STATISTICAL ANALYSIS PLAN
TPL-RPX-01

Study Title:	A multicenter, open-label, randomized pilot clinical study of efficacy and safety of Reparixin for prevention of early allograft dysfunction in patients undergoing orthotopic liver transplantation.
Study Number:	TPL-RPX-01
Study Phase:	2
Name of the product: Indications:	Reparixin Prevention of early allograft dysfunction in patients undergoing orthotopic liver transplantation
Sponsor:	Dompé farmaceutici s.p.a.
Statistical Analysis Plan Version - Date:	Version No. 3.0 –Final 12 April 2017

STATISTICAL ANALYSIS PLAN

Name	Statistical Analysis Plan (SAP) on Protocol TPL-RPX-01
Version	Final Version, 3.0

Study drug	Reparixin
Study code	TPL-RPX-01
Title of Study	A multicenter, open-label, randomized pilot clinical study of efficacy and safety of Reparixin for prevention of early allograft dysfunction in patients undergoing orthotopic liver transplantation.
Sponsor	Dompé farmaceutici s.p.a.
CRO	PPD

Version Control

Version	Version Date	Change reason
CCI		CCI

Reviewed/Approved by:

PPD

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1. LIST OF ABBREVIATIONS

Abbreviation	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AP	Arterial Pressure
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CI	Confidence Interval
CLcr	Creatinine Clearance
CPB	Cardiopulmonary Bypass
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CXCL8; IL-8	Interleukin-8
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ESR	Erythrocyte Sedimentation Rate
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyltransferase
HBV, HCV	Hepatitis B and C
HIV	Human Immunodeficiency Virus
i.v.	Intravenous
IC	Informed Consent
ICH	International Conference on Harmonization
ICH GCP	Guidelines for Good Clinical Practice of the International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRI	Ischemia-reperfusion Injury
ITT	Intent-to-treat
LDH	Lactate Dehydrogenase
LME	Linear Mixed Effect Model
LOCF	Last observation carried forward
LT	Liver Transplant
Mean	Mean value
MELD	Model for End-Stage Liver Disease
MITT	Modified Intent-to-Treat population
N	Number of observations
NSAID	Non-steroidal Anti-inflammatory Drug
OLT	Orthotopic liver transplantation
PCR	Polymerase chain reaction
PK	Pharmacokinetic
PP	Per Protocol

Abbreviation	Explanation
PTT	Prothrombin Time
p-value	p-value for H_0 of test performed
RNA	Ribonucleic Acid
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
$t_{1/2}$	Half-life
TESS	Treatment Emergency Sign and Symptom
WHO	World Health Organization

2. INTRODUCTION

This document contains further details to the statistical analyses described in the protocol TPL-RPX-01 and is the primary source of all statistical analyses for the study.

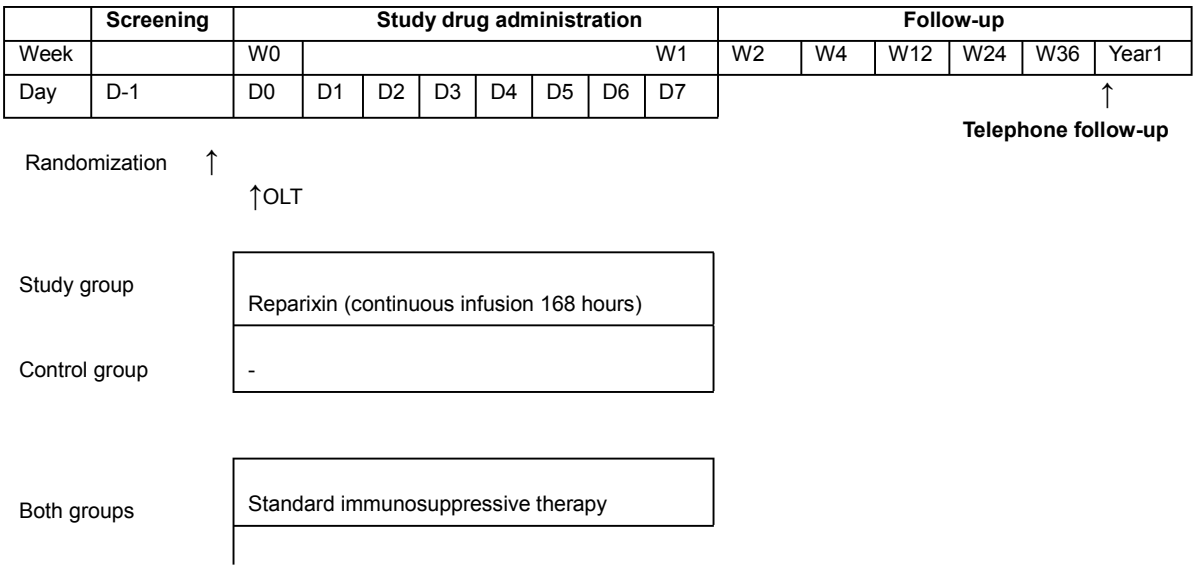
2.1 STUDY DESIGN

This study is a multicenter, open-label, randomized pilot study to evaluate the efficacy and safety of Reparixin for prevention of early allograft dysfunction in patients undergoing OLT. All patients who participate in the study will receive standard immunosuppressive therapy in accordance with the Russian Transplant Society Guidelines for Liver Transplantation (2013). It is planned that the study will be conducted at 5-8 sites for liver transplantation in Russia and Belarus. Recruitment will be competitive among the study sites, until the planned number of patients is enrolled.

Randomization will be performed before or at the day of the surgical operation. The patients will be randomized in a 1:1 manner into the Reparixin or the control group.

Reparixin will be administered to patients as a continuous infusion for 7 days (168 hours). Infusion of the study product will start approximately 60-90 minutes before the anticipated time of OLT. The control group will include patients who do not receive Reparixin therapy. Follow-up of patients will last for approximately 1 year after OLT.

Figure 1. Design of clinical trial TPL-RPX-01



PK data should be obtained ideally in the morning (on Day 1, 3, 5 after OLT) and just prior (Day 7) to the end of study drug administration, and then 1, 3, 5, 6, 8, and 12 hours after the end of study drug administration, only in patients randomized to Reparixin in stage 1 of the study.

2.2 STUDY OBJECTIVES

To evaluate the efficacy and safety of Reparixin treatment (2.772 mg/kg body weight/hour intravenous continuous infusion for 7 days) based on incidence of early allograft dysfunction within the first 7 days after orthotopic liver transplantation (OLT) and overall indicators of allograft dysfunction in the early postoperative period (within 14 days after OLT). The safety of Reparixin in the specific clinical setting will be also evaluated.

3. INTERIM ANALYSIS, FINAL ANALYSIS AND UNBLINDING

One interim analysis is planned during the study flow. Such analysis is planned to review the data at some point of the study. All available data at the time of interim analysis will be presented with listings, tables and figures (see shells). Descriptive statistics will be used for summarize efficacy and safety data. Statistical tests will be done for all efficacy data available at the moment of interim database lock.

The final analysis will be performed after Last patient had Last Visit and the Database lock. No unblinding procedures are necessary as this is an open label trial.

4. ENDPOINTS AND COVARIATES

- Incidence of early allograft dysfunction within 7 days after OLT (primary endpoint).
- Primary nonfunction within 14 days after OLT.
- Overall indicators of the liver allograft dysfunction during the early postoperative period (within 14 days after OLT), including:
    - Primary nonfunction,
    - Early allograft dysfunction,
    - Extracorporeal detoxification.
- The frequency of identification of laboratory examination values corresponding to early allograft dysfunction, 3 days after the operation (Day 4 of the study drug administration).
- The incidence of early allograft dysfunction in case of transplantation of donor organs differing by the degree of steatosis and by the time of allograft removal from the donor and up to its reperfusion after engraftment (duration of cold and warm ischemia).
- The incidence of early allograft dysfunction in transplantation from donors having additional adverse factors (infectious complication, death of the brain, hypotension, etc.), and with regard to the interval between the diagnosis of brain death and removal of liver graft from a donor (in the case of the death of brain of the donor).
- The incidence of early allograft dysfunction in transplant recipients with liver diseases of different etiology (viral, alcoholic, autoimmune, etc.) and with different baseline characteristics (age, activity of hepatitis B, kidney function, score in scales of end-stage liver disease (MELD), Child-Turcotte-Pugh, etc.).
- Time for normalization of liver function parameters (alanine aminotransferase, aspartate aminotransferase and bilirubin levels, gamma-glutamyltransferase, lactate dehydrogenase, etc.) after OLT.
- The incidence of hyperacute, acute and chronic liver allograft rejection (defined by histological evaluation).
- Mortality within 1 year after OLT.
- Graft survival at 1 year after OLT.

4.1 EFFICACY ENDPOINTS

Primary efficacy endpoint

- Incidence of early allograft dysfunction within 7 days after OLT

Efficacy of the investigational therapy will be assessed based on the incidence of early allograft dysfunction after OLT.

Early allograft dysfunction will be determined in accordance with the international

standards (Olthoff et al. 2010), as having one of the following parameters obtained during one week after OLT (Day 7 of Week 1):

- ALT > 2000 U/ml during first 7 days after OLT,
- AST > 2000 U/ml during first 7 days after OLT,
- Total bilirubin ≥ 10 mg/dl (on Day 7 only),
- INR ≥ 1.6 (on Day 7 only).

Secondary efficacy endpoints

- Primary nonfunction within 7 days after OLT.

Primary nonfunction is defined as absence of graft function leading to allograft loss, re-transplantation or death of the patient within 14 days after OLT for reasons not related to hepatic artery thrombosis, biliary complications, and acute exacerbations of chronic diseases or acute allograft rejection.

- Overall indicators of the liver allograft dysfunction during the early postoperative period (within 14 days after OLT), including:
    - Primary nonfunction,
    - Early allograft dysfunction,
    - Extracorporeal detoxification.
- The frequency of identification of laboratory examination values corresponding to early allograft dysfunction, 3 days after the operation (Day 4 of the study drug administration).
- The incidence of early allograft dysfunction in case of transplantation of donor organs differing by the degree of steatosis and by the time of allograft removal from the donor and up to its reperfusion after engraftment (duration of cold and warm ischemia).
- The incidence of early allograft dysfunction in transplantation from donors having additional adverse factors (infectious complication, death of the brain, hypotension, etc.), and with regard to the interval between the diagnosis of brain death and removal of liver graft from a donor (in the case of the death of brain of the donor).
- The incidence of early allograft dysfunction in transplant recipients with liver diseases of different etiology (viral, alcoholic, autoimmune, etc.) and with different baseline characteristics (age, activity of hepatitis B, kidney function, score in scales of end-stage liver disease (MELD), Child-Turcotte-Pugh, etc.).
- Time for normalization of liver function parameters (alanine aminotransferase, aspartate aminotransferase and bilirubin levels, gamma-glutamyltransferase, lactate dehydrogenase, etc.) after OLT.
- The incidence of hyperacute, acute and chronic liver allograft rejection (defined by histological evaluation).
- Mortality within 1 year after OLT.
- Graft survival at 1 year after OLT.

4.2 SAFETY ENDPOINTS

- The incidence of adverse events (AEs) and serious adverse events (SAEs) of different severity within 12 weeks and 1 year after OLT according to subjective complaints, physical examination, vital signs, laboratory tests (including liver and kidney function parameters), ECG, vascular ultrasound of the liver and kidneys with Doppler sonography.

4.3 PHARMACOKINETIC ENDPOINTS

C_{max} Maximum plasma concentration of reparixin and metabolites

t_{max} Time of maximum plasma concentration reparixin and metabolites

λ_z Terminal phase rate constant of reparixin and metabolites

t½ Terminal half-life of reparixin and metabolites

AUC0-t Area under the plasma concentration-time curve from time zero to time t (time of last quantifiable plasma concentration) of reparixin and metabolites

AUC0-∞ Area under the plasma concentration-time curve from time zero to infinity of reparixin and metabolites

Vz Volume of distribution of reparixin

CL Clearance of reparixin

Pharmacokinetic evaluation will be performed only in patients randomized to Reparixin in stage 1 of the study.

5. ANALYSIS SETS

5.1 EFFICACY ANALYSIS SETS

Eligibility of patients (classification to populations) will be confirmed by the sponsor before the start of analysis.

5.1.1 MITT population

Modified population of patients who received treatment (MITT = modified intent-to-treat) corresponds to all patients who received any dose of study drug. MITT population is the additional population for further evaluation.

5.1.2 Per Protocol (PP) population

Per protocol population includes all participants randomized into the trial, who were compliant with, and treated according to, the protocol, and who fulfil the following criteria: compliance with all inclusion criteria, absence of major clinical trial protocol violations with respect to factors likely to affect the efficacy of treatment, and adequate (not less than 70%) compliance with trial medication in the study treatment group.

5.2 SAFETY ANALYSIS SET

Safety population will include all patients who received any dose of the study drug and also the patients from the control group who are included in the study.

5.3 PROTOCOL DEVIATIONS

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database lock.

6. HANDLING OF MISSING VALUES

6.1 EFFICACY PARAMETERS

Replacement of missing data is not planned for efficacy parameters.

6.2 SAFETY PARAMETERS

6.2.1 Missing onset dates in AE

AE with missing onset date will be counted as TESS (Treatment Emergency Sign and Symptom).

In case of AE date is incomplete following rules will be used:

Day	Month	Year	Condition
Missing	Missing	In place	In case of month and year of onset > date of start study time (IC date) - TESS
Missing	Missing	In place	In case of year of onset ≥ year of start study time (IC date) - TESS
Missing	Missing	Missing	TESS
Missing	In place	Missing	TESS
Missing	Missing	In place	Year of onset ≥ year of start study time (IC date) - TESS

6.2.2 Pharmacokinetic Parameters

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (i.e., not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular treatment with ≥ 3 evaluable measurements. For statistical analyses, PK parameters coded as NC will also be set to missing; and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

Statistical analysis will be done using statistical software R (www.r-project.org).

For the statistical analysis is planned to use descriptive statistics, ANOVA model, non-parametric statistics – Mann-Whitney test, Fisher exact test, logistic regression model, survival curves and permutation tests (see section 8).

7.2 STATISTICAL ANALYSES

7.2.1 Primary Efficacy Analysis

Primary efficacy analysis will be performed for the MITT and PP sets.

Cases of early allograft dysfunction (EAD) within 7 days after OLT will be presented as nominal data. For proportions of EAD in treatment groups, 95% CI will be presented (exact Clopper-Pearson confidence interval). Treatments will be compared using exact Fisher test. Additionally, Kaplan-Meyer curves will be provided for time-to-event (EAD) with 95% CI. Treatment groups will be compared by time-to-event (time to EAD) using logrank test.

7.2.2 Secondary Efficacy Analyses

Secondary efficacy analyses will be performed for the MITT Set.

Primary allograft nonfunction within 7 days after OLT and **overall indicators of**

allograft dysfunction within 14 days after OLT (primary nonfunction, early allograft dysfunction, extracorporeal detoxification) will be described by treatment groups as nominal data. Treatment groups will be compared for frequency of allograft nonfunction/dysfunction within 7/14days after OLT. Fisher exact test will be used for such purpose. Treatment groups also will be compared for prevalence of any type of allograft dysfunction (primary nonfunction, early allograft dysfunction, extracorporeal detoxification). For this specific purpose, permutation tests will be used.
Secondary parameter defined in the protocol as "**the frequency of identification of laboratory examination values corresponding to early allograft dysfunction, 3 days after the operation (Day 4 of the study drug administration)**" will be summarize with appropriate descriptive statistics.

The frequency of identification of laboratory examination values corresponding to early allograft dysfunction, 3 days after the operation (Day 4 of the study drug administration) will be presented with a descriptive statistic of laboratory ALT and AST deviations more than 2000 U/L for time point Day 3 by early allograft dysfunction event (EAD) (see Table 9.28).

The incidence of early allograft dysfunction in case of transplantation of donor organs differing by the degree of steatosis and by the time of allograft removal from the donor and up to its reperfusion after engraftment (duration of cold and warm ischemia) will be presented with a descriptive statistic by the EAD. Data will be presented as a nominal data and continuous data. Each variable will be cut to ranges with an idea to have approximately equal counts of patients in each range.

Reparixin and Control groups will be compared for each of the parameter (degree of allograft steatosis and duration of cold ischemia as nominal data) using Cochran-Mantel-Hensel (CMH) test with control EAD (see Table 9.29 and Table 9.30).

The incidence of early allograft dysfunction in transplantation from donors having additional adverse factors (infectious complication, death of the brain, hypotension, etc.), and with regard to the interval between the diagnosis of brain death and removal of liver graft from a donor (in the case of the death of brain of the donor) will be presented with a descriptive statistic by the EAD, but without statistical inferential tests (see Table 9.32).

The incidence of early allograft dysfunction in transplant recipients with liver diseases of different etiology (viral, alcoholic, autoimmune, etc.) and with different baseline characteristics (age, activity of hepatitis B, kidney function, score in scales of end-stage liver disease (MELD), Child-Turcotte-Pugh, etc.) will be presented with a descriptive statistic by the EAD, but without statistical inferential tests (see Table 9.33).

Time for normalization of liver function parameters (alanine aminotransferase, aspartate aminotransferase and bilirubin levels, gamma-glutamyltransferase, lactate dehydrogenase, etc.) after OLT.

Target parameters defined as: ALT, AST, GGT, LDH, total bilirubin, conjugated bilirubin.

For each of the patients at each time point a flag of normality for all enumerated laboratory parameters will be derived. ALL of parameters must be in normal ranges to have the flag settled as NORMAL. In case of missing values in any of the parameter total flag will be counted as ABNORMAL.

Time from the OLT to the date of normalization of ALL enumerated parameters will be

presented with a Kaplan-Mayer curves and median with 95% CI (if possible). See Table 9.34 and Figure 9.3.

The incidence of hyperacute, acute and chronic liver allograft rejection (defined by histological evaluation) will be presented with a descriptive statistic according to the CRF flags (page 51 "REPARIXIN INFUSION" and page 87 "PRIMARY REASON FOR ENDING PARTICIPATION IN THE STUDY"). Data from such two pages (51 and 87) will be additionally checked for consistency.

Binary data will be described by risk ratio (RR) and 95% CI estimates and treatment groups were compared by exact Fisher's test (Table 9.35).

General survival and graft survival ("graft loss" will be qualified as an event for "graft survival") within 1 year will be presented with Kaplan-Mayer curves and survival time median with 95% CI. Treatment groups will be compared using logrank test.

7.3 OTHER

7.3.1 Disposition of Subjects

Disposition of all subjects (enrolled, randomized, discontinued) in analyzed population will be presented.

7.3.2 Demographic and baseline characteristics

This data will be presented for MITT analysis set by treatments group.

Continuous data will be presented with number of non-missing values, mean, standard deviation, median, minimal and maximal values.

Nominal data will be presented with absolute and relative (percent) frequencies.

Between groups continuous data will be compared using unpaired Student's *t*-test (for normally distributed data) or Mann-Whitney test (for free distribution data). Between groups binominal data will be compared using Fisher exact test, for categorical data Mann-Whitney test will be used.

7.4 SAFETY ANALYSIS

7.4.1 Pharmacokinetics

7.4.1.1 Calculation of PK parameters

PK Parameter	Definition
AUC_{0-t}	Area under the plasma concentration-time curve from *time zero* to *time* t (time of last quantifiable plasma concentration) of reparixin and metabolites. Will be calculated using the linear trapezoidal rule. If all concentrations are below the limit of quantification (BLQ), AUC_{0-t} will be reported as zero. $$AUC_{0-t} = \sum \frac{C_n + C_{n-1}}{2}(t_n - t_{n-1})$$
$AUC_{0-\infty}{}^{*}$	Area under the plasma concentration-time curve from time zero to infinity of reparixin and metabolites. $$AUC_{0-\infty} = AUC_t + \frac{C_{last}}{\lambda_z},$$ where C_{last} is the estimated concentration at the last measurable concentration (if possible).

PK Parameter	Definition
C_{max}	Maximum plasma concentration of reparixin and metabolites. Maximum observed plasma concentration obtained by inspection of the data. If all observations are BLQ, C_{max} will be reported as zero.
T_{max}	Time of maximum plasma concentration reparixin and metabolites. First time at which C_{max} is observed and is obtained by inspection of the data. If all observations are BLQ, T_{max} will be reported as not determined (ND).
λ_z	Terminal phase rate constant of reparixin and metabolites. Estimated as the absolute value of the slope of a linear regression during the terminal phase of the natural-logarithm (ln) transformed concentration-time profile (if possible).
$t_{1/2}$*	Terminal half-life of reparixin and metabolites. $t_{1/2} = \frac{\ln(2)}{\lambda_z}$ (if possible)
$AUC_{0-t}/AUC_{0-\infty}$	Ratio of AUC_{0-t} to $AUC_{0-\infty}$ $100 * \frac{AUC_{0-t}}{AUC_{0-\infty}}$
V_z	Volume of distribution of reparixin. $V_z = \frac{FD}{AUC_{0-\infty}\lambda_z}$, where D – dose, F – fraction of dose absorbed (assumed F=1);
CL	Clearance of reparixin. $CL = \frac{FD}{AUC_{0-t}}$

*=if data permits

PK parameters for reparixin and its metabolites (DF2243Y and ibuprofen) will be summarized using descriptive statistics for the safety population (see

Table 9.36).

“Spaghetti” diagrams example for PK data for all subjects will be graphed using nominal sampling time (**Figure 1**).

Mean and Median profiles will be graphed on linear and log-linear scales. For summary graphs a nominal time will be used. For individual graphs a real PK sample time will be used.

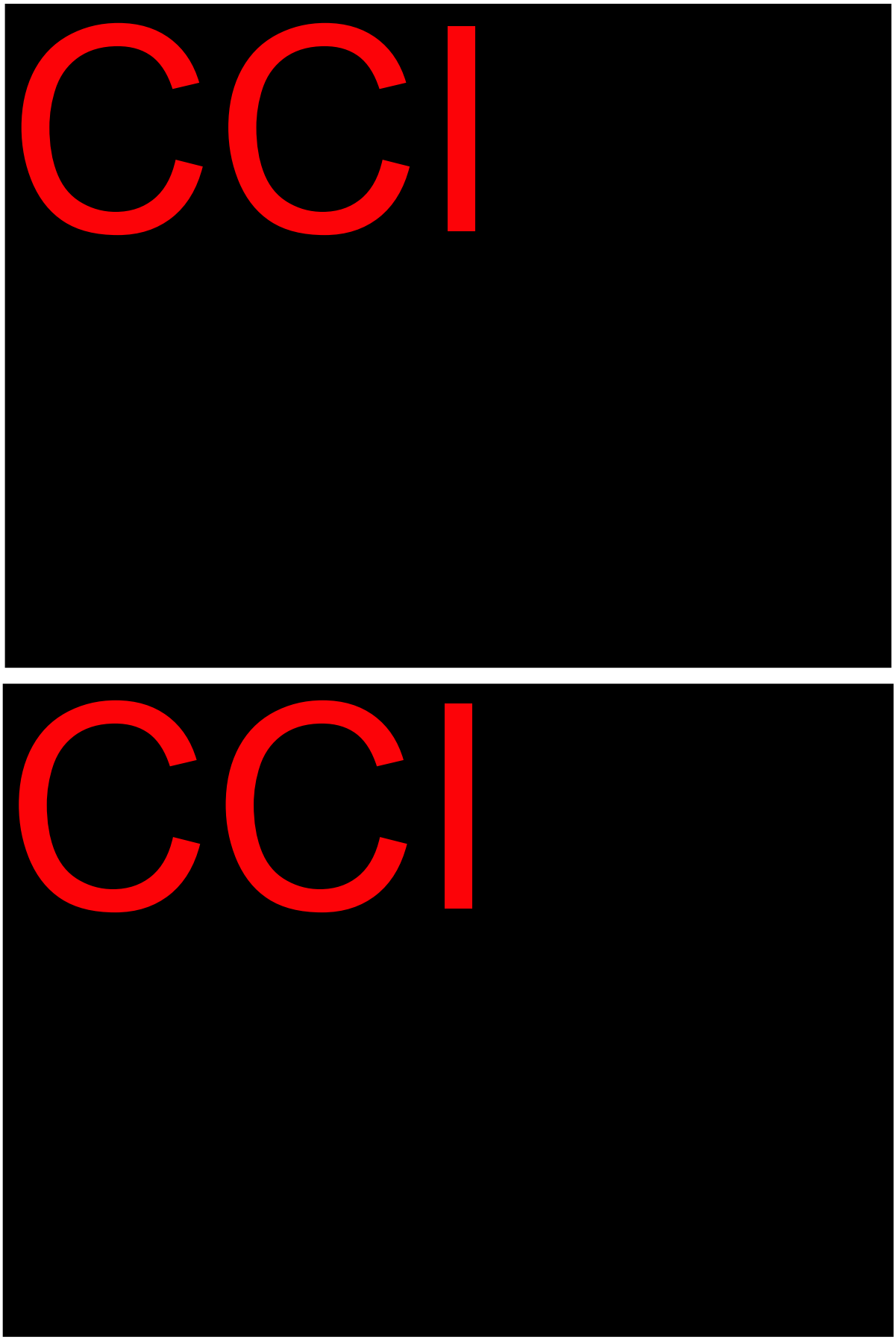


Figure 3 Mean of concentration (log scale) by time

Similar graphics will be produced for concentration medians.

7.4.2 Adverse Events

Adverse Events will be summarized by treatment groups for two periods – up to 12 weeks after OLT and up to 1 year after OLT (all AEs/SAEs).

Relation of AE to the therapy will be defined by AE onset date and period start date for the patient. All AEs will be coded with MEDDRA dictionary. AEs will be summarized by SOC (System Organ Class) and PT (Preferred Terms).

AE frequencies will be compared between treatment groups. For such comparisons MedDRA Preferred Terms (PT) will be used. Treatment groups will be compared by set of frequencies of PT terms using permutation tests. One p-value will be provided (H_0: treatment groups are equal in set of AE frequencies).

7.4.3 Laboratory Data

Laboratory data will be summarized by treatment group as clinical relevance (normal/abnormal, without clinical relevance/ abnormal, with clinical relevance) and as continuous data (absolute values).

All laboratory data and changes from baseline will be described as continuous variables at each visit.

Additionally, deviations from the normal values and absolute values for ALT and AST parameters will be compared between treatment groups at day 0-7, 14, 28, 84 and 168.

Proportion of patients with total bilirubin <1.1 mg/dL in reparixin and control group at day 7, 14, 28, 84 and 168 will be described and compared using Fisher exact test.

7.4.4 Extend of exposure

Total duration of Reparixin infusion (hours), total Reparixin dose (mg/kg/hours) and deviations in infusion time/dose will be presented by descriptive statistics.

7.4.5 Vital Signs Data

Vital signs data such as blood pressure, heart rate and body temperature will be summarized as continuous data by treatment group.

All vital signs data and changes from baseline will be described at each visit.

7.4.6 Physical Examination Data

Physical examination data will be summarized as normal/abnormal data.

Physical examination data will be compared between treatment groups as each time point using permutation tests.

7.4.7 Concomitant Treatments

Concomitant therapy and immunosuppressive therapy during the study time will be summarized by treatment groups. Drugs will be presented by ATC groups as nominal data (absolute and relative frequencies).

7.4.8 Listings

Additionally, combined listings from the database will be presented for:

- Laboratory data
- Adverse events and serious adverse events data.

Laboratory data listings will be presented with patient number, age of patient, study period, group of treatment and laboratory data with units and flag of clinically significant abnormalities. Separately the same format listing will be presented for laboratory data but for patients who had abnormal values.

7.5 CHANGES IN THE PLANNED ANALYSES

Any changes in the planned statistical methods will be documented and justified in the Clinical Study Report.

8. REFERENCES

Permutation Tests methodology for the section 7.1 is described in:

- Helmut Strasser & Christian Weber (1999). On the asymptotic theory of permutation statistics. **Mathematical Methods of Statistics** *8*, 220-250.
- Torsten Hothorn, Kurt Hornik, Mark A. van de Wiel & Achim Zeileis (2006). A Lego System for Conditional Inference. **The American Statistician**, *60*(3), 257-263.
- Torsten Hothorn, Kurt Hornik, Mark A. van de Wiel & Achim Zeileis (2008). Implementing a class of permutation tests: The coin package, **Journal of Statistical Software**, *28*(8), 1-23. http://www.jstatsoft.org/v28/i08

9. TABLE EXAMPLES[1]

Table 9.1 Disposition

	Reparixin n (%)	Control n (%)
Enrolled subject	xx	xx
Randomized subjects	xx (xx.x%)	xx (xx.x%)
MITT Analysis Set	xx (xx.x%)	xx (xx.x%)
Safety Analysis Set	xx (xx.x%)	xx (xx.x%)
Completed Study per protocol	xx (xx.x%)	xx (xx.x%)
Discontinued prematurely	xx (xx.x%)	xx (xx.x%)
Adverse Event	xx (xx.x%)	xx (xx.x%)
Graft loss	xx (xx.x%)	xx (xx.x%)
Hyperacute transplant rejection	xx (xx.x%)	xx (xx.x%)
Acute transplant rejection	xx (xx.x%)	xx (xx.x%)
Chronic transplant rejection	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)
Death	xx (xx.x%)	xx (xx.x%)
Lost to follow-up	xx (xx.x%)	xx (xx.x%)
Consent withdrawn	xx (xx.x%)	xx (xx.x%)
Investigator decision	xx (xx.x%)	xx (xx.x%)
Protocol violation, including non-compliance	xx (xx.x%)	xx (xx.x%)
Protocol entry criteria not met	xx (xx.x%)	xx (xx.x%)
Study is stopped by Sponsor decision	xx (xx.x%)	xx (xx.x%)
Study is stopped by regulatory authorities / ethics committee	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)
Pregnancy	xx (xx.x%)	xx (xx.x%)

Table 9.2 Demographic and other baseline characteristics. MITT Analysis Set. Screening (baseline). N = xx

Parameter	Reparixin N = XX	Control N = XX	p-value
Age (years)			
N	xx	xx	0.xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	
Median	xx.x	xx.x	
Min - Max	xx.x – xx.x	xx.x – xx.x	
Gender			
Male	xx (xx.x%)	xx (xx.x%)	0.xxx
Female	xx (xx.x%)	xx (xx.x%)	
Race			
Caucasian	xx (xx.x%)	xx (xx.x%)	
Other	xx (xx.x%)	xx (xx.x%)	
No data	xx (xx.x%)	xx (xx.x%)	
Height (cm)			
N	xx	xx	---
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	
Median	xx.x	xx.x	
Min - Max	xx.x – xx.x	xx.x – xx.x	
Weight (kg)			
N	xx	xx	---
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	
Median	xx.x	xx.x	
Min – Max	xx.x – xx.x	xx.x – xx.x	
BMI (kg/m^2)			
N	xx	xx	0.xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	
Median	xx.x	xx.x	
Min - Max	xx.x – xx.x	xx.x – xx.x	
Ideal weight (kg)			
N	xx	xx	---
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	

[1] Tables in the report may differ from this templates but meaning and information presented should be kept

Parameter	Reparixin N = XX	Control N = XX	p-value
Median	xx.x	xx.x	
Min - Max	xx.x – xx.x	xx.x – xx.x	
Severity of recipient's liver disease			
MELD index			
N	xx	xx	===
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	
Median	xx.x	xx.x	
Min - Max	xx.x – xx.x	xx.x – xx.x	
40 or more -- 71.3% mortality	xx (xx.x%)	xx (xx.x%)	0.xxx
30-39 -- 52.6% mortality	xx (xx.x%)	xx (xx.x%)	
20-29 -- 19.6% mortality	xx (xx.x%)	xx (xx.x%)	
10-19 -- 6.0% mortality	xx (xx.x%)	xx (xx.x%)	
<9 -- 1.9% mortality	xx (xx.x%)	xx (xx.x%)	
Child-Turcot te-Pugh			
N	xx	xx	---
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	
Median	xx.x	xx.x	
Min - Max	xx.x – xx.x	xx.x – xx.x	
5-6 points - Grade A (least severe liver disease)	xx (xx.x%)	xx (xx.x%)	0.xxx
7-9 points - Grade B (moderately severe liver disease)	xx (xx.x%)	xx (xx.x%)	
10-15 points - Grade C (most severe liver disease)	xx (xx.x%)	xx (xx.x%)	
Liver disease etiology			
Viral	xx (xx.x%)	xx (xx.x%)	0.xxx
Alcohol	xx (xx.x%)	xx (xx.x%)	
Autoimunne	xx (xx.x%)	xx (xx.x%)	
Other	xx (xx.x%)	xx (xx.x%)	
Degree of allograft steatosis			
N	xx	xx	0.xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	
Median	xx.x	xx.x	
Min - Max	xx.x – xx.x	xx.x – xx.x	
Adverse factors			
Infectious complications	xx (xx.x%)	xx (xx.x%)	0.xxx
Hypotension	xx (xx.x%)	xx (xx.x%)	
Death of the donor's brain	xx (xx.x%)	xx (xx.x%)	
Other	xx (xx.x%)	xx (xx.x%)	
Express HIV test			
Negative	xx (xx.x%)	xx (xx.x%)	---
Positive	xx (xx.x%)	xx (xx.x%)	
No data	xx (xx.x%)	xx (xx.x%)	

Table 9.3 Creatinine clearance. MITT Analysis Set. Screening (baseline). N = xx

Parameter	Reparixin N = XX	Control N = XX	p-value
CC (mL/min). Males			
N	xx	xx	0.xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	
Median	xx.x	xx.x	
Min - Max	xx.x – xx.x	xx.x – xx.x	
CC (mL/min). Females			
N	xx	xx	0.xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	
Median	xx.x	xx.x	
Min - Max	xx.x – xx.x	xx.x – xx.x	

Table 9.4 Medical history. MITT Analysis Set. Screening (baseline). N = xx

MedDRA System Organ Class term *MedDRA Preferred term*	Severity	Reparixin n (%) *x (%)*	*Y*	Control n (%) *x (%)*	*Y*
BODY SYSTEM CODE		xx (xx.x)	xx	xx (xx.x)	xx
Term 1	Mild	xx (xx.x)	xx	xx (xx.x)	xx
Term 2	Moderate	xx (xx.x)	xx	xx (xx.x)	xx
…					

Table 9.5 Ongoing diseases/diagnosis/abnormalities. MITT Analysis Set. Screening (baseline). N = xx

MedDRA System Organ Class term *MedDRA Preferred term*	Severity	Reparixin n (%) *x (%)*	*Y*	Control n (%) *x (%)*	*Y*
BODY SYSTEM CODE		xx (xx.x)	xx	xx (xx.x)	xx
Term 1	Mild	xx (xx.x)	xx	xx (xx.x)	xx
Term 2	Moderate	xx (xx.x)	xx	xx (xx.x)	xx
…					

Table 9.6 Immunosuppressive therapy. Safety Set. During the study. N = xx

ATC code Drug	Reparixin n (%) N = XX	Control n (%) N = XX
Group		
Total	xx (xx.x%)	xx (xx.x%)
DRUG (ATC)	xx (xx.x%)	xx (xx.x%)
…		

Table 9.7 Concomitant medication. Safety Set. During the study.N = xx

ATC code Drug	Reparixin n (%) N = XX	Standard n (%) N = XX
Group		
Total	xx (xx.x%)	xx (xx.x%)
DRUG (ATC)	xx (xx.x%)	xx (xx.x%)
…		

Table 9.8 Physical examination. Safety Set. N = xx

Category	Reparixin n (%) N = XX	Control n (%) N = XX	p-value
Screening (baseline)			0.xxx
Overall appearance			
Normal	xx (xx.x%)	xx (xx.x%)	
Abnormal	xx (xx.x%)	xx (xx.x%)	
Not done	xx (xx.x%)	xx (xx.x%)	
Eyes, ears, nose, throat			
Normal	xx (xx.x%)	xx (xx.x%)	
Abnormal	xx (xx.x%)	xx (xx.x%)	
Not done	xx (xx.x%)	xx (xx.x%)	
Neck (including thyroid)			
Normal	xx (xx.x%)	xx (xx.x%)	
Abnormal	xx (xx.x%)	xx (xx.x%)	
Not done	xx (xx.x%)	xx (xx.x%)	
..			
Week 0. Day 0 (12 HRS)			0.xxx
…			
Week 0. Day 1			0.xxx
…			

Category	Reparixin n (%) N = XX	Control n (%) N = XX	p-value
Week 0. Day 2			0.xxx
…			

Table 9.9 Vital signs. Safety Set. N = xx

	Reparixin N = XX	Control N = XX
Screening (baseline)		
Body temperature (°C)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x
HR (beats/min)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x
RR (/min)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x
Systolic blood pressure (Hg mm)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x
Diastolic blood pressure (Hg mm)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x
Week 0. Day 0		
…		
Week 0. Day 0. Change from baseline		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x
p-change	0.xxx	0.xxx
Week 0. Day 1		
…		
Week 0. Day 1. Change from baseline		
…		

Table 9.10 Urine pregnancy test (females only). Safety Set. N = xx

	Reparixin n (%) N = XX	Control n (%) N = XX
Screening		
Positive	xx (xx.x%)	xx (xx.x%)
Negative	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)
Follow-up. Week 24		
Positive	xx (xx.x%)	xx (xx.x%)
Negative	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)

	Reparixin n (%) N = XX	Control n (%) N = XX
Follow-up. 1 year		
Positive	xx (xx.x%)	xx (xx.x%)
Negative	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)

Table 9.11 12-lead electrocardiography. Safety Set. N = xx

	Reparixin n (%) N = XX	Control n (%) N = XX
Screening (baseline)		
Abnormal	xx (xx.x%)	xx (xx.x%)
Normal	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)
Week 0. Day 1 (12 HRS)		
Abnormal	xx (xx.x%)	xx (xx.x%)
Normal	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)
Week 0. Day 2		
Abnormal	xx (xx.x%)	xx (xx.x%)
Normal	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)
Week 0. Day 4		
…		
Week 1. Day 7		
…		

Table 9.12 Viral loading (for patients with HBV and/or HCV). Safety Set. Screening. N = xx

	Reparixin N = XX	Control N = XX
Screening (baseline)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x

Table 9.13 State of post-operative wound. Safety Set. N = xx

	Reparixin n (%) N = XX	Control n (%) N = XX
Week 0. Day 0 (12 HRS after OLT)		
Better than usual	xx (xx.x%)	xx (xx.x%)
As ususal	xx (xx.x%)	xx (xx.x%)
Worse than ususal	xx (xx.x%)	xx (xx.x%)
Is difficult to define	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)
Week 0. Day 1		
…		
Week 0. Day 2		
…		

Table 9.14 Clinically significant changes in post-operative wound. Safety Set. N = xx

	Reparixin n (%) N = XX	Control n (%) N = XX
Week 0. Day 0 (12 HRS after OLT)		
Bleeding	xx (xx.x%)	xx (xx.x%)
Hematoma	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)
Week 0. Day 1		
…		
Week 0. Day 2		
…		

Table 9.15 Doppler abdominal ultrasonography. Safety Set. N = xx

	Reparixin n (%) N = XX	Control n (%) N = XX
Screening (baseline)		
Abnormal	xx (xx.x%)	xx (xx.x%)
Normal	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)
Week 0. Day 1		
…		
Week 0. Day 4		
…		

Table 9.16 Laboratory parameters. Hematology. Deviation from normal values. Safety Set. N = xx

	Reparixin n (%) N = XX	Control n (%) N = XX
Screening (baseline)		
Hemoglobin		
CS deviation	xx (xx.x%)	xx (xx.x%)
Normal	xx (xx.x%)	xx (xx.x%)
Leukocytes		
CS deviation	xx (xx.x%)	xx (xx.x%)
Normal	xx (xx.x%)	xx (xx.x%)
…		
Week 0. Day 1		
…		

Table 9.17 Laboratory parameters. Biochemistry. Deviation from normal values. Safety Set. N = xx

Similar

Table 9.18 Laboratory parameters. Hematology. Absolute values. Safety Set. N = xx

	Reparixin N = XX	Control N = XX
Screening (baseline)		
Hemoglobin (g/L)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x
Leukocytes (10^9/ml)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)

	Reparixin N = XX	Control N = XX
Median	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x
Week 0. Day 0		
…		
Week 0. Day 0. Change from baseline		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x
p-change	0.xxx	0.xxx
Week 0. Day 1		
…		
Week 0. Day 1. Change from baseline		
…		

Table 9.19 Laboratory parameters. Biochemistry. Absolute values. Safety Set. N = xx

Similar

Table 9.20 Biochemistry. ALT and AST deviation from normal values. Safety Set. N=XX

	Reparixin n (%) N = XX	Control n (%) N = XX	p-value[1]
Screening and randomization (Day -1)			
ALT			**0.xxx**
Lower	xx (xx.x%)	xx (xx.x%)	
Normal	xx (xx.x%)	xx (xx.x%)	
Higher	xx (xx.x%)	xx (xx.x%)	
No data	xx (xx.x%)	xx (xx.x%)	
AST			**0.xxx**
Lower	xx (xx.x%)	xx (xx.x%)	
Normal	xx (xx.x%)	xx (xx.x%)	
Higher	xx (xx.x%)	xx (xx.x%)	
No data	xx (xx.x%)	xx (xx.x%)	
Total bilirubin			**0.xxx**
< 1.1 ng/mL	xx (xx.x%)	xx (xx.x%)	
≥ 1.1 ng/mL	xx (xx.x%)	xx (xx.x%)	
No data	xx (xx.x%)	xx (xx.x%)	
Study therapy (WEEK 0) Day 1			
…			
Study therapy (WEEK 0) Day 2			
…			
Study therapy (WEEK 0) Day 3			
…			
Study therapy (WEEK 0) Day 4			
…			
Study therapy (WEEK 0) Day 5			
…			
Study therapy (WEEK 0) Day 6			
…			
Study therapy (WEEK 1) Day 7			
…			
Follow-up (WEEK 2)			
…			
Follow-up (WEEK 4)			
…			
Follow-up (WEEK 12)			
…			

[1] Mann-Whitney test

	Reparixin n (%) N = XX	Control n (%) N = XX	p-value[1]
Follow-up (WEEK 24)			

Table 9.21 Biochemistry. ALT and AST absolute values comparison. Safety Set. N=XX

	Reparixin N = XX	Control N = XX	p-value[1]
Screening and randomization (Day -1)			0.xxx
ALT (U/L)			
N	xx	xx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	
Median	xx.x	xx.x	
Min - Max	xx.x – xx.x	xx.x – xx.x	
AST (U/L)			
N	xx	xx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	
Median	xx.x	xx.x	
Min - Max	xx.x – xx.x	xx.x – xx.x	
Study therapy (WEEK 0) Day 1			
…			
Study therapy (WEEK 0) Day 2			
…			
Study therapy (WEEK 0) Day 3			
…			
Study therapy (WEEK 0) Day 4			
…			
Study therapy (WEEK 0) Day 5			
…			
Study therapy (WEEK 0) Day 6			
…			
Study therapy (WEEK 1) Day 7			
…			
Follow-up (WEEK 2)			
…			
Follow-up (WEEK 4)			
…			
Follow-up (WEEK 12)			
…			
Follow-up (WEEK 24)			
…			

Table 9.22 Extend of exposure. Safety Set. N = XX

	Reparixin N = XX
Reparixin infusion duration (hours)	
N	xx
Mean (SD)	xx.x (xx.x)
Median	xx.x
Min – Max	xx.x – xx.x
Total Reparixin dose (mg/kg/hours)	
N	xx
Mean (SD)	xx.x (xx.x)
Median	xx.x
Min - Max	xx.x – xx.x
Reparixin infusion stopped prematurely	
No	xx (xx.x%)
Yes	xx (xx.x%)
An allergic reaction to Reparixin	xx (xx.x%)
Complications related to the surgery (OLT)	xx (xx.x%)
…	

[1] ANOVA or Mann-Whitney test

Table 9.23 Early allograft dysfunction. MITT Set. N = xx

	Reparixin n (%) N = XX	Control n (%) N = XX
Has early allograft dysfunction been determined within 7 days after OLT?		
No	xx (xx.x%)	xx (xx.x%)
Yes	xx (xx.x%) 95% CI [xx.x%; xx.x%]	xx (xx.x%) 95% CI [xx.x%; xx.x%]
p-value		0.xxx
ALT > 2000 U/L	xx (xx.x%)	xx (xx.x%)
AST >2000 U/L	xx (xx.x%)	xx (xx.x%)
Total bilirubin > 10 mg/dl	xx (xx.x%)	xx (xx.x%)
INR ≥ 1.6	xx (xx.x%)	xx (xx.x%)
Resolved	xx (xx.x%)	xx (xx.x%)
Ongoing	xx (xx.x%)	xx (xx.x%)
Median time to early allograft dysfunction		
Median time	xx.x 95% CI [xx.x; xx.x]	xx.x 95% CI [xx.x; xx.x]
p-value		0.xxx

Figure 9.1 Time to early allograft dysfunction. MITT Set. N = XX

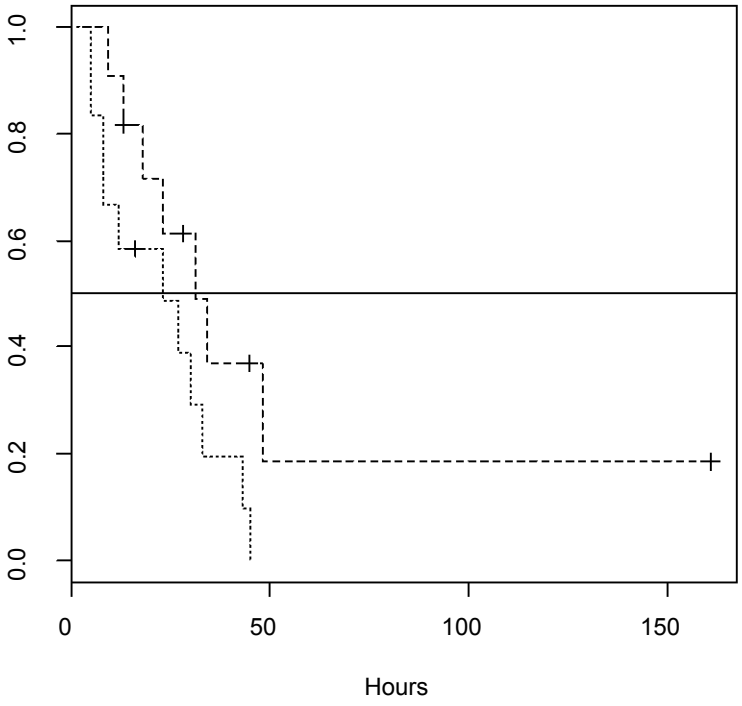


Table 9.24 Early allograft dysfunction. PP Set. N = xx

Similar

Figure 9.2 Time to early allograft dysfunction. PP Set. N = XX

Similar

Table 9.25 Efficacy assessment. MITT Set. N = XX

	Reparixin n (%) N = XX	Control n (%) N = XX
Has primary nonfunction been determined within 7 days after OLT?		
No	xx (xx.x%)	xx (xx.x%)
Yes	xx (xx.x%)	xx (xx.x%)
p-value		0.xxx
Has allograft dysfunction been determined within 14 days after OLT?		
No	xx (xx.x%)	xx (xx.x%)
Yes	xx (xx.x%)	xx (xx.x%)
p-value		0.xxx
Specify signs of allograft nonfunction		
Primary nonfunction allograft	xx (xx.x%)	xx (xx.x%)
Early allograft dysfunction	xx (xx.x%)	xx (xx.x%)
Extracorporeal detoxification	xx (xx.x%)	xx (xx.x%)
p-value		0.xxx

Table 9.26 Logistic model of early allograft dysfunction and related risk factors. MITT Set. N = XX

For the statistician's decision

Table 9.27 Survival within 1 year. MITT Set. N = XX

	Reparixin n (%) N = XX	Control n (%) N = XX
Patient survival		
Median 95% CI	xx (xx.x%) 95% CI [xx.x%; xx.x%]	xx (xx.x%) 95% CI [xx.x%; xx.x%]
p-value		0.xxx
Graft survival		
Median 95% CI	xx (xx.x%) 95% CI [xx.x%; xx.x%]	xx (xx.x%) 95% CI [xx.x%; xx.x%]
p-value		0.xxx

Table 9.28 ALT/AST > 2000 U/L and Early allograft dysfunction detected. MITT Set. N=XX

Parameter	Reparixin n (%) N = xx Early allograft dysfunction detected		Control n (%) N = xx Early allograft dysfunction detected	
	No	Yes	No	Yes
Study therapy (WEEK 0) Day 3				
ALT > 2000 U/L	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
AST > 2000 U/L	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ALT and AST > 2000 U/L	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 9.29 Early allograft dysfunction and potential prognostic factors. MITT Set. Nominal data. N=XX

Parameter	Reparixin n (%) N = xx Early allograft dysfunction detected		Control n (%) N = xx Early allograft dysfunction detected	
	No	Yes	No	Yes
Degree of allograft steatosis				
0-10%[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
10-30%	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
30-50%	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-CMH	**0.xxx**			
Duration of cold ischemia				
less than 5 hours	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(5,6][2] hours	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(6,7] hours	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
more than 7 hours	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-CMH	**0.xxx**			
Duration of warm ischemia				
less than 30 minutes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(30-45] minutes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(45-60] minutes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
more than 60 minutes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-CMH	**0.xxx**			

[1] Right side is included (xx, xx].
[2] Right side is included (xx, xx].

Table 9.30 Early allograft dysfunction and potential prognostic factors. MITT Set. Continuous data. N=XX

Parameter	Reparixin N = xx Early allograft dysfunction detected No	Reparixin N = xx Early allograft dysfunction detected Yes	Control N = xx Early allograft dysfunction detected No	Control N = xx Early allograft dysfunction detected Yes
Degree of allograft steatosis (%)				
N	xx	xx	xx	xx
Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Duration of cold ischemia (hours)				
N	xx	xx	xx	xx
Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Duration of warm ischemia (hours)				
N	xx	xx	xx	xx
Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x

Table 9.31 Early allograft dysfunction and additional adverse factors. MITT Set. Nominal data. N=XX

Parameter	Reparixin n (%) N = xx Early allograft dysfunction detected No	Reparixin n (%) N = xx Early allograft dysfunction detected Yes	Control n (%) N = xx Early allograft dysfunction detected No	Control n (%) N = xx Early allograft dysfunction detected Yes
Infectious complication				
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Death of the brain				
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Hypotension				
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other				
Other 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…				

Table 9.32 Early allograft dysfunction and interval between the diagnosis of brain death and removal of liver graft from a donor (in the case of the death of brain of the donor). MITT population. Nominal data. N=XX

Parameter	Reparixin n (%) N = xx Early allograft dysfunction detected No	Reparixin n (%) N = xx Early allograft dysfunction detected Yes	Control n (%) N = xx Early allograft dysfunction detected No	Control n (%) N = xx Early allograft dysfunction detected Yes
less than 1 hour	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(1,2] hours	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(2,3] hours	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(3,4] hours	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(4,6] hours	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(6,8] hours	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
more than 8 hours	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 9.33 Early allograft dysfunction in transplant recipients with liver diseases of different etiology and with different baseline characteristics. MITT Set. Nominal data. N=XX

Parameter	Reparixin n (%) N = xx Early allograft dysfunction detected		Control n (%) N = xx Early allograft dysfunction detected	
	No	Yes	No	Yes
Viral disease etiology				
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Alcoholic disease etiology				
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Autoimmune disease etiology				
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No data	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other disease etiology				
Other 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…				
Age of recipient (years)				
N	xx	xx	xx	xx
Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
HBV and/or HCV virus loading at screening Day -1				
N	xx	xx	xx	xx
Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Creatinine clearance at screening Day -1 (mL/min)				
N	xx	xx	xx	xx
Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
Min - Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
Severity of recipient's liver disease. MELD index				
<9 - 1.9% mortality	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
10-19 - 6.0% mortality	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
20-29 - 19.6% mortality	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
30-39 - 52.6% mortality	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
40 or more - 71.3% mortality	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severity of recipient's liver disease. Child-Turcotte-Pugh				
5-6 points Grade A (least severe liver disease)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
7-9 points Grade B (moderately severe liver disease)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
10-15 points Grade C (most severe liver disease)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 9.34 Time from the OLT normalization of liver parameters. MITT Set. N = xx

Parameter	Repariin Early allograft dysfunction detected		Control Early allograft dysfunction detected	
	No	Yes	No	Yes
Median with 95% CI[1]	**xx.x [xx.x; xx.x]**	**xx.x [xx.x; xx.x]**	**xx.x [xx.x; xx.x]**	**xx.x [xx.x; xx.x]**

[1] if possible

Figure 9.3 Time from the OLT normalization of liver parameters. MITT Set. N = xx[1]

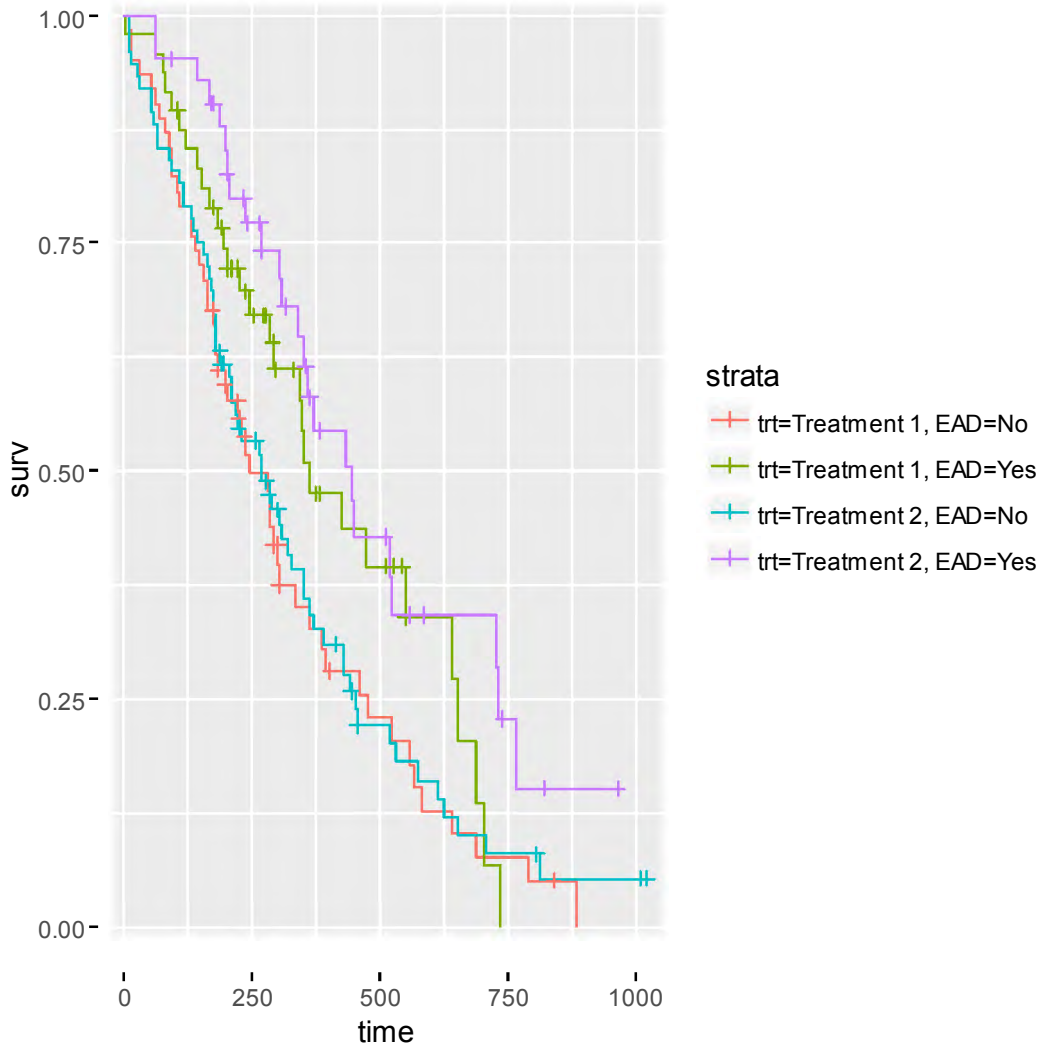


Table 9.35 Hyperacute, acute and chronic transplant rejection (determined by biopsy). MITT Set. N = XX

Hyperacute or acute transplant rejection (determined by biopsy)	Reparixin n (%) N = xx	Control n (%) N = xx
Hyperacute or acute transplant rejection	xx (xx.x%)	xx (xx.x%)
Relative risk Reparixin/Control with 95% CI		xx.x [xx.x; xx.x]
p-value (Fisher)		0.xxx
Chronic transplant rejection	xx (xx.x%)	xx (xx.x%)
Relative risk Reparixin/Control with 95% CI		xx.x [xx.x; xx.x]
p-value (Fisher)		0.xxx
Hyperacute or acute or chronic transplant rejection[2]	xx (xx.x%)	xx (xx.x%)
Relative risk Reparixin/Control with 95% CI		xx.x [xx.x; xx.x]
p-value (Fisher)		0.xxx

[1] Figure is generated for illustration purposes only
[2] All cases acute or hyperacute or chronic

Table 9.36 PK data summary. Safety Set. (N = xx)

Parameter	Reparixin	DF2243Y	Ibuprofen
AUC_{0-t}			
N	xx	xx	xx
CV (%)	xx%	xx%	xx%
Mean (SD; SE)	xx.xx (xx.xx; xx.xx)	xx.xx (xx.xx; xx.xx)	xx.xx (xx.xx; xx.xx)
Median	xx.xx	xx.xx	xx.xx
Min; Max	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx
100 * AUC_0.t/$AUC0_{-\infty}$			
N	xx	xx	xx
CV (%)	xx%	xx%	xx%
Mean (SD; SE)	xx.xx (xx.xx; xx.xx)	xx.xx (xx.xx; xx.xx)	xx.xx (xx.xx; xx.xx)
Median	xx.xx	xx.xx	xx.xx
Min; Max	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx
C_{max}			
N	xx	xx	xx
CV (%)	xx%	xx%	xx%
Mean (SD; SE)	xx.xx (xx.xx; xx.xx)	xx.xx (xx.xx; xx.xx)	xx.xx (xx.xx; xx.xx)
Median	xx.xx	xx.xx	xx.xx
Min; Max	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx
T_{max}			
N	xx	xx	xx
Median	xx.xx; xx.xx; xx.xx	xx.xx; xx.xx; xx.xx	xx.xx; xx.xx; xx.xx
Min; Max	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx
t½ (hours^{-1})			
N	xx	xx	xx
Mean (SD; SE)	xx.xx (xx.xx; xx.xx)	xx.xx (xx.xx; xx.xx)	xx.xx (xx.xx; xx.xx)
Median	xx.xx	xx.xx	xx.xx
Min; Max	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx
V_z			
N	xx	xx	xx
Mean (SD; SE)	xx.xx (xx.xx; xx.xx)	xx.xx (xx.xx; xx.xx)	xx.xx (xx.xx; xx.xx)
Median	xx.xx	xx.xx	xx.xx
Min; Max	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx
CL			
N	xx	xx	xx
Mean (SD; SE)	xx.xx (xx.xx; xx.xx)	xx.xx (xx.xx; xx.xx)	xx.xx (xx.xx; xx.xx)
Median	xx.xx	xx.xx	xx.xx
Min; Max	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx

Table 9.37 Adverse Events (AE/SAE). Up to 12 weeks after OLT. Safety Set. N = xx

MEDDRA System Organ Class term MEDDRA Preferred term	Reparixin n (%)		Control n (%)	
	x (%)	*Y*	*x (%)*	*Y*
SOC term	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 1	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 2	xx (xx.x)	xx	xx (xx.x)	xx
…				

X = Number of subjects having at least one AE from the group.
% = Percent of patients having at least one AE from the group
Y = Total number of events

p-value = 0.xxx

Table 9.38 Adverse Events (AE/SAE). Up to 1 year after OLT (all registered). Safety Set. N = xx

Similar

Table 9.39 Adverse Events (AE/SAE) and severity. Up to 12 weeks after OLT. Safety Set. N = xx

MEDDRA System Organ Class term MEDDRA Preferred term	Severity	Reparixin n (%)		Control n (%)	
		x (%)	*Y*	*x (%)*	*Y*
SOC term		xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 1	Mild	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 2	Moderate	xx (xx.x)	xx	xx (xx.x)	xx
…					

X = Number of subjects having at least one AE from the group.
% = Percent of patients having at least one AE from the group
Y = Total number of events

Table 9.40 Adverse Events (AE/SAE) and severity. Up to 1 year after OLT (all registered). Safety Set. N = xx

Similar

Table 9.41 Adverse Events and relation to study drug(s). Up to 12 weeks after OLT. Safety Set. N = xx

Similar

Table 9.42 Adverse Events and relation to study drug(s). Up to 1 year after OLT (all registered). Safety Set. N = xx

Similar