haematology, blood biochemistry, coagulation (only at screening, upon admission and EOS), and urinalysis.
l Including HbA1c for subjects for renal impaired function (only at screening and upon admission).
m Approximately 24 hours postdose.
n Under fed conditions.
o Blood sampling at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours postdose.
p Blood sampling at 0.5, 1, 2 and 3 hours postdose.
q Two 4-hour intervals of predose urine collection.
r 0-4h, 4-8h, 8-12h, 12-24h, 24-48h, 48-72h postdose urine collection intervals.
s From the time a subject gives informed consent and throughout the study.

18.2 Attachment 2 – Blood Sampling Summary

This table summarises the maximum number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories and bio-analytical assays) during the study.

Fewer venipunctures and blood draws may actually occur if needed for safety purposes, but this will not require a protocol amendment.

The maximum volume of blood drawn for all evaluations throughout this study is around 140 mL for each subject as detailed in the table below.

Purpose	Maximum Blood volume per sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Safety			
Clinical laboratory tests: Haematology	4	5	20
Clinical laboratory tests: Biochemistry	8.5	5	42.5
Clinical laboratory tests: Coagulation	3	3	15
Clinical laboratory tests: Serology	8.5	1	8.5
Provision for repeat tests (local lab)	-	-	20
Pharmacokinetics (PK)			
telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757	2	11	22
Protein binding			

telotristat ethyl, its active metabolite (telotristat) and the inactive metabolite LP-951757	4~~3~~	4	16<u>2</u>
Total over maximum 2.5 months		**Approximately 14~~40~~ mL**	