STATISTICAL ANALYSIS PLAN

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

PROTOCOL VERSION AND DATE:
Version 2.0 – 20 December 2017

Statistical Analysis Plan (SAP) Version	Date
Final Version 2.0	04JUN2018

STUDY NUMBER:	D-FR-01017-002
EUDRACT NUMBER	2017-003948-20
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
SAP VERSION:	Final Version 2.0
SAP DATE:	04JUN2018

Further to your review and agreement to the Statistical Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Medical Director	PPI PPI, R&D IPSEN Biopharm 102 Park Drive, Milton Park, Oxford, OX14 4RY, UK		
Statistician	PPI Ipsen Innovation 5 Avenue du Canada 91940 Les Ulis, France		
Pharmacokineticist	PPI PPI Translational DMPK Safety Department Ipsen Innovation 5 Avenue du Canada 91940 Les Ulis, France		

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Study statistician	PPD Biostatistics Project Leader Biotrial Biometrics 7-9 Rue Jean-Louis Bertrand 35042 Rennes Cedex, France		
Pharmacokineticist	PPD Biotrial 7-9 Rue Jean-Louis Bertrand 35042 Rennes Cedex, France		

IMPORTANT: This completed record (with additional sheets, where required), confirms the above-mentioned Statistical Analysis Plan version became the Final Statistical Analysis Plan

History of Changes				
Version 2.0		14MAR2018	04JUN2018	Reason for Change
Page	Section	Was	Is	
2	Signature page	Department of the clinical PK director was Pharmacokinetics Drug Metabolism	Department of the clinical PK director is Translational DMPK Safety Department	Name of the department changed.
3	Signature page	Pharmacokineticist at Biotrial was PPD PPD	Pharmacokineticist at Biotrial is PPD PPD	Change of PK lead for the study.
25	3.2.2.4.3	If the data permitted, same ANOVA as above will be performed separately for each renal impaired function group on the natural log-transformed C_{maxu}, $AUC_{0\text{-}tlastu}$, and $AUC_{0\text{-}infu}$ for both telotristat ethyl and its active metabolite with renal function group as a fixed term. The same SAS code as the previous analysis will be used. Sensitivity analysis will also be conducted, the same method as described above will be used.	If the data permitted, same ANOVA as above will be performed separately for each renal impaired function group on the natural log-transformed C_{maxu}, $AUC_{0\text{-}tlastu}$, $AUC_{0\text{-}infu}$ **and unbound fractions (fu; no log-transformed)** for both telotristat ethyl and its active metabolite with renal function group as a fixed term. The same SAS code as the previous analysis will be used. Sensitivity analysis will also be conducted, the same method as described above will be used.	ANOVA on unbound fractions was added upon request dated 16MAY2018.
41	Appendix 2: 14.2.3		Titles of tables 14.2.3.5.1.1, 14.2.3.5.1.2, 14.2.3.5.2.1 and 14.2.3.5.2.2 include the unbound fractions.	Titles adapted following the change in the analysis.

TABLE OF CONTENTS

1 INFORMATION TAKEN FROM THE PROTOCOL 10
1.1 Study objectives 10
1.1.1 Primary objective 10
1.1.2 Secondary Study Objectives 10
1.2 Study design 10
1.2.1 Study population 11
1.2.2 Study duration 12
1.3 Methods and procedures 12
1.3.1 Subject identification and allocation to study treatment 12
1.3.2 Subjects assessments 12
1.3.2.1 Efficacy assessments 12
1.3.2.2 Pharmacokinetic assessments 12
1.3.2.3 Safety assessments 13
1.3.2.4 Other Assessments 14
1.3.2.5 Withdrawal/discontinuation 14
1.3.3 Schedule of assessments 15
1.3.4 Planned sample size 18
2 SUBJECT POPULATIONS (ANALYSIS SETS) 18
2.1 Efficacy 18
2.2 Safety 18
2.3 Pharmacokinetics 18
2.4 Included population 18
2.5 Screened population 18
2.6 Primary population 18
3 STATISTICAL METHODS 18
3.1 Statistical analysis strategy 18
3.1.1 Primary efficacy endpoint 18
3.1.2 Secondary efficacy endpoint 18
3.1.3 Pharmacokinetic endpoints 19
3.1.4 Protein binding endpoints 20
3.1.5 Safety endpoints 21
3.1.6 Multiplicity 21
3.1.7 Significance testing and estimation 21
3.2 Analysis methods 21
3.2.1 Efficacy 21
3.2.2 Pharmacokinetics 21
3.2.2.1 PK parameters calculation 21
3.2.2.2 Descriptive statistics and listings 22
3.2.2.3 Graphical representations 23

3.2.2.4 Statistical analyses ... 23
3.2.3 Safety ... 25
3.2.3.1 Adverse events ... 25
3.2.3.2 Laboratory data ... 26
3.2.3.3 Physical examination ... 27
3.2.3.4 Vital signs ... 27
3.2.3.5 ECG ... 27
3.2.3.6 Pregnancy tests ... 28
3.2.4 Missing data and outliers ... 28
3.2.4.1 Missing data ... 28
3.2.4.2 Missing or incomplete dates ... 28
3.2.4.3 Outliers ... 28
3.2.5 Subject disposition ... 29
3.2.6 Withdrawals ... 29
3.2.7 Demographic and baseline characteristics ... 29
3.2.8 Medical and surgical history ... 29
3.2.9 Subject compliance ... 30
3.2.10 Prior and concomitant medications ... 30
3.2.11 Prior and concomitant non-drug therapies ... 30
3.2.12 Concomitant surgical procedures ... 30
3.2.13 Derived data ... 30
3.2.14 Rules and data formats ... 30
3.2.15 Pooling of Centres ... 31
3.2.16 Interim analysis ... 31
3.2.17 Role of data review committee (DRC) ... 31
3.2.18 Covariates and analysis of subgroups ... 31
4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS . 32
4.1 Hardware ... 32
4.2 Software ... 32
4.3 Validation programs ... 32
4.4 Restitution of the programs ... 32
5 CHANGES FROM PROTOCOL ... 32
6 REFERENCES ... 33
7 APPENDICES TO THE SAP TEMPLATE ... 34

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

λ_Z:	Terminal elimination rate constant
Ae:	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
ATC:	Anatomic Therapeutic Class
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
$AUC_{0\text{-}tlastu}$:	Area Under the plasma concentration-time Curve from time 0 to time t corresponding to the last quantifiable unbound concentration
$AUC_{0\text{-}inf}$:	Area Under the plasma concentration-time Curve from time 0 to infinity
$AUC_{0\text{-}infu}$:	Area Under the plasma concentration-time Curve unbound from time 0 to infinity
BLQ:	Below the Limit of Quantification
BMI:	Body Mass Index
BP:	Blood pressure
bpm:	Beats per minute
CI:	Confidence Interval
C_{last}:	Last quantifiable concentration
CL/F:	Apparent total clearance (from plasma)
CL_u/F:	Apparent total clearance (from plasma) unbound
C_{max}:	Observed maximal (peak) concentration
C_{maxu}:	Observed maximal (peak) concentration unbound
CRF:	Case Report Form
CRP:	C reactive protein
CS:	Clinically significant
CSR:	Clinical Study Report
CV:	Coefficient of Variation

DRC:	Data Review Committee
ECG:	Electrocardiogram
eCRF:	Electronic Case Report Form
EMA:	European Medicines Agency
EOS:	End Of Study
FDA:	Food and Drug Administration
FSH:	Follicle Stimulating Hormone
f_u:	Unbound plasma fraction
GFR	Glomerular filtration rate
GGT:	Gamma-Glutamyl Transpeptidase
HbA1C	Glycated haemoglobin A1c
HBsAg:	Hepatitis B Surface Antigen
HCV:	Hepatitis C Virus
HIV:	Human Immunodeficiency Virus
ICH:	International Conference on Harmonisation
IMP:	Investigational Medicinal Product
INR:	International Normalised Ratio
LC-MS/MS:	Liquid chromatography-tandem mass spectrometry
LOQ:	Limit of Quantification
LS:	Least-Squares
MCH:	Mean Cell Haemoglobin
MCHC:	Mean Cell Haemoglobin Concentration
MCV:	Mean Corpuscular Volume
MDRD	Modification of Diet Renal Disease
MedDRA:	Medical Dictionary for Regulatory Activities
MR:	Metabolitic ratios
PDM:	Pharmacokinetics Drug Metabolism
PK:	Pharmacokinetic(s)
PTT	Partial Thromboplastin Time
QTcF:	Corrected QT interval according to Fridericia's formula
RBC:	Red Blood Cell(s)
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SAS®:	Statistical Analysis System®
SD:	Standard Deviation

SI:	International System
$t_{1/2}$:	Apparent terminal elimination half-life
TEAE:	Treatment Emergent Adverse Event
TFLs:	Tables, Figures and Listings
TG:	Triglycerides
t_{last}:	Time to last quantifiable concentration
t_{max}:	Time to maximum observed plasma concentration
V_z/F:	Apparent volume of distribution
V_{zu}/F:	Apparent volume of distribution (unbound)
WBC:	White Blood Cell
WHO-DD:	World Health Organisation – Drug Dictionary

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Study objectives

1.1.1 Primary objective

The primary objective of the study is to compare the pharmacokinetics (PK) of telotristat ethyl and its active metabolite telotristat (LP-778902) 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.

1.1.2 Secondary Study Objectives

The secondary objectives of the study are:

- 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 (LP-778902);
- 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.

1.2 Study design

This study is 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 Glomerular Filtration Rate (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 (LP-778902) 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 (LP-77902)), the PK and protein binding analysis of telotristat ethyl, its active metabolite telotristat (LP-778902) 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).

1.2.1 Study population

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) = $175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African/American})$
Scr: serum creatinine (mg/dL) - GFR reported normalised to 1.73 m² body surface area
Or

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

1.2.2 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.

1.3 Methods and procedures

1.3.1 Subject identification and allocation to study treatment

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.

1.3.2 Subjects assessments

1.3.2.1 Efficacy assessments

There is no efficacy assessment in this study.

1.3.2.2 Pharmacokinetic assessments

Plasma and urine concentrations of telotristat ethyl and its active metabolite telotristat (LP-778902) will be determined by validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods.
Plasma concentrations of telotristat ethyl inactive metabolite (LP-951757) will be determined by validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods.
Pharmacokinetic blood samples will be collected predose (time 0) and up to 72 hours postdose [at timepoints 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (day 2), 48 (day 3), 72 (day 4) hours postdose; see Section 1.3.3].
Urine samples will be collected on day -1 (two 4-hours intervals predose), and up to 72 hours postdose [0-4h, 4-8h, 8-12h, 12-24h, 24-48h (day 2), 48-72h (day 3) postdose urine collection intervals; see Section 1.3.3].

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

Blood samples will be collected for protein binding of telotristat ethyl, its active metabolite telotristat (LP-778902) and the inactive metabolite (LP-951757) on day 1 at 0.5, 1, 2 and 3 hours postdose (see Section 1.3.3).

1.3.2.3 Safety assessments

The safety assessments are:

- Adverse events (AEs) monitored from the time that the subject gives informed consent and throughout the study, elicited by direct, non-leading questioning or by spontaneous reports;
- Clinical safety assessments:
  - Physical examination assessed at screening, Day -1, Day 2 (in case of discharge), Day 4 and EOS/Early discontinuation visit;
  - Vital signs measured at screening, Day -1, Day 2 (approximately 24 h postdose), Day 4 and EOS/ Early discontinuation visit, including supine blood pressures (BP) and heart rate and temperature at Day -1 only;
  - 12-lead electrocardiograms (ECGs) measured at screening, Day -1, Day 2 (approximately 24 h postdose), Day 4 and EOS/ Early discontinuation visit, including sinus rhythm, RR interval, heart rate, PR interval, QRS interval, QT interval, corrected QT (QTc) calculated using Fridericia methodology as well as their clinical significance;
- Clinical laboratory tests measured at screening*, Day -1*, Day 2, Day 4 and EOS*/ Early discontinuation visit:
  - Haematology: erythrocyte count (RBC), haematocrit, haemoglobin, mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), mean cell volume (MCV), leukocyte count (WBC), absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils and platelets count;
  - Clinical chemistry: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), conjugated bilirubin, total bilirubin, total protein, albumin, creatinine, urea, glucose (fasting), glomerular filtration rate (GFR, for renal impaired only and only at screening and day-1), glycated haemoglobin A1c (HbA1C, for renal impaired only and only at screening and day-1), amylase, bicarbonate, C reactive protein (CRP), calcium, chloride, inorganic phosphate, potassium, sodium, total cholesterol, triglycerides (TG);
  - Coagulation (only at flagged * visits): Activated partial thromboplastin time (aPTT) and international normalised ratio (INR);
  - Urinalysis (dipstick): bilirubin, blood, leukocyte, nitrite, glucose, ketones, specific gravity, pH, proteins, urobilinogen;
  - Urinalysis (quantitative results): Potassium, sodium, chloride, bicarbonates, urea and creatinine.
- Pregnancy tests at screening, Day -1 and EOS/ Early discontinuation visit (women of childbearing potential only).

1.3.2.4 Other Assessments

- Demographics (country, sex, race, ethnicity, age) at screening;
- Eligibility criteria at screening and day -1;
- Medical or surgical history, including ongoing medical history at screening and Day -1;
- Body height at screening, body weight and BMI at screening and Day-1 and EOS/ Early discontinuation;
- Urine drug of abuse tests (cannabis and metabolites, cocaine, amphetamines, opiates, methamphetamines, barbiturates, benzodiazepines) at screening and Day-1;
- Alcohol breath test at screening and Day-1;
- Tobacco, caffeine and alcohol use at screening;
- Serology at screening only: Hepatitis B surface antigen, Hepatitis C (HCV ribonucleic acid) and Human immunodeficiency virus (HIV);
- Endocrine (FSH) (if applicable) at screening;
- Postmenopausal status at screening;
- Prior and concomitant medications, prior and concomitant non-drug therapies and concomitant surgical procedures;
- For renal impaired subjects only: renal function classification at screening.

1.3.2.5 Withdrawal/discontinuation

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 the sponsor 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.

1.3.3 Schedule of assessments

Here are the schedules of assessments extracted from the protocol:

Table 2 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

Table 3 Study schedule of assessments (Continued)

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.

1.3.4 Planned sample size

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 Food and Drug Administration (FDA) and European Medicines Agency (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 $AUC_{0\text{-}inf}$ 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.

2 SUBJECT POPULATIONS (ANALYSIS SETS)

2.1 Efficacy

There is no efficacy assessment in this study.

2.2 Safety

The safety population is all subjects who received the single oral dose of study drug.

2.3 Pharmacokinetics

The pharmacokinetics valid population is 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.

2.4 Included population

The included population is all screened subjects who are included in the study.

2.5 Screened population

The screened population is all subjects screened i.e. who signed the informed consent.

2.6 Primary population

The analyses of safety data will be performed based on the safety population. The analyses of PK will be performed on the PK population.

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with ICH E9 guideline and will be based on the pooled data from the individual study sites, unless otherwise stated.

Statistical analyses described in this document will be performed by Biotrial Biometrics, Rennes, France.

3.1.1 Primary efficacy endpoint

There is no efficacy assessment in this study.

3.1.2 Secondary efficacy endpoint

There is no efficacy assessment in this study.

3.1.3 Pharmacokinetic endpoints

The following PK plasma parameters for total telotristat ethyl, its active metabolite telotristat (LP-778902) and its inactive metabolite (LP-951757) will be derived by non-compartmental analysis of the plasma concentration-time profiles on Day 1 (pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12 hours post-dose), Day 2 (24 h), Day 3 (48 h) and Day 4 (72 h):

- C_{max}: Maximum observed plasma drug concentration
- t_{max}: Time to maximum observed plasma concentration
- $AUC_{0\text{-}inf}$: Area under the plasma concentration-time curve from time 0 to infinity calculated as follows:

  $$AUC_{0\text{-}inf} = AUC_{0\text{-}tlast} + C_{last}/\lambda_z,$$

  with C_{last} as the last quantifiable concentration
- $AUC_{0\text{-}tlast}$: Area under the plasma concentration-time curve from 0 to time t corresponding to the last quantifiable concentration
- $t_{1/2}$: Apparent terminal elimination half-life calculated as follows:

  $t_{1/2} = Ln(2)/\lambda_z$
- 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, there will be 4 replicates by timepoint.

For C_{max} and AUC, the following active metabolite/parent (i.e telotristat ethyl) and active metabolite (LP-778902)/[active metabolite+ telotristat ethyl] ratios (normalized and not normalized) will also be calculated:

- MRC_{max} = (C_{max} LP-778902)/ (C_{max} telotristat ethyl)
- $MRC_{maxNorm}$ = (C_{max} LP-778902/Molecular weight$(MW)_{LP\text{-}778902}$)/ (C_{max} telotristat ethyl/$MW_{telotristat\ ethyl}$)
- $MRAUC_{0\text{-}inf}$ = ($AUC_{0\text{-}inf}$ LP-778902)/ ($AUC_{0\text{-}inf}$ telotristat ethyl)
- $MRAUC_{0\text{-}infNorm}$ = ($AUC_{0\text{-}inf}$ LP-778902/$MW_{LP\text{-}778902}$)/ ($AUC_{0\text{-}inf}$ telotristat ethyl/$MW_{telotristat\ ethyl}$)
- $MRAUC_{0\text{-}tlast}$ = ($AUC_{0\text{-}tlast}$ LP-778902)/ ($AUC_{0\text{-}tlast}$ telotristat ethyl)
- $MRAUC_{0\text{-}tlastNorm}$ = ($AUC_{0\text{-}tlast}$ LP-778902/$MW_{LP\text{-}778902}$)/ ($AUC_{0\text{-}tlast}$ telotristat ethyl/$MW_{telotristat\ ethyl}$)
- $MRC_{maxTotal}$ = (C_{max} LP-778902)/ (C_{max} LP-778902 + C_{max} telotristat ethyl)
- $MRC_{maxTotalNorm}$ = (C_{max} LP-778902/$MW_{LP\text{-}778902}$)/ (C_{max} LP-778902/$MW_{LP\text{-}778902}$ + C_{max} telotristat ethyl/$MW_{telotristat\ ethyl}$)
- $MRAUC_{0\text{-}infTotal}$ = ($AUC_{0\text{-}inf}$ LP-778902)/ ($AUC_{0\text{-}inf}$ LP-778902 + $AUC_{0\text{-}inf}$ telotristat ethyl)
- $MRAUC_{0\text{-}infTotalNorm}$ = ($AUC_{0\text{-}inf}$ LP-778902/$MW_{LP\text{-}778902}$)/ ($AUC_{0\text{-}inf}$ LP-778902/$MW_{LP\text{-}778902}$ + $AUC_{0\text{-}inf}$ telotristat ethyl/$MW_{telotristat\ ethyl}$
- $MRAUC_{0\text{-}tlastTotal}$ = ($AUC_{0\text{-}tlast}$ LP-778902)/ ($AUC_{0\text{-}tlast}$ LP-778902 + $AUC_{0\text{-}tlast}$ telotristat ethyl)
- $MRAUC_{0\text{-}tlastTotalNorm}$ = ($AUC_{0\text{-}tlast}$ LP-778902/$MW_{LP\text{-}778902}$)/ ($AUC_{0\text{-}tlast}$ LP-778902/$MW_{LP\text{-}778902}$ + $AUC_{0\text{-}tlast}$ telotristat ethyl/$MW_{telotristat\ ethyl}$)

For the calculation of metabolic ratios (MR) for $AUC_{0\text{-}tlast}$, t_{last} for telotristat ethyl could be different from t_{last} for its active metabolite telotristat (LP-778902).

The amount of unchanged telotristat ethyl and its active metabolite telotristat (LP-778902) excreted in urine (A_e) will also be determined (where possible).

3.1.4 Protein binding endpoints

The unbound concentrations for telotristat ethyl, its active metabolite telotristat (LP-778902) and its inactive metabolite (LP-951757) will be derived at each time point available as follows : $C_u = C_{Total}$*mean(f_u), where mean(f_u) represents the mean of the unbound fractions by timepoint.

The following PK parameters for unbound telotristat ethyl and its active metabolite telotristat (LP-778902) will be calculated using the unbound fraction F_u (defined for each subject as the mean over all time points of the mean of f_u):

- C_{maxu}: Maximum plasma concentration calculated by: $C_{maxu}=C_{max}*F_u$
- $AUC_{0\text{-}infu}$: Area under the concentration-time curve unbound from 0 to infinity calculated by: $AUC_{0\text{-}infu}=AUC_{0\text{-}inf}*F_u$
- $AUC_{0\text{-}tlastu}$: AUC from 0 to the last quantifiable unbound concentration calculated by: $AUC_{0\text{-}tlastu}=AUC_{0\text{-}tlast}*F_u$
- CL_u/F: Apparent total clearance from plasma calculated by: $CL_u/F=CL/F*F_u$
- V_{zu}/F: Apparent volume of distribution calculated by: $V_{zu}/F=V_z/F*F_u$.

For C_{maxu} and AUC_u, the following MR (normalized and not normalized) will also be calculated:

- MRC_{maxu} = (C_{maxu} LP-778902)/ (C_{maxu} telotristat ethyl)
- $MRC_{maxuNorm}$ = (C_{maxu} LP-778902/Molecular weight$(MW)_{LP\text{-}778902}$)/ (C_{maxu} telotristat ethyl/$MW_{telotristat\ ethyl}$)
- $MRAUC_{0\text{-}infu}$ = ($AUC_{0\text{-}infu}$ LP-778902)/ ($AUC_{0\text{-}infu}$ telotristat ethyl)
- $MRAUC_{0\text{-}infuNorm}$ = ($AUC_{0\text{-}infu}$ LP-778902/$MW_{LP\text{-}778902}$)/ ($AUC_{0\text{-}infu}$ telotristat ethyl/$MW_{telotristat\ ethyl}$)
- $MRAUC_{0\text{-}tlastu}$ = ($AUC_{0\text{-}tlastu}$ LP-778902)/ ($AUC_{0\text{-}tlastu}$ telotristat ethyl)
- $MRAUC_{0\text{-}tlastuNorm}$ = ($AUC_{0\text{-}tlastu}$ LP-778902/$MW_{LP\text{-}778902}$)/ ($AUC_{0\text{-}tlastu}$ telotristat ethyl/$MW_{telotristat\ ethyl}$)
- $MRC_{maxuTotal}$ = (C_{maxu} LP-778902)/ (C_{maxu} LP-778902 + C_{maxu} telotristat ethyl)
- $MRC_{maxuTotalNorm}$ = (C_{maxu} LP-778902/$MW_{LP\text{-}778902}$)/ (C_{maxu} LP-778902/$MW_{LP\text{-}778902}$ + C_{max} telotristat ethyl/$MW_{telotristat\ ethyl}$)
- $MRAUC_{0\text{-}infuTotal}$ = ($AUC_{0\text{-}infu}$ LP-778902)/ ($AUC_{0\text{-}infu}$ LP-778902 + $AUC_{0\text{-}infu}$ telotristat ethyl)
- $MRAUC_{0\text{-}infuTotalNorm}$ = ($AUC_{0\text{-}infu}$ LP-778902/$MW_{LP\text{-}778902}$)/ ($AUC_{0\text{-}infu}$ LP-778902/$MW_{LP\text{-}778902}$ + $AUC_{0\text{-}infu}$ telotristat ethyl/$MW_{telotristat\ ethyl}$
- $MRAUC_{0\text{-}tlastuTotal}$ = ($AUC_{0\text{-}tlastu}$ LP-778902)/ ($AUC_{0\text{-}tlastu}$ LP-778902 + $AUC_{0\text{-}tlastu}$ telotristat ethyl)
- $MRAUC_{0\text{-}tlastuTotalNorm}$ = ($AUC_{0\text{-}tlastu}$ LP-778902/$MW_{LP\text{-}778902}$)/ ($AUC_{0\text{-}tlastu}$ LP-778902/$MW_{LP\text{-}778902}$ + $AUC_{0\text{-}tlastu}$ telotristat ethyl/$MW_{telotristat\ ethyl}$)

3.1.5 Safety endpoints

The safety endpoints are:

- AEs;
- Clinical safety endpoints: physical examination, vital signs, 12-lead ECGs;
- Clinical laboratory tests: haematology, coagulation, biochemistry, urinalysis;
- Pregnancy tests at screening, Day -1 and EOS/ Early discontinuation visit.

3.1.6 Multiplicity

A multiplicity correction will be used in the statistical analysis to compare renal impaired function groups to the healthy group. A Bonferroni procedure will be used to keep the overall type 1 error equals to 10%. For each test, the statistical level of significance will be 10% divided by the number of hypotheses tested.

3.1.7 Significance testing and estimation

A 90% confidence interval (CI) will be calculated for the geometric least square mean ratios from the analysis of the variance (ANOVA) on the log transformed C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}tlast}$ to illustrate the difference between renal impaired group versus the control group with normal renal function. If the data permitted, 90% CI will also be calculated for PK parameters of the unbound fractions.
Moreover, 90% CI of the median difference for t_{max} will be produced using Hodges-Lehmann estimation.
The statistical analysis of safety is only descriptive therefore no formal statistical significance testing will be performed.

3.2 Analysis methods

3.2.1 Efficacy

Not applicable.

3.2.2 Pharmacokinetics

The PK analysis will be performed by a non-compartmental approach using Phoenix® WinNonLin® version 7.0 (Pharsight) and will be performed on the PK population.

3.2.2.1 PK parameters calculation

The Ipsen PDM (Pharmacokinetics Drug Metabolism) instructions (version dated 20JUN2014) for PK parameters calculation will be followed.

The following rules will be used:

- Actual sampling times will be used for deriving PK parameters.
- If an entire concentration-time profile is below the limit of quantification (BLQ), the profile will be excluded from the PK analysis
- For plasma concentrations: all BLQ values occurring before C_{max} will be replaced by 0, the first BLQ concentration after C_{max} will be replaced by LOQ/2 and the following BLQ concentrations after C_{max} will be treated as missing.
- A non-BLQ data after 2 BLQ data or a BLQ data between 2 measurable concentrations will be treated as missing.
- If the pre-dose concentration is ≤ 5% of the C_{max} value for a particular subject, that subject's data without baseline correction can be included in all PK and statistical analysis. If the pre-dose value is > 5% of C_{max}, descriptive statistics will be reported with and without the specific concerned subject(s).

- If the percentage of extrapolated part of $AUC_{0\text{-}inf}$ exceeds 20% of $AUC_{0\text{-}inf}$, the value of $AUC_{0\text{-}inf}$ is not reported.
- All estimations of λ_z will be determined using at least the three last measurable concentration data (excluding the C_{max}) and over a time interval equal to at least 2 times the estimated elimination half-life ($t_{1/2}$). Moreover, only those data points judged to describe the terminal log-linear decline resulting in an adjusted coefficient of determination value > 0.7 will be used in the regression. If at least one of these 3 conditions is not fulfilled λ_z will be flagged. If λ_z is flagged, the derived parameters ($t_{1/2}$, $AUC_{0\text{-}inf}$…) are flagged accordingly.
- The AUC will be estimated using lin/log trapezoidal rule with at least 4 measurable concentrations including at least 3 consecutive time points.
- AUC of a subject should represent more than 5% of the geometric mean AUC for each renal function group. If not, the subject is considered to have a very low plasma concentration and is not included in the calculation of descriptive statistics. However, concentrations for that subject will be reported in the appendix of the report.
- If the conditions on PK parameters detailed above are not fulfilled, unreliable PK parameters will be flagged in listings and excluded from the analysis.

Following oral administration of telotristat etiprate, absorption of telotristat ethyl was rapid and it was almost completely converted to the active metabolite telotristat (LP-778902). Therefore, as reported in the previous studies, some PK parameters for telotristat ethyl may not be calculated due to the telotristat ethyl concentrations being under the Limit of Quantification (LOQ).

No quantitative exposure data are available yet on the inactive metabolite (LP-951757) after oral administration of telotristat etiprate in humans. From the mass-balance study in humans, around 10% of the inactive metabolite (LP-951757) are retrieved in plasma from the initial amount of telotristat etiprate. Therefore, some LP-951757 concentrations may be under the LLOQ, making the estimation of the corresponding PK parameters difficult.

3.2.2.2 Descriptive statistics and listings

Descriptive summaries for each renal function group (arithmetic means, Standard Deviation (SD), Coefficient of Variation (CV%), geometric mean, geometric CV%, median, minimum, maximum, n and missing) of the plasma concentrations are calculated only if at least 2/3 of the data are above LOQ. If not, only minimum and maximum are reported.
For descriptive statistics on concentration data, the following rules will be followed:
For BLQ concentrations before C_{max}:

- If at least 2/3 of values are either BLQ values replaceable by zero and/or numeric values: statistics will be calculated considering replaceable and numeric values.
- If more than 1/3 of values are BLQ values not replaceable by zero (i.e. subjects for whom all values are BLQ): mean (SD) will not be calculated and considered as BLQ. Minimum (BLQ) and maximum value will be presented.

For BLQ concentrations after C_{max}:

- If at least 2/3 of values are not BLQ: statistics will be calculated with BLQ values replaced by the numerical value (LOQ/2).

- If more than 1/3 of values are BLQ: mean (SD) will not be calculated and considered as BLQ. Minimum (BLQ) and maximum value will be presented.

Descriptive summaries (arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum, maximum, n and missing) of the PK parameters will be presented by renal function group. Only median, [Min-Max] and n will be reported for t_{max}.

The descriptive statistics on the PK parameters will be calculated only if at least 2/3 of the data are well determined. Otherwise only minimum and maximum values will be reported.

All concentrations below LOQ or missing data will be labelled as such in the concentration data listings.
In case of outliers, two analyses will be performed: one considering the outliers and one excluding the outliers.
All listings will be sorted by renal function group, subject and measurement time.

3.2.2.3 Graphical representations

The following rules for plasma concentration versus time graphic representation will be used:

- No graphic representation will be made if all values are BLQ.
- BLQ values occurring before C_{max} will be replaced by "0".
- The first BLQ concentration after C_{max} will be replaced by LOQ/2 and the following BLQ concentrations after C_{max} will be treated as missing.

Nominal times are to be used to display the concentration plots.
The graphic representation of PK parameters will be made only if at least 2/3 of the data are well determined.

3.2.2.4 Statistical analyses

3.2.2.4.1 Plasma pharmacokinetics

For each of the 3 analytes, listings with plasma concentrations (including PK blood sampling dates and times), plasma PK parameters and metabolic ratios will be provided by renal function group and subject.
Descriptive statistics on plasma concentrations of telotristat ethyl, its active metabolite telotristat (LP-778902) and its inactive metabolite (LP-951757) will be computed for each renal function group, overall and by gender.
The individual plasma concentration-time profiles of telotristat ethyl, its active metabolite telotristat (LP-778902) and its inactive metabolite (LP-951757) will be presented graphically on linear and log/linear coordinates for each renal function group in a separated graph, using different colors for males and females. Graph of arithmetic mean (±SD) on linear and log/linear coordinates will be presented with all renal function groups on the same graph and also for each renal function group by gender. All graphs will be presented on scales 0-24 h and 0-72 h.

Descriptive statistics on PK parameters and metabolic ratios for telotristat ethyl, its active metabolite telotristat (LP-778902) and its inactive metabolite (LP-951757) will be computed for each renal function group, overall and by gender.

Scatter plots and box-whisker plots will be presented for the comparison of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ of renal function groups versus healthy control group, overall and by gender.
Additionally, for each of the 3 analytes, a linear-linear plot will be performed for C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}tlast}$, with individual PK parameters (y-axis) versus the respective individual estimated GFR value at baseline (x-axis). All subjects will be on the same graph.

An ANOVA will be performed separately for each renal impaired function group on the natural log-transformed C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ for both telotristat ethyl and its active metabolite with renal function group as a fixed term. Geometric mean ratios and corresponding 90% CI for each renal impaired group (Test) versus the healthy control group (Reference) will be computed using the following sample SAS code:

```
proc mixed data=ADPP;
        where=(<Renal function group> in (Healthy Severe)
                        /* (Healthy Moderate) (Healthy Mild) */);
        model log(AVAL) = <Renal function group>;
        lsmeans <Renal function group> / cl alpha=0.10/<nb of hypotheses>;
        estimate "Renal impaired / Healthy" <Renal function group> -1 1 / cl
alpha=0.10/<nb of hypotheses>;
run;
```

The resulting least-squares (LS) means, difference in LS means between two groups (test minus reference), and corresponding 90% CIs will be exponentiated. The exponentiation of the difference in LS means will yield the estimated ratio of the PK parameter for a renal impaired function group relative to healthy subjects. These ratios will be expressed as a percentage relative to the reference group (test [mild, moderate, or severe renal impaired groups] versus reference [healthy group]).
For each test, a Bonferroni correction will be applied to adjust the statistical level of significance in order to keep the overall type 1 error equals to 0.10 (see section 3.1.6 for details).
No analysis will be performed if more than 1/3 of the values are not determined.
In case of exclusion of subjects in the severe renal impaired function group or in the healthy group, a sensitivity ANOVA will be performed with the included subjects and only including their matching subjects.

For t_{max}, an estimate of the median difference and 90% CI of the median difference will be provided using Hodges-Lehmann estimation, based on Walsh averages, using the following SAS code:

```
proc npar1way hl alpha=0.1 data= ADPP;
        where <Renal function group> in (Severe Healthy) and
                PARAMCD='TMAX';
        class <Renal function group>;
        var AVAL;
        exact hl;
run;
```

The Wilcoxon-Mann-Whitney test will be used to test for the difference in t_{max} between healthy subjects and each renal function group.

3.2.2.4.2 Urine pharmacokinetics

Listings with urine concentrations (including PK urine sampling dates and times), and urine PK parameters will be provided by renal function group and subject.
Descriptive statistics on urine concentrations and urine PK parameter (Ae) of telotristat ethyl and its active metabolite telotristat (LP-778902) will be computed for each renal function group, overall and by gender.
Individual urine cumulative recovered amount versus time profiles of telotristat ethyl and its active metabolite telotristat (LP-778902) will be presented graphically for each renal impaired function group with all subjects on the same graph.
The graph of arithmetic mean + SD over time will be provided for urine concentration of telotristat ethyl and its active metabolite telotristat (LP-778902) with all renal function groups on the same graph, as well as for urine cumulative recovered amount (Ae), overall and by gender.

3.2.2.4.3 Protein binding

Listings with unbound plasma concentrations (including unbound plasma fraction and PK blood sampling dates and times), unbound plasma PK parameters and metabolic ratios will be provided by renal function group and subject.
Descriptive statistics on plasma unbound concentrations of telotristat ethyl, its active metabolite telotristat (LP-778902) and its inactive metabolite (LP-951757) will be computed for each renal function group, overall and by gender.

Descriptive statistics on unbound PK parameters (including unbound fractions) and metabolic ratios for telotristat ethyl, its active metabolite telotristat (LP-778902) and its inactive metabolite (LP-951757) will be computed for each renal function group, overall and by gender.
Scatter plots and box-whisker plots will be presented for the comparison of C_{maxu}, $AUC_{0\text{-}tlastu}$, $AUC_{0\text{-}infu}$ and unbound fractions of renal function groups versus healthy control group, overall and by gender.

If the data permitted, same ANOVA as above will be performed separately for each renal impaired function group on the natural log-transformed C_{maxu}, $AUC_{0\text{-}tlastu}$, $AUC_{0\text{-}infu}$ and unbound fractions (fu; no log-transformed) for both telotristat ethyl and its active metabolite with renal function group as a fixed term. The same SAS code as the previous analysis will be used. Sensitivity analysis will also be conducted, the same method as described above will be used.

3.2.3 Safety

All safety data will be included in the data listings and summary tables will be based on the safety population.

3.2.3.1 Adverse events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) with the current version at Ipsen coding department at the time of database lock.

Listings will be presented and sorted by renal impaired function group, subject, start date-time, primary system organ class, preferred term and reported term for all AEs recorded during the study.

Listings of all AEs, serious adverse events (SAE), AEs leading to withdrawal and listing of deaths will also be presented.

Treatment Emergent Adverse Events (TEAE) will be flagged (*) in the listing of AEs and will be summarised.

A TEAE is defined as any AE that occurs during the active phase of the study (from the time of the subject giving informed consent until the EOS/early withdrawal) if:

- it was not present prior to administration of IMP, or
- it was present prior to administration of IMP but the intensity increased after administration of IMP.

An overall summary table of all AEs will be presented.

TEAEs will be summarised by renal function group with the number and percentage of subjects with AEs classified by primary system organ class and preferred term. The number of occurrences of a TEAE will also be presented.

In addition, summary tables will also be presented for SAEs, serious TEAEs, TEAEs by decreasing frequency, TEAEs by maximum intensity, TEAEs by most serious causality and TEAEs leading to premature study withdrawal.

In case of missing intensity, the intensity will be considered as severe and in case of missing causality, the causality will be considered as related.

In the event of multiple reports of the same preferred term being reported by the same subject, the maximum intensity (severe > missing> moderate > mild) and the most serious causality (related > not related) will be chosen.

3.2.3.2 Laboratory data

3.2.3.2.1 Standardisation

As in this study several laboratories are involved in the assessment of biological samples, a standardisation method will be used in order to take into account the differences between the reference ranges of these laboratories.

The laboratory which analyses the majority of the samples will be used as the reference laboratory.

In a general way, standardised values will be assessed using the following formula:

$$X_{St} = X_{LRef} + \left(X_{URef} - X_{LRef}\right)\frac{X - X_L}{X_U - X_L}$$ where

X = measured value

X_L = lower limit value for the laboratory of the measured value

X_U = upper limit value for the laboratory of the measured value

X_{LRef} = lower limit value for the laboratory chosen as a reference

X_{URef} = upper limit value for the laboratory chosen as a reference

If a standardised value is negative it will be replaced by 0.

Standardised values will be used for the quantitative analyses, initial values will be used for qualitative analyses.

3.2.3.2.2 Laboratory data

Laboratory data will be displayed in International System (SI) units and a separate listing of normal ranges for SI units will be provided (by gender and age where relevant).

Laboratory data (haematology, biochemistry, coagulation and urinalysis) will be listed in SI units and abnormal values will be flagged (High [H], Low [L], clinically significant [CS]) where applicable. Any unscheduled laboratory assessments will be flagged [U] in the listings.

In addition, a listing will be presented of all values for a subject with at least a clinically significant abnormal laboratory value.

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to IMP administration.

For haematology, biochemistry and coagulation, summary statistics will be presented by renal function group at each scheduled assessment for standardised values and changes from baseline. For haematology and biochemistry, shift tables from baseline to each applicable post baseline visit will be presented using the number and percentage of subjects with low, normal or high values.

For continuous urinalysis, summary statistics will be presented by renal function group at each scheduled assessment for standardised values and changes from baseline.

For categorical urinalysis (absent/trace/positive) frequency tables, by renal function group, will be presented at each scheduled assessment.

Subject plots over time representing all subjects on the same graph will also be presented for creatinine. Normal ranges will also be displayed.

3.2.3.3 Physical examination

A listing with the date of test will be provided by renal function group, subject and date.

3.2.3.4 Vital signs

Vital signs will be listed at each assessment by renal function group and subject. Any unscheduled vital signs will be flagged [U] in the listing.

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to IMP administration.

Summary statistics by renal function group will be presented at each scheduled assessment for actual values and changes from baseline of supine BP, heart rate and weight.

Shift tables will be presented of the number and percentage of subjects with low, normal or high values.

Summary statistics by renal function group will also be presented for body temperature at Day-1.

3.2.3.5 ECG

ECG results will be listed at each assessment by renal function group and subject. Any unscheduled ECG will be flagged [U] in the listings.

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to IMP administration.

For continuous ECG parameters (HR, RR, PR, QRS, QT and QTcF), summary statistics by renal function group will be presented at each scheduled assessment for actual values and changes from baseline. Shift tables will also be presented using the number and percentage of subjects with low, normal or high values.

For interpretation of clinical significance (within normal limits / abnormal, not clinically significant / abnormal, clinically significant / not evaluable), a frequency table will be presented, by renal function group, at each post-dose assessment.

3.2.3.6 Pregnancy tests

A listing with the date of examination, the status of the examination (performed/not performed) and the result (positive/negative) will be provided by renal function group, subject and examination date.

3.2.4 Missing data and outliers

3.2.4.1 Missing data

No missing value will be replaced.
If a value required a retest, the last reliable non-missing value will be taken into account if measured before the administration of IMP; and the first non-missing reliable value for post-baseline assessments. An assessment will be considered reliable if it is performed without any technical problem and if the result is within the range of plausible values.
Any repeat or additional assessments performed will be included in the individual subject data listings.
If there is a significant number of missing values for a subject (or if there is confirmed data appearing spurious), a decision will be made following consultation with the sponsor regarding the handling of these data in summaries, prior to database lock and will be documented in the minutes of the data review meeting.

3.2.4.2 Missing or incomplete dates

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

(1) The most conservative approach will be systematically considered (i.e. if the onset date of an AE is missing / incomplete, it is assumed to have occurred during the study treatment phase (e.g. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).

(2) A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

(3) If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered (e.g. a medication with partial start and stop dates could be considered as prior and concomitant treatment).

(4) Where this is possible, the derivations based on a partial date will be presented as superior inequalities (e.g. for an AE started in FEB2004 after the administration performed on 31JAN2004, the days since last dose will be "≥ 2", similarly the duration of ongoing AEs or medication will be "≥ xx" according to the start and last visit dates).

3.2.4.3 Outliers

Any outlier which is implausible will be excluded from the analysis and will be documented in the minutes of the data review or in a note-to-file. For other identified outliers, the impact should be assessed by performing the statistical analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect.

3.2.5 Subject disposition

A listing of screen failures and a listing of subject disposition will also be presented on the screened population.

The number and percentage of subjects screened and included in each analysis population will be presented by renal function group and overall for the screened population.

A listing of the inclusion and exclusion criteria will be provided by renal function group and subject as well as listings of subjects with inclusion or exclusion criteria not respected. Subject eligibility will also be listed.

The reasons for subject exclusions from each population will also be tabulated and listed by renal function group on the included population.

A summary table will present the extent of subject duration in the study for each renal function group. The definition of the length of study duration is calculated from the date of administration to the last study visit.

A listing of dates of assessments and their study duration will be presented by subject for each renal function group. The number and percentage of subjects at each planned visit during the study will be presented, by renal function group for the Safety population.

3.2.6 Withdrawals

Discontinued subjects will be listed with their reasons for withdrawal and a summary table of the number and percentage of subjects who withdrew from the study and the reasons for withdrawal will be presented by renal function group for the included population.

3.2.7 Demographic and baseline characteristics

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to IMP administration.

All demographic (sex, ethnicity, race) and baseline characteristics (age, height, body weight and BMI at baseline) as well as the substance use (tobacco, caffeine and alcohol) will be listed by renal function group and subject.

Summary statistics will be provided for demographic and baseline characteristics as well as the substance use, by renal function group on the Safety population.

The results of urine drug of abuse tests, alcohol breath test, serology, postmenopausal status and FSH (if applicable) will only be provided in the demographics data listings.

Number and percentages of subjects in each renal function classification will be tabulated by renal function group and renal classification will also be listed with the eGFR results by renal function group on the safety population.

3.2.8 Medical and surgical history

Medical and surgical history will be coded using MedDRA current version at Ipsen coding department at the time of database lock.

Listings will present the primary system organ class, the preferred term and the reported term. The listings will be sorted by renal function group, subject, start date, primary system organ class, preferred term and reported term.

A frequency table of the number and percentage of subjects will be provided for all medical and surgical history by primary system organ class and preferred term for each renal function group and overall for the Safety population.

3.2.9 Subject compliance

All treatment administration information will be listed by renal function group and subject.

Protocol deviations, defined prior to database lock, will be listed by renal function group and subject. Protocol deviations which exclude a subject from the PK population will be flagged. Additionally, major protocol deviations will be summarised on the included population.

3.2.10 Prior and concomitant medications

Concomitant medications will be coded using WHO-DD with the current version at Ipsen coding department at the time of database lock. The therapeutic class will correspond to the second level of Anatomic Therapeutic Class (ATC) code, which corresponds to the first 3 digits.

The date and time of baseline (study day 1) will be used as the cut-off date for the definition of prior and concomitant medications. A medication that started before study day 1 and is continuing at time of day 1 will be considered as both, prior and concomitant. Prior, concomitant and both prior and concomitant medications will be flagged P, C and PC respectively, in all listings.

Listings will be presented for the therapeutic class, preferred name and reported name. The listings will be sorted by renal function group, subject, chronological start date, therapeutic class, preferred name and reported name.

Frequency tables of the number and percentage of subjects with at least one concomitant medication will be provided by therapeutic class and preferred name for each renal function group and overall.

3.2.11 Prior and concomitant non-drug therapies

Prior and concomitant non-drug therapies will be coded using MedDRA Dictionary with the current version at Ipsen coding department at the time of database lock.

Prior and concomitant non-drug therapies will be listed by renal function group, subject, chronological start date, primary system organ class, preferred term, and reported term.

3.2.12 Concomitant surgical procedures

Concomitant surgical procedures will be coded using MedDRA Dictionary with the current version at Ipsen coding department at the time of database lock. Concomitant surgical procedures will be listed by renal function group, subject, chronological start date, primary system organ class, preferred term, and reported term.

3.2.13 Derived data

The derived data are variables which are calculated from the raw data in the eCRF and not included in the database and will be included in the listings (see Appendix 1).

3.2.14 Rules and data formats

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented with the number of decimal places collected, and derived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers). For plasma

concentrations and PK parameters, all values will be reported with 3 significant digits for numbers < 1000, otherwise values will not be rounded.

For summary statistics, the following will be presented: n, missing, arithmetic mean, standard deviation, median and the range (minimum, maximum). Geometric mean, CV% and geometric CV% will also be presented for plasma concentrations and PK parameters (where applicable).

Mean, median and standard deviation values will be reported with one decimal place greater than the raw/derived data that they summarise. Minimum and maximum values will be reported with the same precision as the raw data. For plasma concentrations and PK parameters, all statistics will be reported with 3 significant digits for numbers < 1000, otherwise values will not be rounded.

CV% and ratio will be presented with one decimal place.

Percentages will be reported with 1 decimal place and 0% will not be presented. Percentages will be calculated using a denominator of all subjects in a specified population and by renal function group. The denominator will be specified in a footnote to the tables for clarification if necessary.

All values below or above a limit of detection (e.g. < 0.1 or > 100) will be listed as such. For each safety parameter for which it is possible to have values below or above LOQ, the rule to be used in the statistical tables is to replace values below or above a limit of quantification by LOQ. Rules for BLQ plasma concentrations are detailed in section 3.2.2.1.

All text fields must be left justified and numeric or numeric with some text specification (e.g. not done, unknown, < 4.5, …) must be decimal justified. Dates will be presented in the format [yyyy-mmm-dd] and times in the format [hh:mm].

3.2.15 Pooling of Centres

It is not planned to perform a subgroup analysis on individual or groups of centres.

3.2.16 Interim analysis

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 enrolled in the study.

3.2.17 Role of data review committee (DRC)

Decision to include (or not) subjects with mildly impaired renal function and subjects with moderately impaired renal function will be made by a committee (comprising at least the co-ordinating principal investigator and the sponsor's medical monitor), and 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.

3.2.18 Covariates and analysis of subgroups

Descriptive statistics and graphs for plasma and urine concentrations and plasma PK parameters of telotristat ethyl, its active metabolite telotristat (LP-778902) and its inactive metabolite (LP-951757) as well as Ae will be also performed by gender.

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

The statistical analysis will be performed using PC on a Windows 7 Professionnel operating system.

4.2 Software

Pharmacokinetic data will be analysed using Phoenix® WinNonLin® version 7.0 (Pharsight).

All TFLs will be produced and statistical analysis performed using SAS version 9.4 [2]. All outputs will be in Microsoft Word Format.

4.3 Validation programs

Biotrial Biometrics will provide a validation plan to Ipsen identifying the methods of validation.

The study statistician is responsible for reviewing each output associated with the deliverable product. Program logs are checked by the statistical programmer for logical, syntax and fatal errors. The checks in SAS includes, but is not limited to, all ERRORS, WARNINGS, BY-VALUE merge messages, NOTES, and UNINITIALIZED variables. Program logs are also reviewed for accurate and consistent variable and observation counts following each procedure and data step.

The study statistician is responsible for checking and reviewing the work produced using whatever method he/she feels is appropriate (e.g. SAS code review, hand calculation, etc.) to reassure of the quality of the output.

Outputs are reviewed for typographical errors, misspellings and nonsensical values or results and to check the consistency with the statistical analysis plan. Outputs are cross-checked against each other for accuracy and consistency. For statistical tables, listings, appendix listings, and figures, this procedure includes comparison of subject group numbers, counts of subjects at each observation point, and consistency of results for variables between outputs.

Findings of the quality control reviews are communicated to the party responsible for making necessary changes. The programs will be retested after modifications.

After final review, and when no further change is required to produce the deliverable, the statistical programmer and the study statistician have to complete and sign the quality control and statistical analysis results follow-up's validation checklist, to indicate that they have successfully performed all of their responsibilities. Copies of the internal quality control forms produced for the validation process will be provided to the sponsor to support the validation.

4.4 Restitution of the programs

All programs (including macros and analysis datasets) producing the tables, listings and statistical outputs along with associated logs should be given to the sponsor when the TFLs and statistical analyses have been finalised.

5 CHANGES FROM PROTOCOL

Compared to the final protocol dated 20 December 2017, the included population was added in the SAP.

In section 1.3.2.2, the method of determination of the inactive metabolite (LP-951757) plasma concentrations was precised based on Clarification N°1 to the protocol version 2.0 signed 27 February 2018.

No other change was stated at the time of finalisation of the SAP.

6 REFERENCES

1. International Conference on Harmonisation (ICH) E9 and Federal register Vol. 63, No. 179 (September 1998).

2. SAS, Version 9.4. SAS Institute Inc., Cary, NC, USA, 2012.

7 APPENDICES TO THE SAP TEMPLATE

Appendix 1: Derived Data

The following derived data will be calculated:

(1) **Study day**

Study day will be defined as '-1' for the day prior to IMP administration and as '1' for the day of IMP administration (i.e. day 0 does not exist).

(2) **Study duration**

Study duration (days) will be calculated as (last visit attended - date of IMP administration) + 1.

(3) **Baseline**

Baseline will be derived as the last available (and reliable if applicable) assessment before IMP administration.

(4) **Changes from baseline**

Changes from baseline will be calculated as the difference from baseline (e.g. assessment at the visit – assessment at baseline).

(5) **Therapeutic Class**

The therapeutic class will correspond to the first 3 digits of the ATC code. The decoding of the therapeutic class will be done from the WHO-DD (current version at the time of database lock).

(6) **Prior and concomitant flags**

The date and time of baseline (study day 1) is used as the cut-off date for the definition of prior and concomitant medications. A medication started before study day 1 and continuing at time of Day 1 is considered as both, prior and concomitant. Prior, concomitant and both prior and concomitant will be coded as P, C and PC respectively.

(7) **Prior and concomitant medication duration**

If the start and end dates of the medication are identical then "<1" day will be presented with the duration in hh:mm recorded in the eCRF if it is available. If times are available, the duration of concomitant treatments will be calculated as (end date/time - start date/time). If at least one time is missing, the duration of concomitant treatments will be calculated as (end date - start date) + 1. If the recorded end date is continuing at the end of the study then the end date will be listed as "ongoing" and the duration will be approximated as "≥(last attended visit date – start date) + 1" day(s). If the start date or the end date are partial, the duration will be presented as an inequality "≥xx" day(s) [i.e. ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004] but if both are partial or one is missing the duration will not be presented.

(8) **Medical and surgical history duration**

The duration of medical and surgical history will be calculated as (end date – start date) + 1. If the recorded end date is CONT. (for continuing), the end date will be listed as "ongoing" and the duration will be approximated as "≥ (screening visit date – start date)+1" day(s). If the start date or the end date are partial, the duration will be presented as an inequality "≥ xx"day(s) (i.e. ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004) but if both are partial or one is missing the duration will not be presented.

(9) **AE duration**

If the start and end dates of the AE are identical then "<1" day will be presented with the duration in hh:mm recorded in the eCRF if it is available. If times are available, the duration will be calculated as (end date/time – start date/time) and presented in days hh:mm. If at least one time is missing and if the duration is greater than 24 hours then it will be calculated as (end date - start date) + 1 and presented in days. If the recorded end date is continuing at the end of the study, the end date will be listed as "ongoing" and the duration will be approximated as "≥(last attended visit date – start date) + 1" day(s). If the start date or the end date are partial the duration will be presented as a superior inequality "≥xx" day(s) [i.e. ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004].

(10) **Unbound concentration**

For each subject and at each protein binding timepoint, the mean of the replicates of the unbound fractions (f_{u1}, f_{u2}, f_{u3} and f_{u4}) will be derived. The unbound concentrations at time t for telotristat ethyl, its active metabolite telotristat (LP-778902) and its inactive metabolite (LP-951757) will be derived as follows: $C_{tu} = C_t$* mean(f_{u1}, f_{u2}, f_{u3}, f_{u4}).

Appendix 2: List of TFLs

Listings index

16.1.7 Randomisation Scheme and Codes

Not applicable

16.2 SUBJECT DATA LISTINGS

16.2.1 Discontinued subjects

Listing 16.2.1.1: Subject Disposition – Screened Population

Listing 16.2.1.2: Subject Disposition – Study Withdrawals – Included Population

Listing 16.2.1.3.1: Inclusion Criteria Assessments

Listing 16.2.1.3.2: Inclusion Criteria not respected– Included Population

Listing 16.2.1.4.1: Exclusion Criteria Assessments

Listing 16.2.1.4.2: Exclusion Criteria not respected– Included Population

Listing 16.2.1.5: Screen failures– Screened Population

Listing 16.2.1.6: Assessments Dates – Included Population

16.2.2 Protocol deviations

Listing 16.2.2.1: Subject Eligibility for the Study – Included Population

Listing 16.2.2.2: Protocol Deviations – Included Population

Listing 16.2.2.3: Reasons for Exclusion from the Populations – Included Population

16.2.3 Subjects excluded from the efficacy analysis

Not applicable

16.2.4 Demographic data

Listing 16.2.4.1: Demographics and Baseline Characteristics – Safety Population

Listing 16.2.4.2: Alcohol screen – Safety Population

Listing 16.2.4.3: Urine Drug of Abuse Tests – Safety Population

Listing 16.2.4.4: Substance Use – Safety Population

Listing 16.2.4.5: Serology – Safety Population

Listing 16.2.4.6: Postmenopausal Status – Safety Population

Listing 16.2.4.7: FSH – Safety Population

Listing 16.2.4.8: Renal Function Classification – Safety Population

Listing 16.2.4.9.1: Medical and Surgical History – Reported Terms and Associated MedDRA Terms – Safety Population

Listing 16.2.4.9.2: Medical and Surgical History – Safety Population

Listing 16.2.4.10.1: Prior and Concomitant Medications – WHO-DD Names – Safety Population

Listing 16.2.4.10.2: Prior and Concomitant Medications – Safety Population

Listing 16.2.4.11.1: Prior and Concomitant Non-Drug Therapies – Reported Terms and Associated MedDRA Terms – Safety Population

Listing 16.2.4.11.2: Prior and Concomitant Non-Drug Therapies – Safety Population

Listing 16.2.4.12.1: Concomitant Surgical Procedures – Reported Terms and Associated MedDRA Terms – Safety Population

Listing 16.2.4.12.2: Concomitant Surgical Procedures – Safety Population

16.2.5 Compliance and drug concentration data

Listing 16.2.5.1: Study Treatment Administration – Safety Population

Listing 16.2.5.2: Study Duration – Safety Population

Listing 16.2.5.3.1: Telotristat Ethyl – Plasma Concentrations – Included Population

Listing 16.2.5.3.2: LP-778902 – Plasma Concentrations – Included Population

Listing 16.2.5.3.3: LP-951757 – Plasma Concentrations – Included Population

Figure 16.2.5.4.1: Telotristat Ethyl – Individual Plasma Concentration Time Curves – Pharmacokinetic Population

Figure 16.2.5.4.2: LP-778902 – Individual Plasma Concentration Time Curves – Pharmacokinetic Population

Figure 16.2.5.4.3: LP-951757 – Individual Plasma Concentration Time Curves – Pharmacokinetic Population

Listing 16.2.5.5.1: Telotristat Ethyl – Plasma Pharmacokinetic Parameters – Pharmacokinetic Population

Listing 16.2.5.5.2: LP-778902 – Plasma Pharmacokinetic Parameters – Pharmacokinetic Population

Listing 16.2.5.5.3: LP-951757 – Plasma Pharmacokinetic Parameters – Pharmacokinetic Population

Listing 16.2.5.5.4: Metabolic Ratios – Pharmacokinetic Population

Listing 16.2.5.6.1: Telotristat Ethyl – Urine Concentrations – Included Population

Listing 16.2.5.6.2: LP-778902 – Urine Concentrations – Included Population

Figure 16.2.5.7.1: Telotristat Ethyl - Individual urine cumulative recovered amount versus time profiles – Pharmacokinetic Population

Figure 16.2.5.7.2: LP-778902 - Individual urine cumulative recovered amount versus time profiles – Pharmacokinetic Population

Listing 16.2.5.8.1: Telotristat Ethyl – Urine Pharmacokinetic Parameters – Pharmacokinetic Population

Listing 16.2.5.8.2: LP-778902 – Urine Pharmacokinetic Parameters – Pharmacokinetic Population

Listing 16.2.5.9.1: Telotristat Ethyl – Unbound Plasma Concentrations – Included Population

Listing 16.2.5.9.2: LP-778902 – Unbound Plasma Concentrations – Included Population

Listing 16.2.5.9.3: LP-951757 – Unbound Plasma Concentrations – Included Population

Listing 16.2.5.10.1: Telotristat Ethyl – Unbound Pharmacokinetic Parameters – Pharmacokinetic Population

Listing 16.2.5.10.2: LP-778902 – Unbound Pharmacokinetic Parameters – Pharmacokinetic Population

Listing 16.2.5.10.3: LP-951757 – Unbound Pharmacokinetic Parameters – Included Population

Listing 16.2.5.10.4: Metabolic Ratios for Unbound Pharmacokinetic Parameters – Pharmacokinetic Population

16.2.6 Pharmacodynamic data

Not applicable

16.2.7 Adverse event listings

Listing 16.2.7.1: Adverse Events Key Information

Listing 16.2.7.2: All Adverse Events – Safety Population

Listing 16.2.7.3: Serious Adverse Events – Safety Population

Listing 16.2.7.4: Adverse Events Leading to Withdrawal – Safety Population

Listing 16.2.7.5: Deaths – Safety Population

16.2.8 Listing of individual laboratory measurements by subject

Listing 16.2.8.1: Normal Ranges for SI Units

Listing 16.2.8.2: Haematology (SI Units) [Raw Data and Changes from Baseline] – Safety Population

Listing 16.2.8.3: Biochemistry (SI Units) [Raw Data and Changes from Baseline] – Safety Population

Listing 16.2.8.4: Coagulation (SI Units) [Raw Data and Changes from Baseline] – Safety Population

Listing 16.2.8.5: Urinalysis (SI Units) [Raw Data and Changes from Baseline] – Safety Population

Listing 16.2.8.6: Pregnancy Test – Safety Population

16.2.9 Listing of other safety data

Listing 16.2.9.1: Assessment of Physical Examination – Safety Population

Listing 16.2.9.2: Vital Signs [Raw Data and Changes from Baseline] – Safety Population

Listing 16.2.9.3: 12-lead ECG [Raw Data and Changes from Baseline] – Safety Population

Tables index

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 DEMOGRAPHIC DATA

Table 14.1.1: Subjects Populations - Screened Population

Table 14.1.2: Subjects Disposition - Screened Population

Table 14.1.3.1: Major Protocol Deviations – Included Population

Table 14.1.3.2: Reasons for Exclusion from the Populations – Included Population

Table 14.1.4: Subjects Disposition by Visit – Safety Population

Table 14.1.5: Study Duration – Safety Population

Table 14.1.6: Demographics and Baseline Characteristics – Safety Population

Table 14.1.7: Substance Use – Safety Population

Table 14.1.8: Renal Function Classification – Safety Population

Table 14.1.9: Medical and Surgical History – Safety Population

Table 14.1.10: Concomitant Medications – Safety Population

14.2 PHARMACOKINETIC DATA

14.2.1 PLASMA PHARMACOKINETIC DATA

Table 14.2.1.1.1: Telotristat Ethyl Plasma Concentrations (unit) (Summary Statistics) – Pharmacokinetic Population

Table 14.2.1.1.2: LP-778902 Plasma Concentrations (unit) (Summary Statistics) – Pharmacokinetic Population

Table 14.2.1.1.3: LP-951757 Plasma Concentrations (unit) (Summary Statistics) – Pharmacokinetic Population

Figure 14.2.1.2.1: Graphs of Plasma Concentrations Arithmetic Means (±SD) over Time for Telotristat Ethyl – Pharmacokinetic Population

Figure 14.2.1.2.2: Graphs of Plasma Concentrations Arithmetic Means (±SD) over Time for LP-778902 – Pharmacokinetic Population

Figure 14.2.1.2.3: Graphs of Plasma Concentrations Arithmetic Means (±SD) over Time for LP-951757 – Pharmacokinetic Population

Table 14.2.1.3.1: Telotristat Ethyl Plasma Pharmacokinetic Parameters (Summary Statistics) – Pharmacokinetic Population

Table 14.2.1.3.2: LP-778902 Plasma Pharmacokinetic Parameters (Summary Statistics) – Pharmacokinetic Population

Table 14.2.1.3.3: LP-951757 Plasma Pharmacokinetic Parameters (Summary Statistics) – Pharmacokinetic Population

Table 14.2.1.3.4: Metabolic Ratios (Summary Statistics) – Pharmacokinetic Population

Figure 14.2.1.4.1: Scatter Plots of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ for Telotristat Ethyl – Pharmacokinetic Population

Figure 14.2.1.4.2: Scatter Plots of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ for LP-778902 – Pharmacokinetic Population

Figure 14.2.1.4.3: Scatter Plots of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ for LP-951757 – Pharmacokinetic Population

Figure 14.2.1.5.1: Box-Whisker Plots of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ for Telotristat Ethyl – Pharmacokinetic Population

Figure 14.2.1.5.2: Box-Whisker Plots of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ for LP-778902 – Pharmacokinetic Population

Figure 14.2.1.5.3: Box-Whisker Plots of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ for LP-951757 – Pharmacokinetic Population

Figure 14.2.1.6.1: Plots of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ versus individual eGFR values for Telotristat Ethyl – Pharmacokinetic Population

Figure 14.2.1.6.2: Plots of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ versus individual eGFR values for LP-778902 – Pharmacokinetic Population

Figure 14.2.1.6.3: Plots of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ versus individual eGFR values for LP-951757 – Pharmacokinetic Population

Table 14.2.1.7.1.1: Comparison of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ for Telotristat Ethyl between each Renal Impairment Group and Healthy Control Group (ANOVA) – Pharmacokinetic Population

Table 14.2.1.7.1.2: Comparison of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ for Telotristat Ethyl between each Renal Impairment Group and Healthy Control Group (ANOVA) – Sensitivity analysis – Pharmacokinetic Population

Table 14.2.1.7.2.1: Comparison of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ for LP-778902 between each Renal Impairment Group and Healthy Control Group (ANOVA) – Pharmacokinetic Population

Table 14.2.1.7.2.2: Comparison of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ for LP-778902 between each Renal Impairment Group and Healthy Control Group (ANOVA) - Sensitivity analysis – Pharmacokinetic Population

Table 14.2.1.8.1: Comparison of t_{max} for Telotristat Ethyl between each Renal Impairment Group and Healthy Control Group (Hodges-Lehmann Estimation) – Pharmacokinetic Population

Table 14.2.1.8.2: Comparison of t_{max} for LP-778902 between each Renal Impairment Group and Healthy Control Group (Hodges-Lehmann Estimation) – Pharmacokinetic Population

14.2.2 URINE PHARMACOKINETIC DATA

Table 14.2.2.1.1: Telotristat Ethyl Urine Concentrations (unit) (Summary Statistics) – Pharmacokinetic Population

Table 14.2.2.1.2: LP-778902 Urine Concentrations (unit) (Summary Statistics) – Pharmacokinetic Population

Figure 14.2.2.2.1: Telotristat Ethyl – Graphs of Urine Concentrations Arithmetic Means (+SD) – Pharmacokinetic Population

Figure 14.2.2.2.2: LP-778902 - Graphs of Urine Concentrations Arithmetic Means (+SD) – Pharmacokinetic Population

Table 14.2.2.3.1: Telotristat Ethyl Urine PK parameters (Summary Statistics) – Pharmacokinetic Population

Table 14.2.2.3.2: LP-778902 Urine PK parameters (Summary Statistics) – Pharmacokinetic Population

Figure 14.2.2.4.1: Telotristat Ethyl – Graphs of Cumulative Recovered Amount-Time Curves Arithmetic Means (+SD) – Pharmacokinetic Population

Figure 14.2.2.4.2: LP-778902 - Graphs of Cumulative Recovered Amount-Time Curves Arithmetic Means (+SD) – Pharmacokinetic Population

14.2.3 DERIVED UNBOUND PHARMACOKINETIC DATA

Table 14.2.3.1.1: Telotristat Ethyl Unbound Plasma Concentrations (unit) (Summary Statistics) – Pharmacokinetic Population

Table 14.2.3.1.2: LP-778902 Unbound Plasma Concentrations (unit) (Summary Statistics) – Pharmacokinetic Population

Table 14.2.3.1.3: LP-951757 Unbound Plasma Concentrations (unit) (Summary Statistics) – Pharmacokinetic Population

Table 14.2.3.2.1: Telotristat Ethyl Unbound Pharmacokinetic Parameters and Unbound Fractions (Summary Statistics) – Pharmacokinetic Population

Table 14.2.3.2.2: LP-778902 Unbound Pharmacokinetic Parameters and Unbound Fractions (Summary Statistics) – Pharmacokinetic Population

Table 14.2.3.2.3: LP-951757 Unbound Pharmacokinetic Parameters and Unbound Fractions (Summary Statistics) – Pharmacokinetic Population

Table 14.2.3.2.4: Metabolic Ratios for Unbound Pharmacokinetic Parameters (Summary Statistics) – Pharmacokinetic Population

Figure 14.2.3.3.1: Scatter Plots of C_{maxu}, $AUC_{0\text{-}tlastu}$, $AUC_{0\text{-}infu}$ and unbound fractions for Telotristat Ethyl – Pharmacokinetic Population

Figure 14.2.3.3.2: Scatter Plots of C_{maxu}, $AUC_{0\text{-}tlastu}$, $AUC_{0\text{-}infu}$ and unbound fractions for LP-778902 – Pharmacokinetic Population

Figure 14.2.3.3.3: Scatter Plots of C_{maxu}, $AUC_{0\text{-}tlastu,}$ $AUC_{0\text{-}infu}$ and unbound fractions for LP-951757 – Pharmacokinetic Population

Figure 14.2.3.4.1: Box-Whisker Plots of C_{maxu}, $AUC_{0\text{-}tlastu,}$ $AUC_{0\text{-}infu}$ and unbound fractions for Telotristat Ethyl – Pharmacokinetic Population

Figure 14.2.3.4.2: Box-Whisker Plots of C_{maxu}, $AUC_{0\text{-}tlastu,}$ $AUC_{0\text{-}infu}$ and unbound fractions for LP-778902 – Pharmacokinetic Population

Figure 14.2.3.4.3: Box-Whisker Plots of C_{maxu}, $AUC_{0\text{-}tlastu,}$ $AUC_{0\text{-}infu}$ and unbound fractions for LP-951757 – Pharmacokinetic Population

Table 14.2.3.5.1.1: Comparison of C_{maxu}, $AUC_{0\text{-}tlastu,}$ $AUC_{0\text{-}infu}$ and unbound fractions for Telotristat Ethyl between each Renal Impairment Group and Healthy Control Group (ANOVA) – Pharmacokinetic Population

Table 14.2.3.5.1.2: Comparison of C_{maxu}, $AUC_{0\text{-}tlastu,}$ $AUC_{0\text{-}infu}$ and unbound fractions for Telotristat Ethyl between each Renal Impairment Group and Healthy Control Group (ANOVA) – Sensitivity analysis – Pharmacokinetic Population

Table 14.2.3.5.2.1: Comparison of C_{maxu}, $AUC_{0\text{-}tlastu,}$ $AUC_{0\text{-}infu}$ and unbound fractions for LP-778902 between each Renal Impairment Group and Healthy Control Group (ANOVA) – Pharmacokinetic Population

Table 14.2.3.5.2.2: Comparison of C_{maxu}, $AUC_{0\text{-}tlastu,}$ $AUC_{0\text{-}infu}$ and unbound fractions for LP-778902 between each Renal Impairment Group and Healthy Control Group (ANOVA) - Sensitivity analysis – Pharmacokinetic Population

14.3 SAFETY DATA

14.3.1 Displays of adverse events

Table 14.3.1.1: Overall Summary of Adverse Events – Safety Population

Table 14.3.1.2: Number (%) of Subjects Reporting Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term – Safety Population

Table 14.3.1.3: Number (%) of Subjects Reporting Serious Adverse Events by Primary System Organ Class and Preferred Term – Safety Population

Table 14.3.1.4: Number (%) of Subjects Reporting Serious Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term – Safety Population

Table 14.3.1.5: Number (%) of Subjects Reporting Treatment Emergent Adverse Events Leading to Withdrawal by Primary System Organ Class and Preferred Term – Safety Population

Table 14.3.1.6: Number (%) of Subjects Reporting Treatment Emergent Adverse Events by Decreasing Frequency of Preferred Term – Safety Population

Table 14.3.1.7: Number (%) of Subjects Reporting Treatment Emergent Adverse Events by Maximum Intensity – Safety Population

Table 14.3.1.8: Number (%) of Subjects Reporting Treatment Emergent Adverse Events by Most Serious Causality – Safety Population

14.3.2 Listings of deaths, other serious and significant adverse events

Not applicable

14.3.3 Narratives of deaths, other serious and certain other significant adverse events

Not applicable

14.3.4 Abnormal laboratory value listing

Listing 14.3.4.1: Haematology (SI Units): Abnormal Clinically Significant Values – Safety Population

Listing 14.3.4.2: Biochemistry (SI Units): Abnormal Clinically Significant Values – Safety Population

Listing 14.3.4.3: Coagulation (SI Units): Abnormal Clinically Significant Values – Safety Population

Listing 14.3.4.4: Urinalysis (SI Units): Abnormal Clinically Significant Values – Safety Population

14.3.5 Laboratory measurements

Table 14.3.5.1.1: Haematology (Summary Statistics on Raw Data with Changes from Baseline) – Safety Population

Table 14.3.5.1.2: Haematology (Shift Tables) – Safety Population

Table 14.3.5.2.1: Biochemistry (Summary Statistics on Raw Data with Changes from Baseline) – Safety Population

Table 14.3.5.2.2: Biochemistry (Shift Tables) – Safety Population

Figure 14.3.5.2.3: Biochemistry (Subject Plots over Time) – Safety Population

Table 14.3.5.3: Coagulation (Summary Statistics on Raw Data with Changes from Baseline) – Safety Population

Table 14.3.5.4.1: Urinalysis – Quantitative Parameters (Summary Statistics on Raw Data with Changes from Baseline) – Safety Population

Table 14.3.5.4.2: Urinalysis – Qualitative Parameters (Frequency Tables) – Safety Population

14.3.6 Other safety data

Table 14.3.6.1.1: Vital Signs (Summary Statistics on Raw Data with Changes from Baseline) – Safety Population

Table 14.3.6.1.2: Vital Signs (Shift Tables) – Safety Population

Table 14.3.6.2.1: ECG (Summary Statistics on Raw Data with Changes from Baseline) – Safety Population

Table 14.3.6.2.2: ECG (Shift Tables) – Safety Population

Table 14.3.6.2.3: ECG (Interpretation of Clinical Significance) – Safety Population