CLINICAL STUDY PROTOCOL
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:	Reparixin
Indications:	Prevention of early allograft dysfunction in patients undergoing orthotopic liver transplantation
Sponsor:	Dompé farmaceutici s.p.a.
Protocol Version - Date:	Version No. 2 –Final 13 March 2015

This protocol version results from the translation of the Russian version of the protocol dated 18 February 2014, and revision according to Amendment No. 1 (Final, 3 March 2015).

PROTOCOL APPROVAL I'AGE

SPONSOR

Developrnent Director•· Diabetes and Tra11spla11tation

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PRINCIPAL INVESTIGATOR STATEMENT

<table>
<tr><td colspan="2">FULL NAME:</td></tr>
<tr><td colspan="2">I, the undersigned, hereby certify that I have read and understood the protocol TPL-RPX-01: “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”.

I understand that, as Principal Investigator, I have ultimate responsibility for the protection of the rights and welfare of human subjects, conduct of the study and the ethical performance of the trial. I agree to accept responsibility for the conduct and supervision of this research and the protection of human subjects as set forth in the Declaration of Helsinki and the ICH GCP Guidelines, and as required by local regulatory requirements.</td></tr>
<tr><td>DATE:</td><td>SIGNATURE:</td></tr>
<tr><td>CENTER NUMBER:</td><td>TOWN:</td></tr>
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INVESTIGATIONAL SITES

Full list of investigational sites will be kept in the Trial Master File. Updated versions, if any, will be filed chronologically. Copies will be provided to the sites.

INSTITUTIONS INVOLVED IN THE CLINICAL TRIAL

CRO (site monitoring, medical monitoring, regulatory submissions, site audits)	PPD PPD
Centralized Laboratory for hematology, coagulation, biochemistry, serology and viral load	PPD
Centralized Laboratory for pharmacokinetic assays	Biotech Unit Dompé farmaceutici s.p.a. Via Campo di Pile 67100 L'Aquila – Italy PPD
Data Management, Biostatistics	PPD
Drug Depot	PPD

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AP	Arterial Pressure
APTT	Activated Partial Thromboplastin Time
AE	Adverse Event
ADR	Adverse Drug Reaction
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CLcr	Creatinine Clearance
CPB	Cardiopulmonary Bypass
CRF	Case Report Form
CXCL8; IL-8	Interleukin-8
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ESR	Erythrocyte Sedimentation Rate
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyltransferase
HBV, HCV	Hepatitis B and C
HIV	Human Immunodeficiency Virus
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
i.v.	Intravenous
LDH	Lactate Dehydrogenase
LT	Liver Transplant
MELD	Model for End-Stage Liver Disease
MITT	Modified population of patients who received treatment (Modified intent-to-treat)
NSAID	Non-steroidal Anti-inflammatory Drug
OLT	Orthotopic liver transplantation
PCR	Polymerase chain reaction
PK	Pharmacokinetic
PTT	Prothrombin Time
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SADR	Serious Adverse Drug Reaction
t1/2	Half-life
WHO	World Health Organization

STUDY SYNOPSIS

Sponsor: Dompé farmaceutici s.p.a.

Via San Martino 12, 20122, Milano, Italy

Name of the study drug: Reparixin

Active ingredient: R(-)-4-isobutyl-α-methyl-phenyl-acetyl-methanesulfonamide

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

Study objective:

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.

Efficacy endpoints will be:

- Incidence of early allograft dysfunction within 7 days after OLT (**primary endpoint**).
- Primary nonfunction within 7 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.

Safety endpoints will be:

- 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.

Pharmacokinetics endpoints will be:

Reparixin (total and unbound) and relevant metabolites (DF2243Y and ibuprofen)

- maximum plasma concentration (Cmax).
- time of maximum plasma concentration (tmax).
- terminal phase rate constant (λz).
- terminal half-life (t½).
- area under the plasma concentration-time curve from time zero to time t (AUC0-t).
- area under the plasma concentration-time curve from time zero to infinity (AUC0-∞).
- volume of distribution (Vz).
- clearance (CL).

Rationale:

Dompé farmaceutici s.p.a. (Italy) is developing a new drug Reparixin, which is a new, potent and specific inhibitor of chemokine CXCL8 (Interleukin-8). With regard to the mechanism of action of Reparixin, its early preclinical development was aimed at specific inhibition of migration of polymorphonuclear neutrophils and prevention of the ischemia- reperfusion injury associated with solid organ transplantation. The clinical study of Reparixin was initially focused on the prevention of delayed allograft function and its primary nonfunction in transplantation of solid organs (kidneys, lungs) and pancreatic islets [1, 2, 3, 4].

This pilot clinical study is designed to evaluate the efficacy and safety of Reparixin as an agent to prevent early allograft dysfunction caused by ischemia-reperfusion injury in post- orthotopic liver transplantation patients.

Study Design:

This 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 orthotopic liver transplantation.

Patients will be accrued in this study using a two-stage Simon's design [5, 6]. Forty-four patients (22 per each group) will be enrolled in the first stage. If less than 5 patients from the study drug group will experience early graft dysfunction in the first stage, up to 34 patients (17 per group) will be enrolled in the second stage. If 5 or more patients from the study drug group will experience early graft dysfunction, the study will terminate enrollment early.

Considering a possible 7% early discontinuation rate and the inability to assess the primary endpoint for some patents, up to 84 patients will be randomized in the study. This number of patients is based on a statistical power of 80% with an alpha of 0.05 and 1:1 randomization. In

total, considering a possible 15% screening failure rate, about 100 patients planned for OLT will need to be screened in the study.

The study is planned to be conducted at 5-8 transplantation sites in Russia and Belarus. Recruitment will be competitive among the study sites, until the planned number of patients is enrolled.

Patients admitted to the transplant center immediately before OLT, will be screened against the inclusion and exclusion criteria. Eligible patients will be randomized (randomization number assigned) by an Investigator (or designee) prior to start procedures for preparation of the dosing solution of the Investigational Product.

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.

In the group of the study therapy, Reparixin will be administered as a continuous infusion for 7 days (168 hours). Infusion of the study drug will start approximately 60-90 minutes before the anticipated time of OLT.

The control group will include patients who do not receive Reparixin therapy. All the patients who participate in the study will receive standard immunosuppressive therapy in accordance with the Russian Transplant Society Guidelines for liver transplantation (2013).

The clinical study will consist of the following stages:

Screening. The patients admitted to the transplant center immediately before OLT, will be screened (Day -1). The screening procedures may be performed within 24 hours before planned surgery. The results at screening will be considered as baseline values.

Randomization. Patients fulfilling all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 manner into the treated or the control group.

Treatment. On Day 0, 60-90 minutes before OLT, the patients, who were randomized to the Reparixin group, will start to receive the infusion of the study drug, which will continue for 7 days (168 hours). OLT will be performed during the continuous infusion of Reparixin. Post- operative examinations will be performed daily within the first 7 days after OLT (from Day 0 to Day 6). The final assessment of safety parameters and of the primary endpoint will be performed after the end of the infusion of the study drug, on Day 7 after OLT.

The patients, who will randomized to the control group, will not receive any study drug.

The patients in both groups will receive the standard immunosuppressive therapy with tacrolimus only or together with mycophenolates, or a combination of tacrolimus/cyclosporine with mycophenolates and/or glucocorticosteroids. The patients with hepatocellular carcinoma and impaired renal function can receive a combination of drugs that includes everolimus. Basiliximab in association with methylprednisolone will be used for the induction of immunosuppression.

Follow-up. The status of patients and allograft survival will be monitored up to 1 year after OLT. At Week 2 and Week 4 the patients will visit the center with mandatory control of the basic functions of the liver transplant and general condition of the patient. Then, the patients will visit the center on Week 12, Week 24 and 1 year after OLT in order to control the safety parameters.

Study Population:

Adult patients aged 18 years and older requiring OLT.

Main inclusion/exclusion criteria

To be enrolled in this clinical study, the patients shall meet the following inclusion/exclusion criteria.

Inclusion Criteria:

1. Male and female patients aged 18 years and older needing a whole organ OLT, listed on the waiting list for liver transplantation.
2. Severity score of the initial condition of the patient (hepatocellular dysfunction) according to the scales of Child-Turcotte-Pugh ≥ 7 points or MELD 15-40 points (or both).
3. The possibility of insertion of a central catheter for infusion of the study drug.
4. Signed Patient Informed Consent Form.
5. Ability to comply with all the requirements of the protocol.
6. Consent to use adequate contraception means throughout the study. The adequate contraception methods include use of condom with spermicide.

Exclusion criteria:

1. Split-liver transplantation or transplantation from a living donor.
2. Re-transplantation or multivisceral transplantation.
3. The presence of extrahepatic tumor foci or sepsis (Appendix 9).
4. Gastrointestinal bleeding caused by portal hypertension within 3 months prior to screening.
5. Body mass index (BMI) less than 18.5 or more than 40 kg/m^2.
6. HIV infection.
7. Significant cardiovascular disease at the present time or within 6 months prior to screening, including: class III or IV chronic heart failure (the New York Heart Association classification), myocardial infarction, unstable angina, hemodynamically significant cardiac arrhythmias, ischemic or hemorrhagic stroke, uncontrolled arterial hypertension.
8. Preoperative renal impairment (glomerular filtration rate estimated with the Cockcroft- Gault formula ≤ 45 mL/min).
9. Significant, in the opinion of the Investigator, drug or alcohol abuse within 6 months prior to screening.
10. Hypersensitivity to:
    a) ibuprofen or to more than one non-steroidal anti-inflammatory drug (NSAID),
    b) more than one medication belonging to the class of sulfonamides, such as sulfamethazine, sulfamethoxazole, sulfasalazine, nimesulide or celecoxib; hypersensitivity to sulphanilamide antibiotics alone (e.g. sulfamethoxazole) does not qualify for exclusion.
11. Pregnant or lactating women, or women planning a pregnancy during the clinical study, fertile women not using adequate contraception methods.
12. Participation in another clinical study currently or within 30 days prior to screening, use of any investigational drug within 30 days or 5 half-lives (whichever is longer) prior to screening.
13. The patient's and his/her relatives' failure to understand the need for lifelong immunosuppressive therapy, as well as the risk and difficulty of the pending operation and the subsequent dynamic treatment.

14. Inability to read or write; unwillingness to understand and comply with the procedures of the study protocol; failure to comply with the treatment, which, in opinion of the Investigator, may affect the results of the study or the patient's safety and prevent the patient from further participation in the study; any other associated medical or serious mental conditions that make the patient unsuitable for participation in the clinical study, limit the validity of informed consent or may affect the patient's ability to participate in the study.

Investigational product, doses and mode of administration:

Investigational product: Reparixin

Active ingredient: R(-)-4-isobutyl-α-methyl-phenyl-acetyl-methanesulfonamide

Dosage: 2.772 mg/kg/hour for 7 days (168 hours)

Dosage form: Reparixin will be provided as 33 mg/ml concentrated solution to be diluted for i.v. infusion, CCI [redacted] The dosing solution will be placed in a 1000 ml sterile empty Infusion Bag. Dosing solutions will be prepared and used within 72 hours from preparation, unless the site has more restrictive rules.

Mode of administration: continuous intravenous infusion into a central vein for 7 days (168 hours).

Manufacturer: PPD

Reference product:

None.

Standard immunosuppressive therapy:

The patients of both groups will receive the standard immunosuppressive therapy with tacrolimus only or together with mycophenolates, or a combination of tacrolimus/cyclosporine with mycophenolates and/or glucocorticosteroids. The patients with hepatocellular carcinoma and impaired renal function can receive a combination of drugs that includes everolimus. Basiliximab in association with methylprednisolone will be used for the induction of immunosuppression.

Duration of the study:

The overall duration of a patients' participation in the study will be approximately 1 year (1 week of treatment and up to 1 year of post-transplant follow-up). The start of enrollment (first-patient-in) is expected for March 2015. It is planned that the last patient randomized in the first stage will complete all study visits by March 2017. The end of the study (last visit of the last patient randomized in the second stage of the study) is expected by December 2017.

Statistical methods:

Analysis of efficacy endpoints:

The primary efficacy endpoint is the frequency of early allograft dysfunction after OLT (Week 1) among patients who received Reparixin and patients in the control group. The frequency of early allograft dysfunction comprises about 25% (in the interval between 9,3 up to 43,7%; it depends on various specifications and classifications of the state). It is expected that Reparixin treatment can decrease the frequency of early allograft dysfunction.

The analysis of the primary efficacy endpoint will be conducted in accordance with the Simon's minimax two-stage design [5, 6]. This model can trace the tendency in the efficacy parameters of the study drug in the small number of patients. Thus, it can assist in getting the results and making the decision on the following study of the drug.

In accordance with this model, the analysis of the efficacy will be conducted in two stages:

- During Stage 1 of the study the primary efficacy endpoint will be assessed in 22 patients in each group. In case of early allograft dysfunction in < 5 out of 22 patients from the group of the study drug, the transition to Stage 2 of the study will be deemed possible. In the case of early allograft dysfunction in ≥ 5 out of 22 patients from the group of the study drug, further study of Reparixin in this study population will be considered inappropriate.

- During Stage 2 of the study, the primary efficacy endpoint will be assessed in additional 17 patients in each group (in the total number of 39 patients in each group). Development of early allograft dysfunction in < 6 out of 39 patients from the group of the study drug gives grounds for a conclusion of the efficacy of Reparixin in this population and the appropriateness of the subsequent large-scale comparative Phase III clinical study. In case early allograft dysfunction develops in ≥ 6 out of 39 patients from the group of the study drug, further study of Reparixin in this study population can be considered inappropriate.

Appropriate descriptive statistics will be produced for secondary efficacy endpoints.

Analysis of safety endpoints:

All AEs will be presented by primary system organ class systems and preferred term, in terms of the incidence, relationship to the study drug and severity. SAEs will be presented in the same way.

Vital signs at each time point and laboratory parameters will be presented using descriptive statistics methods.

PK analysis:

Plasma levels of reparixin (total and unbound) and relevant metabolites (DF2243Y and ibuprofen) will be summarized using descriptive statistics.

Sample size:

Simon's minimax two-stage design for Phase II clinical trials was used to calculate the sample size [5, 6]. With an alpha level of 0.05 and 80% of power, a total of 39 evaluable patients treated with Reparixin are required to test the study hypothesis. Twenty-two patients will be treated at Stage I. In case of early allograft dysfunction in 5 or more patients in the first 22 patients, the study will early terminate enrollment.

Data received from the control group will also be used in the study in order to control the validity of the information on frequency of early allograft dysfunctions.

In case of early discontinuation of patients from the study prior to receiving study treatment or inability to evaluate the primary efficacy endpoint, the patient can be replaced (see paragraph 6.13). Considering a possible 7% early discontinuation rate and the inability to assess the primary endpoint for some patents, up to 84 patients will be randomized in the study. This number of patients is based on a statistical power of 80% with an alpha of 0.05 and 1:1 randomization. In total, considering a possible 15% screening failure rate, about 100 patients planned for OLT will need to be screened in the study.

Randomization:

Patients will be randomized in a 1:1 manner into the treated or the control group (in accordance with a randomization list).

Number and date of the current version of the protocol:

Protocol Version No. 2 – Final 13 March 2015.

1 INTRODUCTION

Liver transplantation is currently the treatment of choice for end-stage liver cirrhosis of different origin, as well as for a number of inborn metabolism disorders and liver tumors. The need to perform a liver transplantation is high and amounts to 10 – 20 patients per 1 million population per year. The indication for liver transplantation is the presence of irreversible liver disease with estimated life expectancy of less than 12 months, absence of another treatment, presence of chronic liver disease, significantly reducing the patient's quality of life and ability to work, as well as progressive liver disease with a life expectancy less than in the case of liver transplantation (after liver transplantation 85% of patients survive for 1 year and 70% - for 5 years).

Currently, about 200 liver transplantations are performed annually in Russia, which is more than 10 times lower than the existing need and is far below the number of similar operations performed abroad. For example, in the USA, more than 4,000 liver transplantations (per 315 million people) are performed annually, in the UK – 650 transplantations (per 63 million people), which satisfy the current demand by 75 – 85%. According to Gauthier S. and Tsirulnikova O.M. [7], mortality on the waiting list for liver transplantation in Russia is 57.4%. In Western Europe and the USA this figure is 4 – 10%.

The vast majority of liver transplants for adult recipients are performed using liver allografts from cadaveric donors. The rigorous list of requirements for a transplant restricts significantly the use of cadaveric liver. Thus, the need to expand the pool of donor organs suitable for transplantation is a pressing issue.

Experimental and clinical evidence demonstrate the harmful short and long-term effects of ischemia-reperfusion injury (IRI) of the donor organ on the outcome of the intervention performed. Severe manifestations of IRI of the liver transplant (LT) is one of the main reasons for the increased length of hospitalization, the high cost of treating patients during the post- surgery period, the development of persistent early allograft dysfunction or loss, frequent crises of acute rejection, acute renal and multiple organ failure, and mortality of the operated patients. IRI caused by the termination and subsequent restoration of blood flow is more or less inevitable for all donor organs. The mechanism of ischemia-reperfusion syndrome involves interaction between vascular endothelium, interstitial space, circulating cells and a variety of biochemical reactions, with the primary link in the chain of pathological processes of local and generalized nature being microcirculatory disorders. Early allograft dysfunction is an important predictor of severe complications and mortality after OLT [8].

The incidence of early allograft dysfunction is approximately 25% (ranging from 9.3 to 43.7% subject to different definitions and classifications of the condition). Retrospective evaluation of the incidence of early allograft dysfunction performed in the Russian leading transplantation institution – N.V. Sklifosovsky Research Institute of Emergency Care, confirmed the development of this type of complication in 25% of cases (N = 202). Death has occurred in the population of patients with early allograft dysfunction at almost twice the rate of patients with normal functioning of the transplant during the first 7 days after OLT ($p < 0.005$).

Therefore, as yet, the search of the drugs that may be effective in the prevention of early allograft dysfunction is still a relevant issue.

Dompé farmaceutici s.p.a. (Italy) is developing a new drug Reparixin, which is a new, potent and specific inhibitor of chemokine CXCL8 (Interleukin-8). With regard to the mechanism of action of Reparixin, its early preclinical development was aimed at specific inhibition of migration of polymorphonuclear neutrophils and prevention of ischemia- reperfusion injury. The clinical study of Reparixin was initially focused on the prevention of

delayed allograft function and primary nonfunction in transplantation of solid organs (kidneys, lungs) and pancreatic islets.

Reparixin has received the orphan drug designation in EU in September 2001 and in USA in January 2003 for prevention of delayed graft function after solid organ transplantation. More recently orphan drug designation has been granted in EU (September 2011) for the "prevention of graft loss in pancreatic islet transplantation" and in the US (September 2012) for the "prevention of graft loss in islet cell transplantation".

This pilot clinical study is designed to evaluate the efficacy and safety of Reparixin as an agent to prevent early allograft dysfunction caused by ischemia-reperfusion injury in patients undergoing orthotopic liver transplantation.

2 THE OBJECTIVES AND ENDPOINTS OF THE CLINICAL STUDY

2.1 Study objective

To evaluate efficacy and safety of continuous intravenous infusion of Reparixin (2.772 mg/kg body weight/hour intravenous continuous infusion for 7 days) based on the incidence of early allograft dysfunction (within the first 7 days after 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.

2.2 Study endpoints

Efficacy endpoints will be:

- Incidence of early allograft dysfunction (EAT) within the first 7 days after OLT (**primary endpoint**).
- Primary nonfunction within 7 days after OLT.
- Overall indicators of the liver allograft dysfunction during the early postoperative period (within 14 days after OLT), including:

  - Primary nonfunction (PNF),

  - 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 HBV, kidney function, score in scales of end-stage liver disease (MELD), Child-Turcotte-Pugh, etc.).
- Time for normalization of liver function parameters (alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin levels, gamma-glutamyltransferase (GGT), lactate dehydrogenase (LDH), 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.

Safety endpoints will be:

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

Pharmacokinetics endpoints will be:

Reparixin (total and unbound) and relevant metabolites (DF2243Y and ibuprofen)

- maximum plasma concentration (Cmax).
- time of maximum plasma concentration (tmax).
- terminal phase rate constant (λz).
- terminal half-life (t½).
- area under the plasma concentration-time curve from time zero to time t (AUC0-t).
- area under the plasma concentration-time curve from time zero to infinity (AUC0-∞).
- volume of distribution (Vz).
- clearance (CL).

3 STUDY DESIGN

3.1 Overall design and study plan

Dompé farmaceutici s.p.a. offers a program of clinical development of the drug Reparixin, which is a new, potent and specific inhibitor of the chemokine CXCL8 (Interleukin-8), as a drug for the prevention of early allograft dysfunction in patients undergoing orthotopic liver transplantation (OLT) patients.

The aim of the present clinical phase 2 trial is to obtain preliminary efficacy data and evaluate the safety of Reparixin in terms of prevention of early allograft dysfunction after OLT.

3.2 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.

3.3 Screening

Patients admitted to the transplant center immediately before OLT surgery who signed the Patient Informed Consent Form will undergo screening procedures (Day -1). Screening can be carried out within 24 hours before planned surgery. The results at screening will be considered as baseline values.

During the screening physical examination, assessment of vital signs, baseline scores according to MELD, Child-Turcotte-Pugh, laboratory tests and ECG, vascular ultrasound of the liver and kidneys with Doppler sonography will be performed. Patients fulfilling all the inclusion criteria and none of the exclusion criteria will be randomized.

Considering a possible 7% early discontinuation rate and the inability to assess the primary endpoint for some patents, up to 84 patients will be randomized in the study. This number of patients is based on a statistical power of 80% with an alpha of 0.05 and 1:1 randomization. In total, considering a possible 15% screening failure rate, about 100 patients planned for OLT will need to be screened in the study.

3.4 Study drug administration and surgery

Patients who meet all inclusion criteria and do not conflict with the exclusion criteria will be randomized into the Reparixin or the control group. In the group of the study therapy, Reparixin will be administered as a continuous infusion for 7 days (168 hours). Infusion of the study drug will start approximately 60-90 minutes before the anticipated time of OLT. The patients, who will be randomized in the control group, will not receive any study therapy.

The operation will be carried out according to the Russian Transplant Society Guidelines for liver transplantation and standard procedures adopted at the clinical sites (Appendix 7). In

addition to standard criteria approved by the health authorities of the Russian Federation to assess the extent of hepatodepression (liver problems), the Investigator will evaluate organ suitability for transplantation relying on histopathologic findings from biopsy. In this clinical setting, grafts with macrovesicular steatosis degree >50% will be considered as non-suitable for transplantation. During the study the patients of both groups will receive necessary concomitant medications, including immunosuppressive therapy in accordance with the Russian Transplant Society Guidelines for liver transplantation (Appendix 7).

The patients of both groups will receive the standard immunosuppressive therapy with Tacrolimus only or together with mycophenolates, or a combination of Tacrolimus/Cyclosporine with mycophenolates and/or glucocorticosteroids. The patients with hepatocellular carcinoma and impaired renal function can receive a combination of drugs that includes everolimus. Basiliximab in association with methylprednisolone will be used for the induction of immunosuppression.

Post-operative examinations will be performed daily during 7 days after OLT (Day 0 – Day 6). The final assessment of safety parameters and primary end-point will be conducted 7 days after OLT (in the group of the study therapy it will be held after the end of the infusion).

3.5 Follow-up

At the end of the 7-day period of the study therapy, the patients will receive the necessary prescription and recommendations for further treatment as appropriate for the standard management of patients after liver transplantation. The patients will be followed-up during 1 year after OLT. At Week 2 and Week 4 the patients will visit the center for mandatory control of the basic functions of the liver transplant and general condition of the patient. Then, the patients will visit the center on Weeks 12, 24 and 1 year after OLT in order to control safety parameters.

At Week 36, the patients (or their families) will be contacted by the Investigator through telephone call to monitor graft and patient survival. The status of patient and allograft survival will be monitored up to 1 year from the date of OLT. The patient will receive all the necessary medical assistance in accordance with the standard of patient management after liver transplantation.

Design of clinical trial TPL-RPX-01 is presented below.

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

	Screening	**Study drug administration**								**Follow-up**					
Week		W0							W1	W2	W4	W12	W24	W36	Year1
Day	D-1	D0	D1	D2	D3	D4	D5	D6	D7					↑	

Telephone follow-up

Randomization ↑

↑OLT

Study group	Reparixin (continuous infusion 168 hours)
Control group	-

Both groups	Standard immunosuppressive therapy

The flow chart of the study is presented in **Table 1**.

Table 1 Study TPL-RPX-01 flow chart

Phase	Screening and randomization	Study drug administration									Follow-up						ED[m]
Week		W0								W1	W2	W4	W12	W24	W36[g]	Y1	
Day	D(-1)	D0			D1	D2	D3	D4	D5	D6	D7							
Time window/ Visit period	from 24 h up to 90 min prior to planned surgery	0 h (start of the Reparixin infusion)	60-90 min from the start of the Reparixin infusion	12 h from the start of the Reparixin infusion or 11 h after OLT (±30 min)								±2 days	±3 days	±7 days	±7 days	±7 days	±14 days	
Patient informed consent	☒																	
Patient registration	☒																	
Demographic data	☒																	
Medical history	☒																	
MELD and Child-Turcotte-Pugh Scores	☒																	
Complete physical examination	☒										☒	☒	☒	☒	☒		☒	☒
Short physical examination				☒	☒	☒	☒	☒	☒	☒								
Vital signs	☒	☒		☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒		☒	☒
Height and Weight[a]	☒										☒	☒	☒	☒	☒		☒	☒
ECG (12 leads)	☒			☒[b]		☒		☒			☒	☒	☒	☒	☒		☒	☒
Laboratory tests																		
- Hematology	☒				☒	☒		☒			☒	☒	☒	☒	☒		☒	☒
- Biochemistry	☒				☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒		☒	☒
- Coagulation profile	☒				☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒		☒	☒
- HIV (express test)	☒																	
- Viral load: DNA HBV, RNA HCV[c]	☒																	
- Urinalysis	☒					☒		☒			☒	☒	☒	☒	☒		☒	☒
- Pregnancy test[d]	☒												☒	☒	☒		☒	☒
- PK sampling					☒[h]		☒[h]		☒[h]		☒[k]							
Doppler US of the abdomen	☒				☒			☒			☒	☒	☒	☒	☒		☒	☒
Evaluation of inclusion/exclusion criteria	☒																	
Randomization	☒[e]																	
Reparixin infusion (in the group of investigational therapy)		**168 hours continuous infusion**																
OLT[f]			☒															
Concomitant therapy	☒	☒		☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒		☒	☒
Adverse events assessment	☒	☒		☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒		☒	☒
Phone follow-up																☒		

Abbreviations:

W – week,

D – day,

Y – year,

ECG – electrocardiography,

OLT – orthotopic liver transplantation,

US – ultrasound examination,

ED – early discontinuation

Footnotes:

[a] Height will be measures only once during the trial (at screening).

[b] On the operation day (Day 0) ECG data can be gathered via bedside monitor.

[c] Viral load is determined only for patients with the past HBV/HCV.

[d] Pregnancy test is carried out in the center with the help of test strips to women of childbearing potential only (including women in menopause of less than two years).

[e] Patient randomization will be held before or on the day of surgical operation and only after confirmation of all inclusion/exclusion criteria. Inclusion/exclusion criteria, that depend on laboratory parameters, could be assessed on the basis of results obtained from a local laboratory of the center (without waiting for results from a centralized laboratory).

[f] OLT will be carried in accordance with the Russian Transplant Society Guidelines for liver transplantation and as per center local standard clinical practice. All the patients that take part in the study will receive necessary concomitant medications, including standard immunosuppressant therapy.

[g] Investigator will contact the patient on Week 36 for telephone follow-up to monitor status of patient and allograft survival.

[h] Obtain PK ideally in the morning (on Day 1, 3, 5 after OLT), only in patients randomized to Reparixin in stage 1 of the study.

[k] Obtain a PK sample just prior 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.

[m] The patient should attend the ED visit not later than in 4 weeks from the end of the study drug infusion (no later than 5 weeks after OLT for patients from the control group). In case of withdrawal from the study after Week 12, the ED visit is not needed.

3.6 Rationale of the study design

Clinical study of Reparixin was initially focused on the prevention of delayed transplant function and primary graft nonfunction after the transplantation of solid organs (kidneys, lungs) and pancreatic islets. This multicenter, randomized, pilot open-label Phase 2 clinical study is aimed, first of all, to evaluate preliminary efficacy and safety of Reparixin treatment (2,772 mg/kg body weight/hour intravenous continuous infusion for 7 days) to prevent the development of early allograft dysfunction in patients undergoing OLT. The results of this study will allow conducting a subsequent study of Reparixin for this indication in the larger population of patients. In case of positive study results, an extension of donor criteria may be considered to expand the pool of potential organs for transplantation and to maximize donor organ utilization, minimizing waiting list delay.

Reparixin is a specific inhibitor of chemokine CXCL8 (Interleukin-8), which plays an important role in ischemia-reperfusion injury of the transplant [9]. Safety of the drug was studied in Phase I studies in healthy volunteers and in patients with impaired renal function, and in phase II studies in patients with lung, kidney, and pancreatic islets transplants, as well as after coronary artery bypass surgery [10].

Relevant phase 1, 2 and 3 clinical data are summarized in paragraph 3.8. Please also refer to the Investigator's Brochure for more detailed information.

The dosage of the drug proposed in this study as a continuous 7-day infusion was studied in the clinical trial of pancreatic islets transplantation. The infusion will be conducted only at the time of hospital treatment under the strict supervision of the Investigator.

In this study Reparixin is first used in a population of patients who underwent liver transplantation. The proposed design of the study with the use of Simon's minimax model [5, 6] will help to track the tendency in the parameters of drug efficacy in a small group of patients and thus will help to decide on further study of the drug for this indication in a large population of patients.

Simon's minimax two-stage design for Phase II clinical trials was used to calculate the sample size. With the help of this model it is possible to receive preliminary data on presence or absence of drug effect in order to make a decision on further clinical development of the drug. This method is used worldwide in the sphere of clinical studies on oncology and transplantation [11, 12].

Simon's minimax two-stage design is optimal for the first study of Reparixin among patients with OLT. The following aspects should be taken into account:

1. The limited number of patients who undergo OLT (only about 200 surgeries per year in Russia).
2. Ischemia-reperfusion syndrome is the acute reaction that is expressed in the early allograft dysfunction. Drugs of the standard immunosuppressive therapy, as well as other medications that are given to OLT patients, are currently not aimed at the correction of this syndrome and do not prevent early allograft dysfunction. Thus, there is no, so-called, gold standard treatment for such conditions or a possible alternative way of treatment that could be used like a reference drug.
3. The usage of placebo as a reference substance is not possible due to ethical reasons and because of difficulties in administration of the drug (constant intravenous infusion during 168 hours and also during the surgical operation). Administration of placebo could be an unjustified risk for the patients that undergo operation and also in the early post-surgical period.

4. All the patients that participate in the study will receive standard immunosuppressive therapy and other essential medications. Thus, the participation in the study does not mean that patients will be left without drugs that are shown to be effective in the transplantation setting. However, it has already been stated that these drugs do not assist in correction and conducting preventive measures of states that are connected with ischemia-reperfusion syndrome and will not affect evaluation of study results.
5. There is a global statistics concerning the frequency of early allograft dysfunction that matches the Russian data (Center of liver transplantation, N.V. Sklifosovsky Research Institute of Emergency Care). Early allograft dysfunction is observed in 25% of cases, i.e. in 50 patients out of 200 who undergo such a surgery in Russia (data for a period of 1 year). It doubles the risk of fatal case.
6. During the previous studies that were connected with pancreas β-cells transplantation Reparixin showed excellent efficacy and safety results for the same dose regime (2,772 mg/kg body weight/hour intravenous continuous infusion for 168 hours).
7. When the preliminary data concerning the presence of a certain effect are confirmed, a large-scale comparative study will be held to prove the drug's efficacy. Otherwise further study of Reparixin in this study population will be considered inappropriate.
8. Inclusion of the control group will help to map out any treatment effects more clearly, providing a better understanding of any effects of Reparixin.
9. As a result of the study, it is expected to demonstrate the efficacy of the drug in the prevention of early allograft dysfunction caused by ischemia-reperfusion injury in patients undergoing OLT. Interim evaluation between two stages of patients' enrollment in the study will provide preliminary data on presence of the expected effect of the study drug and will allow termination of the study in case of its absence.

Early allograft dysfunction develops within one week after OLT. Therefore, the assessment of the primary end point will be held 7 days after surgery, and after the end of infusion of the study drug. Patients will visit the clinical site for 1 year to monitor the more remote indicators of liver transplant function. Survival rate of patients and the transplanted organs will be monitored up to 1 year from the date of OLT.

Safety parameters will be monitored during the study; and information on adverse events will be collected. More attention will be paid to parameters of liver function (liver enzymes, clotting parameters, albumin, glucose, and bilirubin). Renal function (creatinine, urea) and the cardiovascular system (vital signs, ECG) will also be evaluated. The Investigator may decide to early discontinue the patient from the study in case of development and progression of acute renal and hepatic failure.

3.7 Duration of the study and the dates

The overall duration of a patients' participation in the study will be approximately 1 year (1 week of treatment and up to 1 year of post-transplant follow-up).

The start of enrollment (first-patient-in) is scheduled for March 2015. It is planned that the last patient randomized in the first stage will complete all study visits by March 2017. The end of the study (last visit of the last patient randomized in the second stage of the study) is expected by December 2017.

3.8 Previous experience with Reparixin

A total of 404 subjects have been involved in phase 1 and phase 2 completed clinical studies. Among these, 266 subjects have been exposed to Reparixin.

Table 2 shows the clinical studies of Reparixin completed to date. Please also refer to the Investigator's Brochure (Reparixin Final Version[redacted]) for more detailed information.

Table 2 Reparixin clinical trials

	Protocol number	Design	Subjects	Dosage	Treatment duration	Phase	No. of subjects who received treatment with the drug
[redacted]							

Overall, Reparixin was safe and well tolerated in both healthy subjects and critically ill patients.

3.8.1 Phase I Clinical Studies

The safety and efficacy of Reparixin was evaluated in seven completed sponsor-initiated clinical studies.

In the first of seven phase I clinical studies conducted to date, Reparixin L-lysine salt 1 to 16 mg/kg was administered by short infusion (30min). The compound was well tolerated at all doses, with minor and unspecific AEs which were not dose-related.

In the second study, the compound was administered as 48h i.v. infusion targeting to Reparixin steady-state concentrations (CSCs) of 10, 20 and 30 µg/mL. Reparixin resulted well tolerated; again AEs were minor and not dose related. The local reactions were observed to subside by administering a more diluted solution at a higher infusion rate.

In the third study (interaction study), co-administration of midazolam/tolbutamide (probe substrates for CYP3A4 and CYP2C9) with Reparixin did not raise safety concerns.

The fourth study was performed in subjects with different degree of renal impairment. The i.v. infusion of 2 mg/kg/h of Reparixin L-lysine salt was safe and well tolerated both in patients with different degree of renal impairment and in subjects with normal renal function. Very few AEs were reported, the majority of which were mild in intensity and unlikely due to Reparixin.

Two studies were performed in the cantharidin blister model to assess if Reparixin can reduce the influx of PMNs inflammatory mediators, during acute inflammation. In the first study, there was a very high variability in the response to cantharidin. Only two out of 8 subjects were evaluable. The analysis did not detect any significant difference between treatments (Reparixin versus placebo) and unfortunately the blister volumes were not sufficient to evaluate the differences in the inflammatory mediators. The second of these two studies was to evaluate the effect of dexamethasone and Reparixin on inflammatory mediators in this model. There were no statistically significant differences observed in the inflammatory mediators from the two groups. Due to errors in sample handling with flow cytometry samples, no conclusion could be made regarding these data. The safety of Reparixin was confirmed in both of these studies.

The seventh study in oncology was opened in July 2011 and the primary objective was to achieve the Proof of Concept that Reparixin targets CSCs in patients and that such targeting translates into potential for clinical benefit. Based on the aforementioned preclinical data, a Phase 1b study to evaluate the safety and pharmacokinetic profile of Reparixin oral tablets in combination with paclitaxel, and to explore the effects of Reparixin on disease response and breast CSCs and the tumor microenvironment was initiated and has now completed enrollment. A Phase 2 study has also been initiated to evaluate the use of single agent Reparixin in the selective targeting of CSCs in breast cancer in the early stage setting. In addition, a new phase 2 study is in start up to evaluate Reparixin in combination with paclitaxel in metastatic triple- negative breast cancer.

3.8.2 Phase II Clinical Studies

Three Phase II studies have been completed to date. Two studies investigating the efficacy of Reparixin in the prevention of primary graft dysfunction/delayed graft function in lung/kidney transplantation were conducted with Reparixin administered by continuous intravenous infusion, up to a maximum of 48h. Neither of the two studies was able to show a statistically significant effect of Reparixin on short- and long- term functional and clinical outcomes after transplantation. In the lung study, a total of 7 patients died, all in the placebo group. The AE profile was similar for both placebo and Reparixin groups. Twenty-eight patients experienced SAEs; 8 SAEs in 6 patients were judged possibly related to the study drug. During the renal

transplant study, one patient in the Reparixin intermittent infusion group and one patient in the placebo group died. The AE profile was similar for both Reparixin and placebo groups. SAEs were reported in 21 patients. SAEs possibly related to study drug were reported for only 2 patients, both in the Reparixin continuous infusion group. An assessment performed by DMC on a possible study-related higher incidence of thrombosis, excluded the potential relationship of Reparixin with these events.

A phase II study evaluating the efficacy of Reparixin in improving transplant outcome in type 1 diabetes patients undergoing pancreatic islet transplantation was conducted with Reparixin administered by intravenous infusion over 7 days. This study shows a clinical benefit of Reparixin in terms of improved β-cell function and islet transplant clinical outcomes, and provides a preliminary clinical proof of its potential in pancreatic islet transplantation in patients with type 1 diabetes. Data obtained from this pilot trial further support the safety of Reparixin in this clinical setting. In patients treated with a 7 day course of Reparixin a few AEs were reported which were judged to be at least possibly related to Reparixin treatment. There were 11 reports of SAEs in 3 patients taking Reparixin compared with 1 report in 1 patient in the control group. The safety profile was in line with previous clinical experience and there were no safety issues that would preclude further development of Reparixin in islet transplantation.

3.8.3 Phase III Clinical Studies

Due to encouraging data obtained in the pilot trial, a phase 3 study is ongoing in 8 sites in 4 EU countries and 1 site in the US to further evaluate the efficacy and safety of Reparixin in pancreatic islet transplantation in T1D. A total of at least 42 (up to a maximum of 72) pancreatic islet transplant recipients will be randomly (2:1) assigned to receive either Reparixin [continuous i.v. infusion for 7 days (168hrs), starting approximately 12 hours before each islet transplant (treatment group)] or matched placebo (control group), administered as an added on treatment to the immunosuppressant regimen. Patients may receive up to 2 islet transplants, the 2nd one to occur between 3 and 12 months after the 1st one in patients who retain graft function (fasting C- peptide > 0.3 ng/mL). Primary endpoint is the AUC for the serum C-peptide level during the first 2 hours of a Mixed Meal Tolerance Test (MMTT), normalized by the number of IEQ/kg, calculated at day 75$\pm$5 after the 1st islet infusion and day 365$\pm$14 after the last islet infusion.

To date, 49 patients have been randomized, and 44 have gone on to treatment and transplant. 23 patients have received a second islet infusion. 13 patients have completed one year follow-up after last transplant (either the 1st or the 2nd). 66 SAEs (excluding co-manifestations) have been reported to date in 30 patients. Most of the events involved the gastrointestinal system (e.g. abdominal pain, nausea, vomiting); blood and lymphatic system disorders (leukopenia, neutropenia, anemia, hemoperitoneum), other body system disorders (increased liver enzyme, hepatic hematoma, bleeding, raise in donor specific antibodies): overall the kind of SAEs reported were well known events associated to the transplant procedure. The following cases were considered by the investigator to be at least possibly related to the IP, either Reparixin or placebo: one case of neutropenia and leukopenia, one case of anemia, intra-abdominal haemorrhage and abdominal pain lower; one case of adenocarcinoma and cytomegalovirus colitis, two cases of transplant rejection, one case of pneumonia, one case of implant site haemorrhage.

In addition, a phase 2/3 is being conducted at 6 centers in the US to assess the efficacy and safety of Reparixin in pancreatic islet auto-transplantation (IAT) in patients undergoing total pancreatectomy due to chronic pancreatitis. One Canadian center is going to be opened. The goal of this study is to reach a total of 100 adult patients who are randomized and receive IAT. Patients will be randomly (1:1) assigned to receive either Reparixin [continuous i.v. infusion for 7 days (168 hours)], or matched placebo (control group),starting approximately 12 hours before islet infusion. The primary endpoint is the proportion of insulin-independent patients at one year after the transplant. To date, 34 patients have been randomized and transplanted. 41 SAEs have

been reported to date in 26 patients. Most of the events involved the gastrointestinal system (e.g. abdominal pain, nausea, vomiting, clostridium difficile) and are known events associated to the transplant procedure. All cases were considered unrelated.

3.8.4 Academic clinical studies

Two academic independent clinical trials were conducted by the Medical University of Vienna. The results of the first study indicated that lipopolysaccharide -induced neutrophilia was not significantly affected by Reparixin in human volunteers. No AEs were reported. The second study was conducted in patients undergoing elective coronary artery bypass grafting with cardiopulmonary bypass. The rise of the neutrophil count after CPB was less marked in the Reparixin group.

3.9 Risk/benefit ratio

3.9.1 General risks

OLT is the therapy of choice for terminal chronic liver disease and acute liver failure. OLT is associated with serious potential risk of patient's life and health both during the operation and in the post-transplant period due to acute or chronic allograft rejection, regardless of study participation.

3.9.2 Risks related to the administration of Investigational Product

Results from preclinical studies support the level of drug exposure planned in this study. Also, past clinical experience with the same dose as planned in this study provides a clear cut evidence of Reparixin safety.

The very short half-life of Reparixin (t1/2 1.0-1.5hrs) represents an important safety factor as plasma levels decline rapidly after drug discontinuation. This pharmacokinetic profile, coupled with the mechanism of Reparixin action (reversible inhibition), makes readily effective appropriate stopping rules.

Administration via a high flow central vein, which was proven to be safe in lung and kidney recipients, as well as in patients undergoing islet transplant, is proposed for the study to minimize the risk of infusion-site toxicity seen in a cohort of volunteers receiving i.v. infusion via a peripheral vein.

As to Adverse Drug Reactions (ADRs), infusion site reactions, mainly erythema or aseptic thrombophlebitis, were one of the most common ADRs. The relatively high frequency was due to a cluster of events occurring in cohort 1 of the phase 1 48h-infusion study. Local toxicity was clearly related to drug concentration since the use of a more diluted solution at a higher infusion rate markedly reduced the incidence, type and severity of infusion site reactions.

Cumulative summary tabulation of ADRs is reported in Appendix 8.

The most frequent (>10%) ADRs observed in the phase 1 and phase 2 studies completed to date were:

Nervous system disorders (about 22%), including headache, dizziness, hypoaesthesia, somnolence.

Gastrointestinal disorders (about 22%), including nausea, vomiting, abdominal pain, dyspepsia, flatulence, gastroesophageal reflux disease.

General disorders and administration site conditions (about 19%), including cannula site reaction, injection site thrombosis, infusion site oedema and peripheral oedema, fatigue, lethargy.

Data obtained in the pilot trial in islet transplantation further support the safety profile of the

proposed dose, even after a 7 days administration, repeated twice in a few patients. Most frequent ADRs were erythema, hypotension, nausea, vomiting; great majority of these were mild to moderate in nature and none required discontinuation of the Investigational Product. Nausea, vomiting and severe gastrointestinal bleeding associated with anaemia developed in a female patient early after the beginning of Reparixin infusion because the patient received a dose of reparixin 3 times as high as that foreseen in the protocol (medical error). These events were assessed as serious by the investigator and by the Sponsor.

3.9.3 Central line

The study drug will be administered as a continuous i.v. infusion over 7 days with a catheter inserted in a (high flow) central vein. The risks of a central line positioning are not considered study-related risks since it is routinely used during the early post-transplant period in patients undergoing orthotopic liver transplantation. In patients, who will receive the study drug, i.v. access may be maintained for a slightly longer time that routinely used. Nevertheless, routinely care of the catheter as practiced by the participating sites will minimize the risk of thrombosis and infections.

3.9.4 Potential benefits for patients

Preliminary pilot clinical study in patients with type I diabetes undergoing islet transplantation confirm that Reparixin improves function of the graft and prevents its early rejection. Taking into account the common mechanisms of ischemia-reperfusion injury after organ transplantation, it is expected that Reparixin will contribute to the prevention of early allograft dysfunction and improve graft survival rate and function.

4 SELECTION OF THE STUDY POPULATION

4.1 Study population

The study population will comprise adult patients aged 18 and older that require OLT.

Considering a possible 7% early discontinuation rate and the inability to assess the primary endpoint for some patents, up to 84 patients will be randomized in the study. This number of patients is based on a statistical power of 80% with an alpha of 0.05 and 1:1 randomization. In total, considering a possible 15% screening failure rate, about 100 patients planned for OLT will need to be screened in the study.

During Stage 1 of the study the primary efficacy endpoint will be assessed in 22 patients in each group. In case of early allograft dysfunction in < 5 out of 22 patients from the group of the study drug, the transition to Stage 2 of the study will be deemed possible. In the case of early allograft dysfunction in ≥ 5 out of 22 patients from the group of the study drug, further study of Reparixin in this study population will be considered inappropriate.

During Stage 2 of the study, the primary efficacy endpoint will be assessed in additional 17 patients in each group (in the total number of 39 patients in each group). Development of early allograft dysfunction in < 6 out of 39 patients from the group of the study drug gives grounds for a conclusion of the efficacy of Reparixin in this population and the appropriateness of the subsequent large-scale comparative Phase III clinical study. In case early allograft dysfunction develops in ≥ 6 out of 39 patients from the group of the study drug, further study of Reparixin in this study population can be considered inappropriate.

4.2 Inclusion criteria

Inclusion Criteria:

1. Male and female patients aged 18 years and older needing a whole organ OLT, listed on the waiting list for liver transplantation.
2. Severity score of the initial condition of the patient (hepatocellular dysfunction) according to the scales of Child-Turcotte-Pugh ≥ 7 points or MELD 15-40 points (or both).
3. The possibility of insertion of a central catheter for infusion of the study drug.
4. Signed Patient Informed Consent Form.
5. Ability to comply with all the requirements of the protocol.
6. Consent to use adequate contraception means throughout the study. The adequate contraception methods include use of condom with spermicide.

4.3 Exclusion criteria

Patients with any of the following conditions shall not be included in the study:

1. Split-liver transplantation or transplantation from a living donor.
2. Re-transplantation or multivisceral transplantation.
3. The presence of extrahepatic tumor foci or sepsis (Appendix 9).
4. Gastrointestinal bleeding caused by portal hypertension within 3 months prior to screening.
5. BMI less than 18.5 or more than 40 kg/m^2.
6. HIV infection.
7. Significant cardiovascular disease at the present time or within 6 months prior to screening, including: class III or IV chronic heart failure (the New York Heart Association

classification), myocardial infarction, unstable angina, hemodynamically significant cardiac arrhythmias, ischemic or hemorrhagic stroke, uncontrolled arterial hypertension.

8. Preoperative renal impairment (glomerular filtration rate estimated with the Cockcroft-Gault formula ≤ 45 mL/min).
9. Significant, in the opinion of the Investigator, drug or alcohol abuse within 6 months prior to screening.
10. Hypersensitivity to:

    a) ibuprofen or to more than one non-steroidal anti-inflammatory drug (NSAID),

    b) more than one medication belonging to the class of sulfonamides, such as sulfamethazine, sulfamethoxazole, sulfasalazine, nimesulide or celecoxib; hypersensitivity to sulphanilamide antibiotics alone (e.g. sulfamethoxazole) does not qualify for exclusion.
11. Pregnant or lactating women, or women planning a pregnancy during the clinical study, fertile women not using adequate contraception methods.
12. Participation in another clinical study currently or within 30 days prior to screening, use of any investigational drug within 30 days or 5 half-lives (whichever is longer) prior to screening.
13. The patient's and his/her relatives' failure to understand the need for lifelong immunosuppressive therapy, as well as the risk and difficulty of the pending operation and the subsequent dynamic treatment.
14. Inability to read or write; unwillingness to understand and comply with the procedures of the study protocol; failure to comply with the treatment, which, in opinion of the Investigator, may affect the results of the study or the patient's safety and prevent the patient from further participation in the study; any other associated medical or serious mental conditions that make the patient unsuitable for participation in the clinical study, limit the validity of informed consent or may affect the patient's ability to participate in the study.

4.4 Criteria for selection of donor organ for OLT

In addition to standard criteria approved by the health authorities of the Russian Federation [13] for the assessment of the extent of hepatodepression (liver problems), the Investigator will evaluate organ suitability for transplantation relying on histopathologic findings from biopsy.

In this clinical setting, grafts with macrovesicular steatosis degree >50% will be considered as non-suitable for transplantation.

4.5 Retesting and rescreening

In the case of ambiguous or equivocal results of laboratory studies during the screening, retest can be conducted with approval of the SponsorPPD Medical Monitor.

In case of cancellation of surgery patients can undergo rescreening procedure. In this case, all screening procedures will be carried out again, including the procedure for obtaining informed consent and the assignment of a new identification number.

5. STUDY DRUG

5.1 Description of study drug

Investigational product is Reparixin 33 mg/ml; a concentrate solution to be diluted for i.v. infusion. Patients from control group will not receive the study therapy.

Study drug:	Reparixin
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

5.2 Manufacturing, packaging and labeling

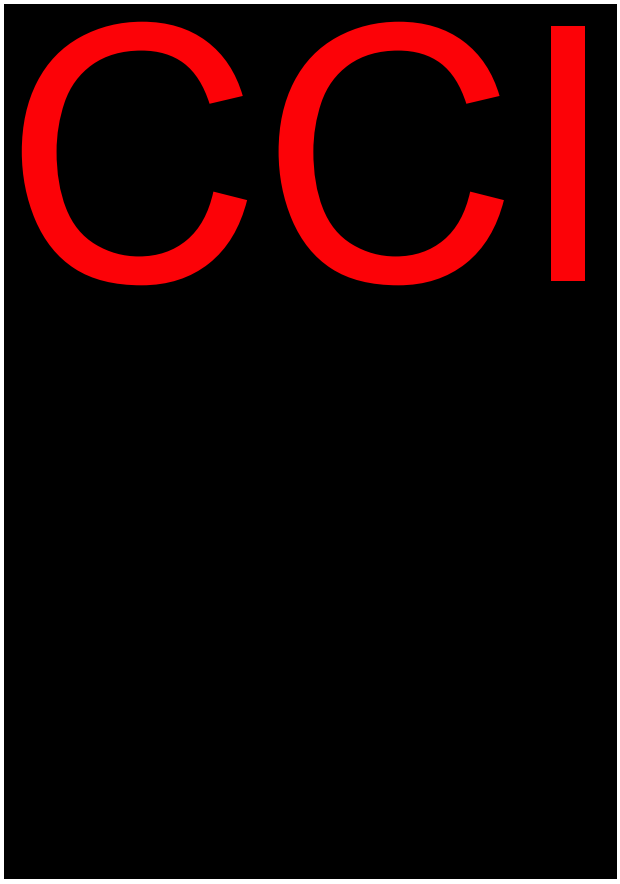
Reparixin will be manufactured by PPD [redacted] and packaged and labeled by PPD [redacted]. Each vial of reparixin will be packed individually in a 34x10x20cm cardboard box together with 1 sterile CCI [redacted] Infusion Bag for preparation of infusion solution and label for Infusion Bag.

The investigational product will be packaged and labeled in accordance with the current legislation of the Russian Federation and the Republic of Belarus and the applicable regulatory requirements, in particular with the Federal Law of the Russian Federation dated April 12, 2010 No. 61-FZ “On Circulation of Medicines”.

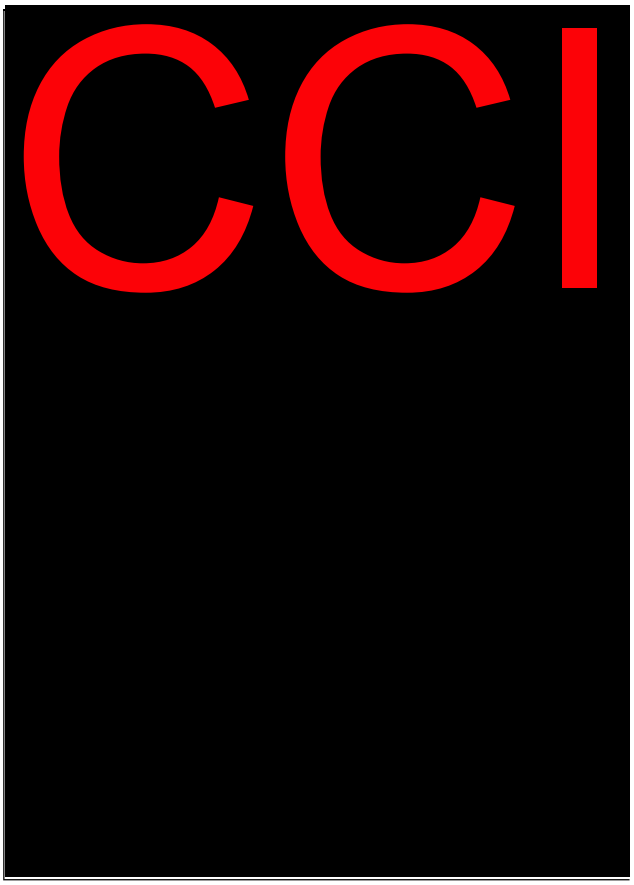
Labels for primary and secondary packaging and labelling are presented below.

Primary packaging

Sample label for Reparixin vial



Sample label for Infusion Bag



Secondary packaging

Sample label for Treatment Kit

5.3 Preparation of the Dosing Solution

The dosing solution for infusion will be prepared at the designated Pharmacy or authorized location within each centre according to local guidelines for sterile re-constitution of i.v. injectable solutions.

Preparation of investigational product solution begins after the confirmation of inclusion of the patient in the study immediately before the infusion of study drug. A self-adhesive label will be attached to each prepared Infusion Bag, reporting patient number and relevant information (preparation time and date and expiry time and date).

CCI

The concentrated Reparixin solution has a pale yellow color. Sometimes during the preparation of the diluted Reparixin solution appears a temporary foaming surface layer that disappears in a short time.

Prepared infusion solution should be used within 72 hours, unless the site has more restrictive rules. The Pharmacist (or designee) will make the Infusion Bags available to the hospital ward at the requested time.

5.4 Dose, course and calculation of Reparixin administration

Patients in the group of the study therapy will receive Reparixin CCI for 7 days (168 hours). The prepared solution of Reparixin CCI will be administered as a continuous infusion into a central vein using an automatic infusion pump that provides a constant rate of infusion.

Reparixin infusion will start 60-90 minutes before OLT. The Investigator shall accurately record the time of the beginning of Reparixin infusion in source documents and CRF. Infusion interruption is allowed for no more than 60 minutes. **In case of interruption of the infusion for a longer period, the Investigator shall contact the Sponsor/**PPD **Medical Monitor to discuss tactics with regard to the patient's condition.**

The pump rate will be adjusted to provide an infusion rate of approximately 0.25 ml/kg/hour. Actual infusion rate (mL/hour), adjusted to body weight, is tabulated in Appendix 5.

5.4.1 Criteria for discontinuation of investigational product

The investigational product should be immediately discontinued under any of the following conditions:

1. An allergic reaction to Reparixin.
2. Complications related to the surgery (OLT): intra-abdominal bleeding requiring a surgical reintervention, bile leak requiring a surgical reintervention, hepatic artery thrombosis confirmed by imaging techniques (e.g. ultrasound) or during surgery.
3. Decrease of glomerular filtration rate (GFR) under 20 ml/min (estimated with the Cockcroft-Gault formula).
4. Sepsis (Appendix 9), severe infectious complications (e.g., resulting in one or more organs failure, being considered life threatening or determining graft failure).
5. Hyperacute or acute transplant rejection (determined by biopsy).
6. Gastro-intestinal bleeding requiring a surgical or endoscopic intervention.
7. Increasing hepatic encephalopathy ($\geq 3^{rd}$ grade).

Withdrawal from the study will not interfere with patients' future medical care.

5.5 Randomization

Randomization will be held before or on the day of the surgical operation. Patients fulfilling all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 manner into the Reparixin or the control group.

Patients who do not meet the Inclusion Criteria or meet Exclusion Criteria will be considered screen failures (screen failure number assigned) and will not be allowed for inclusion into the study.

The randomization will be carried out using a randomization list. Each site will receive a kit consisting of a list of randomization numbers and sealed randomization envelopes prior to the start of the study. The investigator will be instructed to consecutively allocate the lowest available randomization number, but open the randomization envelopes containing the information on the allocated treatment group only at randomization to avoid any possible biases that may derive from knowledge of the treatment group to which patient would be assigned.

5.6 Blinding

This study is an open-label with no blinding of investigators or participants.

5.7 Assessment of compliance

Study treatments will be administered only by study staff at clinical site. Compliance will be assured by the person(s) within the center in charge of Investigational Product administration.

A self-adhesive label will be attached to each prepared Infusion Bag, reporting patient number to register actual date and time of infusion start and end. All used Infusion Bags will be retained at the centre to allow the Monitor to perform accountability of the study drug during monitoring visits and assess compliance with treatment.

Actual date and time of infusion start and end for each Infusion Bag will be also recorded in the CRF, as well as the infusion rate(s). Temporary interruptions duration during drug administration should also be reported in the CRF. **In case of Reparixin infusion halt for more than 60 minutes, the Investigator/Monitor shall contact the Sponsor/** PPD **Medical Monitor.**

Compliance with the study product dosing schedule will be evaluated by the Monitor during on-site monitoring visits, as per records in the CRF versus accountability records and information reported on the labels of administered Infusion Bags, and by comparing the number of used and unused treatment kits available at site.

The subject will be reminded of the importance of attending all scheduled follow-up visits on time.

5.8 Supply, Storage and Handling of Investigational Product

An appropriate number of supplies (Reparixin, Infusion Bags) will be initially sent to the site as soon as all essential documents and regulatory/ethics approvals have been obtained. Additional supplies will be sent on demand, according to enrolment rate.

The Investigational Product must be kept at a temperature not exceeding 30°C.

A temperature probe will accompany the drug on shipment. Temperature range reached during shipment will be verified on receipt, so that potential stability concerns during shipment can be investigated and appropriate action taken.

Once received at the site, the Pharmacist (or designee) will check the package for accurate delivery and acknowledge receipt; any deviations from expected package content (inconsistency, damages) should be immediately reported to the CRO, and the use of the drug should be suspended until authorization for its continued use has been given by the Sponsor/CRO.

The Investigational Product must be stored in a secure location, in a temperature controlled room. Temperature records must be available for a Monitor to review during on-site monitoring visits. Any deviations from the recommended storage conditions should be immediately reported to the Sponsor/CRO and the use of the drug suspended until authorization for its continued use has been given by the Sponsor/CRO.

The Investigational Product will be dispensed only by the Pharmacist (or authorized designee). The Investigator will ensure that study treatment is only administered by designated staff within the center. Pharmacists (or authorized designee) will be provided with the "Instructions to the Pharmacy", a booklet detailing instructions for Investigational Product handling and preparation of the dosing solution.

Immunosuppressive agents expected to be administered either for induction or maintenance therapy will not be supplied by the Sponsor since they are drugs routinely used to treat OLT patients and are part of the standard therapy.

5.9 Concomitant medications

All patients will receive appropriate concomitant therapy in accordance with the local standards.

All the related medications and dietary supplements must be registered in source documents and CRF. This includes all medications and supplements that are not included in study therapy, used by patients one month prior to screening and at any time during the clinical study. Name (name of the active ingredient is preferred), dose, frequency, mode of administration, indications for use (including the underlying disease, comorbid conditions, adverse events or prevention), start and end date of concomitant medication use must be registered in source documents and CRF. If the patient continues to receive concomitant medications at the final study visit (defined as the last visit recorded by the Investigator for that patient), the corresponding note should be made in the CRF.

The following drugs do not require registration in the CRF:

- i.v. saline or other oral solutions (including electrolyte solutions) used for hydration.
- Parenteral and enteral nutrition.
- Homeopathic medications.

5.9.1 Standard immunosuppressive therapy

All patients of the study will receive standard immunosuppressive therapy in accordance with the Russian Transplant Society Guidelines for liver transplantation (Appendix 7). The patients will receive tacrolimus only or together with mycophenolates, or a combination of tacrolimus/cyclosporine with mycophenolates and/or glucocorticosteroids. The patients with hepatocellular carcinoma and impaired renal function can receive a combination of drugs that includes everolimus. Basiliximab in association with methylprednisolone will be used for the induction of immunosuppression.

Standard immunosuppressive therapy will be registered in source documents and in the CRF.

5.10 Prohibited medications

The following drugs are prohibited in the study:

- Other study drugs.
- Anti-cytokine medicinal products (TNF-α inhibitors, e.g. infliximab, adalimumab, etanercept; interleukin-1receptor antagonist, e.g. anakinra).
- Low molecular weight dextran sulfates.

6 DESCRIPTION OF PROCEDURES

The study will be performed according to the Good Clinical Practice-International Conference on Harmonization (GCP-ICH) regulations and conducted according to the principles of the Helsinki Declaration and any local regulatory requirements [14].

The Investigator should permit monitoring and auditing by the Sponsor/CRO, and inspections by appropriate regulatory authority(ies). Upon request of the Monitor, auditor, IEC, or regulatory authority, the Investigator should make available for direct access all requested trial-related records.

6.1 Informed consent

Informed consent shall be obtained at screening before conducting any procedures related to the study.

6.2 Patient registration

Every patient who has signed a Patient Informed Consent Form will have an unique registration number assigned, consisting of four digits: the first two digits correspond to the number of the clinical site, the second two digits will be the sequential number of this patient at this site (01, 02, 03, etc.). After randomization of the patient in one of the two groups, a letter will be added to the screening number of the patient that indicates the group (R – Reparixin, C – control).

Thus, the number of the patient will consist of 4 numbers and 1 letter: ☐☐-☐☐-☐.

6.3 Demographic data and medical history

To assess the compliance of patients with inclusion/exclusion criteria it is necessary to collect patient demographic data (gender, date of birth/age, ethnicity/race), and complete medical history, including liver disease history, significant acute and chronic diseases, conditions (e.g., menopause), surgical interventions, and allergic reactions. It is also necessary to gather information on hospitalizations and/or surgical procedures, in addition to the one planned in the study (if applicable). All new diagnoses and conditions identified at screening (including the results of laboratory and instrumental tests) shall be recorded to the patient's medical history.

6.4 Physical examination

A complete physical examination includes an assessment of the overall appearance, skin and mucous membranes condition (including the place of infusion), neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, extremities, lymph nodes, and neurological status.

Short physical examination includes an assessment of the overall appearance, skin and mucous membranes condition (including the place of infusion), lungs, heart, stomach, lymph nodes, and neurological status.

During each physical examination after OLT the state of post-operative wound will also be assessed. The assessment will focus primarily on the search for signs of bleeding, hematoma or bruising. Condition will be evaluated according to the scale: “better than usual”, “as usual”, “worse than usual”, “is difficult to define”.

Clinically significant changes from the initial examination data, as well as an assessment of the state of the wound “worse than usual” shall be registered as an adverse event and recorded appropriately in source documents and CRF.

6.5 MELD and Child-Turcotte-Pugh scores

The initial state of the patient and the severity of liver disease shall be evaluated according to MELD and Child-Turcotte-Pugh scores (Appendices 2 and 3).

6.6 Vital signs, height and weight

This examination includes the measurement of axillary temperature, as well as blood pressure, heart rate and respiratory rate in the supine position after 10 minutes of rest.

Patient's weight and height (without shoes) will also be measured. Height will be measured only once during the study at Visit 1 (screening).

Body mass index (BMI) is also calculated at screening as follows:

BMI = weight/height^2 (kg/m^2), where the weight is in kg and the height is in meters.

Clinically relevant changes in vital signs from baseline values should be registered as adverse events and recorded appropriately in source documents and CRF.

6.7 Electrocardiography

12-lead electrocardiography (ECG) is performed to the patient in the supine position after 10 minutes of rest. The electrodes should be placed at the same points throughout the study. To record ECG it is recommended to use an electrocardiograph with automatic evaluation of intervals. At the day of operation (Day 0) the data can be collected from the bedside monitors.

The Investigator shall review the ECG record, in case of abnormalities assess their clinical significance, sign and date the report. Significant changes in ECG shall be double-checked. Clinically significant ECG changes in comparison with the original data shall be registered as adverse events and recorded appropriately in source documents and CRF.

6.8 Doppler abdominal ultrasonography

Patients will undergo a comprehensive abdominal ultrasound with dopplerography of blood vessels of the liver and kidneys (Doppler ultrasound). This procedure shall be done by a doctor of functional or diagnostic ultrasound department with experience in ultrasound angiology of at least 3 years. Ultrasound scanner of expert class shall be used to carry out this procedure.

The Investigator shall review the conclusion of Doppler ultrasound, in the case of abnormalities assess their clinical significance, sign and date the report. Significant changes in the Doppler ultrasound shall be double-checked. Clinically significant changes in Doppler ultrasound in comparison with the original data shall be regarded as adverse events and recorded appropriately in source documents and CRF.

6.9 Laboratory tests

All laboratory tests described in the protocol, except for the tests for pregnancy and HIV, will be performed at the centralized laboratory level. Hematology, coagulation, biochemistry, serology and viral load testing will be carried out by the Independent Laboratory PPD (Moscow, Russia) whereas pharmacokinetic analyses will be performed by Biotech Unit of Dompé farmaceutici s.p.a. (L'Aquila, Italy).

Centralized laboratory PPD will prepare a Laboratory Manual for the study that will be given to the clinical sites with special instructions for collection, preparation, storage and shipment of all biological samples.

Prior to the initiation of the study, centralized laboratory PPD will provide the required certificates and normal ranges of the laboratory. Centralized laboratory PPD will be responsible for sending the lab reports for hematology, coagulation, biochemistry, serology and viral load to the clinical sites, as well as for reporting about the alarming laboratory tests to the

Investigators, Sponsor and PPD Medical Monitor. The Investigator shall review the lab report, assess clinical significance of all abnormalities if any, sign and date the report. Clinically significant changes in laboratory parameters from baseline values are to be considered as adverse events and shall be recorded appropriately in source documents and CRF (apart from the exemptions listed in Paragraph 6.11.13).

Screening tests will be performed in parallel at the centralized and local laboratories. HIV testing will be carried out only locally (express test). The decision on patient's eligibility to participate in the study will be made based on the results obtained in the local laboratory of the site. Test results from the centralized laboratory will be used as baseline data.

In case of significant differences between the results obtained from centralized and local laboratories, a follow-up test (re-test) may be performed at a centralized laboratory.

Routine laboratory tests during and immediately after the surgery not covered by the protocol may be carried out or repeated at the local laboratory, when needed.

Prior to initiation of the study the local laboratory will also provide the required certificates and normal ranges of the laboratory. Clinically significant changes in the parameters assessed at the local laboratory shall be regarded as adverse events and recorded appropriately in source documents and CRF (apart from the exemptions listed in Paragraph 6.11.13).

6.9.1 Laboratory parameters

The Investigator will obtain blood samples from patients. Sample preparation shall be carried out in accordance with the Laboratory Manual. The prepared samples of whole blood, serum and plasma, as well as urine will be sent to the centralized laboratory for analysis. Necessary laboratory tests will be carried out at certain visits in accordance with the Study flow chart (**Table 1**).

Total volume of blood obtained from patients during the study period will be approximately 200 ml in the control group, and 280 ml in the Reparixin group. **Table 3** shows the parameters of blood tests, which will be assessed as part of this clinical study.

Table 3 List of parameters for blood test

Hematology	Biochemistry			Coagulation profile	Special tests
	General	Liver status	Renal status		
Hemoglobin Hematocrit Red blood cells White blood cells Neutrophils Lymphocytes Monocytes Eosinophils Basophils Platelets Erythrocyte sedimentation rate	Total protein Albumin Glucose Sodium Potassium Total cholesterol Triglycerides	ALT AST GGT LDH Total bilirubin Conjugated bilirubin	Urea Creatinine GFR (according to the Cockroft-Gault formula, Appendix 6)	APTT PTT INR	Screening: Express HIV test (locally) Viral load: DNAHBV RNA HCV

Determination of the viral load will be conducted only for the patients with HBV and/or HCV diagnosis in medical history via real-time PCR method.

Table 4 presents the urine tests which will be conducted in the study.

Table 4 List of parameters for urine test

Urinalysis	Special tests
General parameters: color, transparency, specific gravity, pH, protein, glucose, bilirubin, urobilinogen, ketones, nitrites, hemoglobin Precipitate microscopy: epithelium, erythrocytes, leukocytes, cylinders, bacteria, salts	Pregnancy test (the test is carried out directly in the center only in women able to bear children including menopausal women for less than two years)

6.9.2 PK parameters

Pharmacokinetic evaluation will be performed only in patients randomized to Reparixin in stage 1 of the study. **Table 5** shows the PK parameters, which will be assessed as part of this clinical study.

Table 5 List of PK parameters

Cmax	Maximum plasma concentration of reparixin and metabolites
tmax	Time of maximum plasma concentration reparixin and metabolites
λz	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

6.9.3 Collection, preparation, storage and shipment of biological samples

Collection, preparation, storage and shipment of biological samples will be carried out in accordance with regulatory requirements and Laboratory Manual.

6.9.3.1 Collection, preparation, storage and shipment of PK samples

PK samples preparation shall be carried out in accordance with the Laboratory Manual. The prepared samples of plasma will be sent with other biological samples to the centralized laboratory CCI for temporary storage, and then to Biotech Unit of Dompé farmaceutici s.p.a. (L'Aquila, Italy) for analysis.

Pharmacokinetic evaluation will be performed only in patients randomized to Reparixin in stage 1 of the study. Blood samples will be obtained during the treatment at Day 1, 3 and 5, just prior to the end of study drug administration, and then at 1, 3, 5, 6, 8, and 12 hours after termination of the study drug administration. Details on sample handling are reported in **Table 6** below and Appendix 10.

Table 6 PK sampling schedule

Week	Day	Time point No	Time of sampling
Week 1	**Day 1 after OLT**	**1**	This blood draw should be performed ideally in the morning (it is possible simultaneously with hematology and biochemistry)
	Day 3 after OLT	**2**	This blood draw should be performed ideally in the morning (it is possible simultaneously with hematology and biochemistry)
	Day 5 after OLT	**3**	This blood draw should be performed ideally in the morning (it is possible simultaneously with hematology and biochemistry)
	Day 7 after OLT	**4**	This blood draw should be performed just prior to the end of study drug administration
		5	This blood draw should be performed 1 hour after the end of study drug administration
		6	This blood draw should be performed 3 hours after the end of study drug administration
		7	This blood draw should be performed 5 hours after the end of study drug administration
		8	This blood draw should be performed 6 hours after the end of study drug administration
		9	This blood draw should be performed 8 hours after the end of study drug administration
		10	This blood draw should be performed 12 hours after the end of study drug administration

6.10 Assessment of efficacy

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**).

In addition, the incidence of primary nonfunction of the allograft will be assessed. Primary nonfunction is defined as absence of graft function leading to allograft loss, re-transplantation or death of the patient within 7 days after OLT for reasons not related to hepatic artery thrombosis, biliary complications, and acute exacerbations of chronic diseases or acute allograft rejection.

Cumulative incidence of allograft dysfunction in early postoperative period will also be assessed within the first 2 weeks after OLT (Week 2), including:

- Primary nonfunction,
- Early allograft dysfunction,
- Extracorporeal detoxification.

6.11 Evaluation of Adverse Events (AEs)

6.11.1 Definitions of AEs

Adverse Event (AE) – any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease. In this study, registration of AEs will commence from the moment the patient signs a Patient Informed Consent Form (before the first dose of study medication) and will continue during 1 year after OLT.

Adverse Drug Reaction (ADR) – any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug (at any dose) and the adverse event.

Serious Adverse Event (SAE), and/or Serious Adverse Drug Reaction (SADR) – any unfavorable medical event, which regardless of the dose of the study drug:

- results in death,

- is life-threatening (i.e. the patient was at risk of death at the time of the event),

- requires inpatient hospitalization or prolongation of existing hospitalization,

- results in persistent or significant disability/incapacity,

- is a congenital anomaly/birth defect,

- is an important medical event that may be not immediately life threatening or result in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition above.

Significant medical events that do not pose an immediate threat to life, do not result in death or hospitalization, but put patients at risk or require interventions aimed at the prevention of the above outcomes can also be included in SAE/SADR. Examples of such events may include bronchospasm of allergic genesis, convulsions, malignant neoplasms.

NOTE: Hospitalization for social reasons, visits to day in-patient department, as well as hospitalization or surgery scheduled before enrollment of the patient into the study to treat any previous condition are not considered as SAEs.

Unexpected AE/ADR – AE/ADR, nature or severity of which is not consistent with the known information about the product (e.g., with the Investigator's Brochure). This group also includes AE/ADRs mentioned in the Investigator's Brochure as characteristic for this class of drugs or expected due to the pharmacological properties of the investigational product, but at a specificity or severity not previously observed.

Serious and Unexpected Suspected Adverse Reaction: Any suspected adverse reaction that is both serious and unexpected (SUSAR).

6.11.2 Pregnancy

Women of childbearing potential are not excluded from the study as long as adequate birth control methods are being utilized. Women of childbearing potential are defined as all women physiologically capable of becoming pregnant. Adequate birth control methods are summarized in the protocol's inclusion criteria in Section 4.2.

Pregnancy is not an adverse event, but refers to events that require an urgent reporting to the Sponsor. In case of pregnancy during the study, either occurring in a female patient or in a male patient's partner, the pregnancy status should immediately be reported to the Sponsor. Female

patient will be withdrawn from the study and will be monitored throughout pregnancy and up to 30 days after its outcome. Health conditions of any newborn who was conceived during the study will also be followed up to 30 days after birth (including pregnancy of patient's partner). Relevant information will be recorded in source documents, CRF and Pregnancy Report Form. Pregnancy reports should be completed and e-mailed/faxed following the procedure described in Paragraph 6.11.7.

6.11.3 Reporting of AEs and SAEs

During each visit and examination patients shall report any adverse events in response to open, non-suggestive questions (e.g., "How did you feel after the last visit?"). For each adverse event marked by the patient, the Investigator shall collect and register as source documents and in the CRF all necessary information including the diagnosis or symptoms, start date and end date, outcome, severity, presence of severity criteria, circumstances that might indicate a possible relationship with the study medication or concomitant therapy, underlying diseases or concomitant conditions, study procedures or other causes, actions with respect to the study drug, concomitant medications, medical interventions, results of laboratory and instrumental studies about adverse events, as well as other circumstances which will help to maximize the event to be described.

Increase in severity of the ongoing adverse event shall be considered a new AE. The date of further worsening in severity will be the start date of the new AE, and the previous day shall be the end date of the original AE. The start date of a SAE is the date of occurrence of seriousness criterion. Previous state must be registered as a non-serious AE, if applicable.

If adverse event is serious, the Investigator shall also complete SAE Report Form (specifying the seriousness criteria) and promptly, within 24 hours from first knowledge, send it to the PPD Medical Monitor. New information on the SAE, which become known later shall be recorded and sent to the PPD Medical Monitor in the same manner and within the same timeline. Also, the PPD Medical Monitor shall be provided with certified copies of source documents relevant to the SAEs (discharge summary, autopsy data, death certificate, etc.).

AEs and SAEs shall be followed up and reported from the moment of signing of a Patient Informed Consent Form by patient and up to 1 year after OLT.

In line with ICH E2A provisions on Post-Study events, although such information is not routinely sought or collected by the Sponsor, serious adverse events that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow- up) will possibly be reported by the Investigator to the Sponsor. Such "post-study cases" should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

The Monitor is responsible for source data verification of the CRF and SAE Report Forms.

6.11.4 Assessment of the severity

The Investigator will grade the severity of any AE using the definitions in **Table 7**. It shall be noted that severe adverse event does not always meet the criteria of seriousness and, vice versa, a SAE does not always have to be severe.

Urgency of SAE reporting does not depend on the severity of the event.

For each episode, the highest severity grade attained should be reported.

Table 7 Intensity (Severity) of the Adverse Event

Mild	Grade 1 - does not interfere with patient's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	Grade 2 - interferes to some extent with patient's usual function (enough discomfort to interfere with usual activity [disturbing]).
Severe	Grade 3 - interferes significantly with patient's usual function (incapacity to work or to do usual activities [unacceptable])

6.11.5 Relationship between the AE and the Investigational Product

For each AE the Investigator shall assess its relationship with the investigational product in accordance with categories shown in **Table 8**.

Table 8 Relationship between the AE and the Investigational Product

None (Intercurrent Event)	An event that is not and cannot be related to the Investigational Product, e.g. patient is a passenger in a road traffic accident
Unlikely (remote)	Relationship is not likely e.g. a clinical event including laboratory test abnormality with temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide plausible explanations
Possible	Relationship may exist, but could have been produced by the patient's condition or treatment or other cause
Probable	Relationship is likely, the AE abates upon discontinuation of Investigational Product and cannot be due to the patient's condition
Highly Probable	Strong relationship, the event abates upon discontinuation of Investigational Product and, if applicable, re-appears upon repeat exposure

6.11.6 Assessment of Expectedness

Expectedness will be determined based on the contents of the Investigators' Brochure.

Expected	An adverse reaction, the nature or severity of which is consistent with the applicable product information (e.g. Investigators' Brochure)
Unexpected	An adverse reaction, the nature or severity of which is not consistent with information in the relevant source document (e.g. Investigators' Brochure)

6.11.7 Reporting of SAEs/pregnancy

The Investigator must report all SAEs, regardless of presumed causal relationship, and pregnancies to PPD Medical Monitor and the Dompé Pharmacovigilance, by fax or e-mail within 24 hours of learning of the event. Contact details for SAE/pregnancy reporting are provided below and in the section "Contact Information".

PPD **Medical Monitor:**

PPD

Dompé Pharmacovigilance:

PPD

PPD will be then responsible for verifying consistence of information reported and data included in SAE/Pregnancy Report Form, obtaining and reporting any additional information received from the Investigators, and forwarding fully completed SAE/Pregnancy Report Forms to the Dompé Pharmacovigilance, by e-mail immediately and anyway within 24 hours of knowledge of event. **SAE reports with fatal outcome shall be transmitted to the Dompé Pharmacovigilance as soon as possible, and within a maximum of 12 hours from the time** PPD **has knowledge of the death.**

Information on SAEs will be recorded on a specific SAE Report Form. Electronic and blank paper copies will be provided to the Investigators. Follow-up reports (as many as required) should be completed and faxed/e-mailed following the same procedure above.

Information on pregnancy will be recorded on a specific Pregnancy Report Form. If necessary, the Investigator can contact PPD Medical Monitor for advice or clarification.

The Investigator shall instruct each patient to immediately report the occurrence of SAEs or pregnancy during the study and for 1 year after OLT. The Investigator shall record all the available information about the event on the SAE/Pregnancy Report Form. Every SAE Report Form shall specify at least the following information: information on the patient, the event (signs or symptoms or diagnosis), the criterion of seriousness, the relationship with the investigational product, study drug administration dates and dosage, outcome at the time of the report and Investigator's details.

For the initial report the Investigator shall make the appropriate note on the SAE Report Form – "Initial report." In case additional information on SAE becomes available (e.g., new information on the patient's condition or results of laboratory tests), the Investigator shall complete a new SAE Report Form with a note "Follow-up report" and number of follow up. The original SAE Report Forms shall be stored in the Investigator's File.

The Investigator (or an authorized staff member) will be responsible for reporting any SAEs/SUSARs to the Local Ethics Committee and local institutions in accordance with local regulations and requirements. CRO will be responsible periodic safety reporting to the Regulatory Authorities and Investigators, and expedited reporting of SUSARs to the local Regulatory Authorities, in accordance with local regulations and requirements.

6.11.8 Early patient withdrawal

Patients will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and are not obliged to state their reasons. Any withdrawals must be fully documented in the CRF and should be followed up by the Investigator.

A complete list of the reasons for early withdrawal is provided in Section 6.12**. If possible, the Investigator shall preliminary consult the Sponsor**PPD **Medical Monitor in advance of any withdrawal. Otherwise, the Investigator shall inform the Sponsor/**PPD **A Medical Monitor about patient withdrawal within 24 hours of knowledge of the event**. Contact details of the Sponsor and PPD Medical Monitor are provided in the section "Contact Information".

Additionally, the Investigator may withdraw a patient at any time if (s)he considers this to be in the patient's best interest.

Also, a patient might be withdrawn from the study, at the Investigator's judgment, in case of protocol violations, including (but not limited to) non-compliance with study procedures, patient lost to follow-up or administrative reasons.

6.11.9 Emergency response

The Investigator is responsible for obtaining information on all emergency medical conditions of patients during the study. Investigator's contact information is present in a Patient Informed Consent Form. Patients will be encouraged to contact the Investigator in case of any emergency during the study.

6.11.10 Terms of AE/SAE registration

In this study registration of adverse events will be conducted from the moment of signing of a Patient Informed Consent Form by the patient and up to 1 year after OLT.

In case of patient's withdrawal from the study, the patient's and graft survival will be followed up to 1 year after OLT. In case of the death after patient withdrawal from the study, the data and cause of death shall be recorded in the CRF. In case of liver re-transplantation, the date and reason for re-transplantation will be recorded (SAE Report Form will not be completed).

In line with ICH E2A provisions on Post-Study events, although such information is not routinely sought or collected by the Sponsor, SAEs that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow-up) will possibly be reported by the Investigator to the Sponsor. Such "post-study cases" should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

6.11.11 Expected Adverse Events

The most frequent adverse events recorded in the previous clinical studies of Reparixin are listed in Section 3.10 "Risk/benefit ratio".

6.11.12 Clinically significant abnormalities

Any clinically significant abnormalities of laboratory parameters or results of the instrumental methods of examination noted at screening shall be registered in the patient's medical history. After screening, new or worsened clinically significant abnormalities (apart from the exemptions listed in Paragraph 6.11.13) shall be reported as adverse events in source documents and CRF.

6.11.13 Adverse Event exemption

The following events will neither require recording nor reporting, as they are considered routinely associated to the transplant procedures:

- Increased ALT/AST, bilirubin levels and other blood liver function tests if they are improving during 2 consecutive days, within 2 weeks post-transplant.
- Abnormal electrolytes and INR values if they are improving on 2 consecutive days, within 2 weeks post-transplant.
- Abnormal PTT values during prophylactic anticoagulation with unfractionated heparin.
- Abnormal INR values during prophylaxis with warfarin (Coumadin®, Jantoven®, Marevan®, Uniwarfin®).

6.12 Early patient withdrawal and discontinuation of the study drug

In case of early discontinuation of the investigational product administration, the patient will be able to continue participation in the study (in the absence of other indications). However only patients who received not less than 70% of the total dose of Reparixin will be included in the efficacy analysis (not less than 120 hours of infusion).

The patient has the right to refuse to participate in the study at any stage and for any reason.

If during the course of study therapy any of the following conditions occurs, the investigational product administration will be discontinued, and the patient will be withdrawn from the study:

- An allergic reaction to Reparixin,
- Complications related to the surgery (OLT): intra-abdominal bleeding requiring a surgical reintervention, bile leak requiring a surgical reintervention, hepatic artery thrombosis confirmed by imaging techniques (e.g. ultrasound) or during surgery,
- Decrease of glomerular filtration rate (GFR) under 20 ml/min (estimated with the Cockcroft-Gault formula),
- Sepsis (Appendix 9), severe infectious complications (e.g., resulting in one or more organs failure, being considered life threatening or determining graft failure),
- Hyperacute or acute transplant rejection (determined by biopsy),
- Gastro-intestinal bleeding requiring a surgical or endoscopic intervention,
- Increasing hepatic encephalopathy ($\geq 3^{rd}$ grade).

The patient shall be withdrawn from the clinical study also in the following situations:

- The patient is lost to follow-up,
- Failure or refusal of the patient to follow the protocol requirements,
- The patient's desire to withdraw from the study for any reason,
- Any adverse event that according to Investigator opinion may prevent from patient's further continuation in the study,
- Graft loss,
- Patient's death.

The following reasons require immediate withdrawal from the study:

- The patient began receiving another study drug,
- Pregnancy,
- Significant protocol violations that may affect the safety of the patient and the integrity of the study data.

In case of an early withdrawal from the study, the patient shall be invited to the clinical site, where he/she will undergo all procedures of the Early Discontinuation visit (ED visit). The patient should attend the ED visit not later than in 4 weeks from the end of the study drug infusion (no later than 5 weeks after OLT for patients from the control group). In case of withdrawal from the study after Week 12, the ED visit is not needed.

The status of the patients withdrawn from the trial (patient and transplant survival) shall be followed for 1 year after OLT. The Investigator will contact the patient or his relatives not less than once every 3 months.

The Investigator shall discuss any case of patient withdrawal with the Sponsor/PPD Medical Monitor. The reason for withdrawal shall be recorded in source documents and CRF. If the patient early discontinues from the study for more than one reason, only the main reason shall be listed. In case of consent withdrawal by the patient due to AE or SAE, occurrence of AE or SAE shall be given as a reason.

AEs, SAEs and pregnancy present at the time of the study termination must be followed according to the Protocol, unless another procedure of follow-up is set by agreement between the Investigator and the Sponsor/CRO.

6.13 Patient replacement

Patients that will receive less than 70% (120 hours) of Reparixin treatment **will not be included in the efficacy analyses** and **will be replaced except for the cases where** the treatment will be discontinued due to AE (including conditions listed in paragraph 6.12) judged by the reporting investigator (and confirmed by the DMC) to be related to the study drug.

6.14 Validity of measurements

Evaluation of the efficacy and safety parameters in this study is the standard practice followed for Phase 2 clinical studies in patients with liver diseases.

7 STUDY PROCEDURES

7.1 Selection of the transplant

In addition to standard criteria approved by the health authorities of the Russian Federation [13] to assess the extent hepatodepression (liver problems), the Investigators will evaluate organ suitability for transplantation relying on histopathologic findings from biopsy.

In this clinical setting, grafts with macrovesicular steatosis degree >50% will be considered as non-suitable for transplantation.

7.2 Screening and Randomization, Day -1

(Time window from 24 h up to 90 min prior to planned surgery)

Patients admitted to the facility will undergo the screening procedure immediately before OLT surgery. Screening can be done on the day of surgery.

- Procedure for obtaining of informed consent
- Patient registration
- Demographic data and medical history
- Data collection for receiving concomitant therapy
- Collection of blood and urine samples for laboratory testing: hematology, biochemistry, coagulation profile, express HIV test, viral load in patients with HBV and/or HCV, urinalysis
- Pregnancy test for women able to bear children (including women in menopause less than two years)
- Complete physical examination
- Assessment of vital signs
- Measurement of weight and height
- MELD and Child-Turcotte-Pugh scores
- ECG (12 leads)
- Doppler ultrasound of the abdomen
- Evaluation criteria for inclusion/exclusion

The decision to include in the study will be made on the basis of the results of laboratory tests carried out in a local laboratory (hematology, biochemistry, coagulation profile, express HIV test, urinalysis). Laboratory tests (except the tests for pregnancy and HIV) will be repeated at the centralized laboratory level. Test results from a centralized laboratory will be used as baseline data.

Randomization of patients should be conducted after the Investigator has checked the results of all the measurements that are needed for the assessment of inclusion/exclusion criteria.

In case of ambiguous or equivocal results of laboratory tests re-test may be performed with the approval of the Sponsor/PPD Medical Monitor.

Patients who did not meet all inclusion/exclusion criteria will not be included in the study. In case of cancellation of the surgery the patients can be re-screened. In this case, all screening procedures will be carried out again, including the procedure for obtaining informed consent and the assignment of a new identification number.

7.3 Study therapy, week 0

7.3.1 Day 0

0 hours (start of the Reparixin infusion)

- Evaluation of AEs and concomitant therapy
- Assessment of vital signs
- Start of the 168-hour continuous infusion of Reparixin (in the group of the study therapy)

60-90 minutes after the start of the Reparixin infusion (OLT)

OLT will be conducted in accordance with the Russian Transplant Society Guidelines for liver transplantation (Appendix 7) and the standard procedure adopted in the research center. During and after OLT, patient will undergo all the necessary manipulations, including routine investigations, as well as prescription of immunosuppressive therapy and other concomitant therapy, as usual.

12 hours from the start of the Reparixin infusion or 11 hours after OLT (Time window ± 30 min)

- Evaluation of AEs and concomitant therapy
- Short physical examination
- Assessment of vital signs
- ECG (12 leads) – it's possible to use the bedside monitor

Continuation of the 168-hour uninterrupted infusion of Reparixin (in the group of the study therapy)

7.3.2 Day 1 after OLT

- Evaluation of AEs and concomitant therapy
- Obtaining of blood samples for hematology, biochemistry, coagulation profile
- Obtaining of blood samples for pharmacokinetic analyses (ideally in the morning; only in patients randomized to Reparixin in stage 1 of the study)
- Short physical examination
- Assessment of vital signs
- Doppler ultrasound of the abdomen

Continuation of the 168-hour continuous infusion of Reparixin (in the group of the study therapy)

7.3.3 Day 2 after OLT

- Evaluation of AEs and concomitant therapy
- Obtaining of blood and urine samples for laboratory tests: hematology, biochemistry, coagulation profile, urinalysis
- Short physical examination
- Assessment of vital signs
- ECG (12 leads)

- Continuation of the 168-hour continuous infusion of Reparixin (in the group of the study therapy)

7.3.4 Day 3 after OLT

- Evaluation of AEs and concomitant therapy
- Obtaining of blood samples for biochemical blood analysis, coagulation profile
- Obtaining of blood samples for pharmacokinetic analyses (ideally in the morning; only in patients randomized to Reparixin in stage 1 of the study)
- Short physical examination
- Assessment of vital signs
- Continuation of the 168-hour continuous infusion of Reparixin (in the group of the study therapy)

7.3.5 Day 4 after OLT

- Evaluation of AEs and concomitant therapy
- Obtaining of blood and urine samples for laboratory tests: hematology, biochemistry, coagulation profile, urinalysis
- Short physical examination
- Assessment of vital signs
- ECG (12 leads)
- Doppler ultrasound of the abdomen
- Continuation of the 168-hour continuous infusion of Reparixin

7.3.6 Day 5 after OLT

- Evaluation of AEs and concomitant therapy
- Obtaining of blood samples for biochemistry, coagulation profile
- Obtaining of blood samples for pharmacokinetic analyses (ideally in the morning; only in patients randomized to Reparixin in stage 1 of the study)
- Short physical examination
- Assessment of vital signs
- Continuation of the 168-hour continuous infusion of Reparixin (in the group of the study therapy)

7.3.7 Day 6 after OLT

- Evaluation of AEs and concomitant therapy
- Obtaining of blood samples for biochemistry, coagulation profile
- Short physical examination
- Assessment of vital signs
- Continuation of the 168-hour continuous infusion of Reparixin (in the group of the study therapy)

7.4 Completion of therapy, Day 7 after OLT (end of therapy)

- Evaluation of AEs and concomitant therapy
- Obtaining of blood and urine samples for laboratory tests: hematology, biochemistry, coagulation profile, urinalysis
- Full physical examination
- Assessment of vital signs and body weight
- ECG (12 leads)
- Doppler ultrasound of the abdomen
- Obtaining of blood samples for pharmacokinetic analyses just prior to the end of study drug administration, and at 1, 3, 5, 6, 8, and 12 hours after termination of the study drug administration (only in patients randomized to Reparixin in stage 1 of the study)

In the group of the study therapy visit procedures should be conducted after completion of 168 hour continuous infusion of Reparixin and catheter removal.

7.5 Follow-up period

While being in hospital and after discharge the patient will undergo procedures of follow-up visits on an outpatient basis. During this period the patient will receive necessary treatment in accordance with the standards of patient management after liver transplant.

7.5.1 Week 2 after OLT(Time window ± 2 days)

- Evaluation of AEs and concomitant therapy
- Obtaining of blood and urine samples for laboratory tests: hematology, biochemistry, coagulation profile, urinalysis
- Complete physical examination
- Assessment of vital signs and body weight
- ECG (12 leads)
- Doppler ultrasound of the abdomen

7.5.2 Week 4 after OLT (Time window ± 3 days)

- Evaluation of AEs and concomitant therapy
- Obtaining of blood and urine samples for laboratory tests: hematology, biochemistry, coagulation profile, urinalysis
- Pregnancy test for women able to bear children (including women in menopause less than two years)
- Complete physical examination
- Assessment of vital signs and body weight
- ECG (12 leads)
- Doppler ultrasound of the abdomen

7.5.3 Weeks 12 and 24 after OLT (Time window ± 7 days)

- Evaluation of AEs and concomitant therapy
- Obtaining of blood and urine samples for laboratory tests: hematology, biochemistry, coagulation profile, urinalysis
- Pregnancy test for women able to bear children (including women in menopause less than two years)
- Complete physical examination
- Assessment of vital signs and body weight
- ECG (12 leads)
- Doppler ultrasound of the abdomen

7.5.4 Week 36 after OLT (Time window ± 7 days)

At Week 36, the patients (or their families) will be contacted by the Investigator through telephone call to monitor status of patient and allograft survival.

7.5.5 Year 1 after OLT (Time window ± 14 days)

- Evaluation of AEs and concomitant therapy
- Obtaining of blood and urine samples for laboratory tests: hematology, biochemistry, coagulation profile, urinalysis
- Pregnancy test for women able to bear children (including women in menopause less than two years)
- Complete physical examination
- Assessment of vital signs and body weight
- ECG (12 leads)
- Doppler ultrasound of the abdomen

7.6 Unscheduled visits

For safety reasons, in case of the need for re-examination or procedures there may be an unscheduled visit at any time during the clinical trial at the discretion of the Investigator. During unscheduled visits the Investigator may carry out the necessary procedures, including lab tests. Unscheduled visits shall be registered in source documents and CRF. Conducting of unscheduled visits shall not affect the schedule of planned visits in the protocol of the clinical trial.

7.7 Visit of early discontinuation (ED)

In case of early discontinuation of investigational product administration, the patient will be able to continue participation in the study (in the absence of other indications). However, the efficacy analysis will include only patients who received at least 70% of the total dose of Reparixin (infusion for at least 120 hours).

In case of early withdrawal from the study, the patient will be invited to Early Discontinuation visit (ED visit) no later than 4 weeks after the end of the investigational product administration (no later than 5 weeks after OLT for patients from the control group).

<u>In case of patient withdrawal from the study after Week 12, ED visit is not necessary.</u>

The following procedures should be carried out during the ED visit:

- Evaluation of AEs and concomitant medications

- Obtaining of blood and urine samples for laboratory tests: hematology, biochemistry, coagulation profile, urinalysis
- Pregnancy test for women of reproductive age (including women with menopause for less than 2 years)
- Complete physical examination
- Assessment of vital signs and body weight
- ECG (12 leads)
- Doppler ultrasound of the abdomen

If the ED visit cannot be carried out in full, the Investigator shall coordinate the actions with the PPD Medical Monitor.

Status of patients after early discontinuation (patient and allograft survival) will be monitored for 1 year after OLT at least once every 3 months. The patient will be given recommendations for following standard treatment.

If possible, the Investigator shall preliminary consult the Sponsor/PPD Medical Monitor in advance of any withdrawal.

Otherwise, the Investigator shall inform the Sponsor/PPD Medical Monitor about patient withdrawal within 24 hours of knowledge of the event. Contact details of PPD Medical Monitor are provided below and in the section "Contact Information".

8 QUALITY ASSURANCE

This clinical study will be conducted in accordance with standard operating procedures (SOPs) of the Sponsor/CRO, the Good Clinical Practice-International Conference on Harmonisation (GCP-ICH) regulations and the principles of the Helsinki Declaration, and in respect of local regulatory requirements. Compliance with the requirements will be monitored by the Sponsor/CRO through carrying out audits of the clinical sites and the data obtained in the study.

In accordance with the protocol the Investigator will record the required data in CRF provided by the CRO. Monitors with a frequency described in the monitoring plan will visit each clinical site to check on CRF completeness and accuracy. In case of missing or contradictory data, queries will be raised (per patient) in order to obtain consistent data. The queries should be answered by the Principal Investigator (or an authorized staff member).

After CRF completion and resolution of all queries, the Investigator will sign and date the CRF of each patient. The completed CRF pages will be checked during the monitoring visits and submitted to Data Management. Upon study completion, the original CRF will be archived by the Sponsor, and a copy of the CRF will be stored at clinical sites.

9 PLANNED STATISTICAL METHODS

9.1 General Terms

This study is a multicenter, open-label, randomized pilot study of efficacy and safety of Reparixin for prevention of early allograft dysfunction in patients undergoing OLT. Methods of descriptive statistics will be used to evaluate the results of the study. Statistical analysis plan will be developed and finalized before closing the database.

9.2 Determination of sample size

The primary efficacy endpoint is the assessment of the incidence of early allograft dysfunction in patients undergoing OLT during therapy with Reparixin.

Simon's minimax two-stage design for Phase II clinical trials was used to calculate the sample size [5, 6]. In this model, the study included patients to the total number = N_{total} (number of patients in each group for which an assessment of endpoint was conducted). Upon reaching the total number of patients who responded to treatment above R_{total}, the therapy will be found suitable for further study. Values of these parameters (with $\alpha = 0.05$ and a power of 80%, $P_0 = 75\%$ and P1 = 90% for early allograft dysfunction) for a positive decision on the efficacy of treatment for further study are listed below.

Efficacy endpoint	**P_0**	**P_1**	**r_1**	**n_1**	**R_{total}**	**N_{total}**	**α**	**1-β**
No early allograft dysfunction	0.75	0.90	> 17	22	> 33	39	0.05	0.80

Thus, 39 patients who underwent OLT and received treatment with Reparixin will provide 80% of power to test the hypothesis of a preliminary assessment of the efficacy of the investigational product and the decision on the further study ($\alpha = 0.05$). Data obtained in the control group will also be used in the study in order to control the correctness of data concerning the frequency of early allograft dysfunction.

In case of early discontinuation of patients from the study prior to receiving study treatment or inability to evaluate the primary efficacy endpoint, the patient can be replaced (see paragraph 6.13). Considering a possible 7% early discontinuation rate and the inability to assess the primary endpoint for some patents, up to 84 patients will be randomized in the study. This number of patients is based on a statistical power of 80% with an alpha of 0.05 and 1:1 randomization. In total, considering a possible 15% screening failure rate, about 100 patients planned for OLT will need to be screened in the study.

9.3 Populations for analysis

9.3.1 Population per protocol

Per protocol population includes all patients who have received at least 70% of the dose of the study drug, with data sufficient for the primary efficacy analysis, and who are considered compliant. Patients are considered compliant in case of absence of any major protocol violations during the study. In the group of the study therapy the patients who received not less than 70% of the study drug dose will be considered compliant. Major protocol violations will be described in more detail in terms of statistical analysis and identified before closure of the database.

9.3.2 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.

9.3.3 Safety population

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.

9.4 Patient allocation, demographic and baseline characteristics

Allocation of patients, demographic and baseline characteristics will be presented in groups, using descriptive statistics. Number and percentage of patients taking concomitant medications will be presented in frequency tables for ATC class and the name of the active substance according to the State Register of Medicines of the Russian Federation. The number of patients with co-morbidities and previous states will also be represented.

9.5 Investigational product administration

Information on dosing of Reparixin including the duration of exposure, interruptions in therapy and common doses will be presented descriptively.

9.6 Statistical Methods

Appropriate descriptive statistics will be produced, according to the nature of the variable. In general, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, standard deviation, median, minimum, maximum and number of patients. Percentages will be rounded to the nearest integer. In tabulations, denominators for calculation of percentages will be taken as the number of non-missing responses in the specified analysis population and treatment group unless otherwise stated. 95% Confidence Interval of continuous and categorical variables will be presented.

Unless otherwise specified, the significance level used for statistical testing will be 5% and two-sided tests will be used.

All reasonable efforts will be made to reduce the rate of missing data, since any method used for imputation for missing observations would be based on untestable assumptions that likely would be invalid. Appropriate descriptive statistics will be produced for the rate and reason for missing data to allow comparison between the treatment groups.

A Statistical Analysis Plan will be issued describing details of all the statistical methods and analysis to be applied to trial results. Any change in the planned analysis will be documented. The data will be presented in the clinical study report.

9.6.1 Demographic and Baseline Characteristics

Summaries of demographic and baseline characteristics data will be produced using the safety population and will be presented by treatment group. All baseline data will also be listed.

9.6.2 Efficacy analysis

Efficacy data will be reviewed on an ongoing basis by a Data Monitoring Committee (DMC). Full details of the activities and responsibilities of the DMC are provided in the study DMC Charter.

Primary endpoint data will not be available until each patient reaches Day 7 post transplantation. The DMC will give careful consideration to the appropriateness of trial continuation if there is emerging evidence of futility of the Reparixin treatment. Main component of this assessment will be the rate of early graft dysfunctions.

The DMC will consider the following guidelines regarding early termination based on the occurrence of early graft dysfunctions. Early termination will be considered if:

- 5 or more patients from the study drug group will experience early graft dysfunction in the first stage,

- 6 or more out of 39 patients from the group of the study drug group will experience early graft dysfunctions.

The DMC will also consider early termination if the quality of conduct of the trial is such that the trial will not be able to provide a timely and reliable answer to the questions it was designed to address.

9.6.2.1 Primary efficacy analysis

The primary efficacy endpoint is the assessment of the incidence of early allograft dysfunction after OLT (Week 1) during the therapy with Reparixin.

The incidence of early allograft dysfunction is approximately 25% (ranging from 9.3 to 43.7% subject to different definitions and classifications of the condition). Retrospective evaluation of the incidence of early allograft dysfunction performed in the Russian leading transplantation institution – N.V. Sklifosovskiy Center of Liver Transplantation under Research Institute of Emergency Care, confirmed the development of this type of complications in 25% of cases (N = 202). Death has occurred in the population of patients with early allograft dysfunction at almost twice the rate in patients with normal functioning of the transplant during the first 7 days after OLT ($p < 0.005$).

Therefore, as a baseline index for the incidence of early allograft dysfunction was selected at the level of 25% ($p_0 = 0.75$). The target level index for the incidence of early allograft dysfunction was selected at the level of 10% ($p_1 = 0.90$). These data can be corrected after the first stage of the study in accordance with the results of the preliminary assessment of early allograft dysfunction rate in the Reparixin and control groups.

The main purpose of this study is to give the primary assessment of Reparixin efficacy in accordance with Simon's minimax two-stage design. This model of statistical analysis in the phase 2 pilot study was chosen to receive the primary efficacy data of Reparixin that is used during OLT for the first time. This model will follow a trend in the parameters of drug efficacy in a small group of patients, and thus, will decide on further study of the drug in the large-scale comparative studies. The analysis will be conducted by the primary efficacy endpoint, which is the incidence of early allograft dysfunction. The obtained preliminary evidence of the efficacy will decide on further studying of the drug for this indication.

According to Simon's minimax model analysis of the efficacy will be conducted in two phases:

- During Stage 1 of the study the primary efficacy endpoint will be assessed in 22 patients in both groups. In case of early allograft dysfunction in < 5 out of 22 patients from the group of the study drug, a transition to Stage 2 of the study will be deemed possible. In the case early allograft dysfunction develops in ≥ 5 out of 22 patients from the group of the study drug, further study of Reparixin in this study population will be considered inappropriate.

- During Stage 2 of the study, the primary efficacy endpoint will be assessed in additional 17 patients in each group (in total number of 39 patients in each group). Early allograft dysfunction in < 6 out of 39 patients from the group of the study drug gives grounds for a conclusion of the efficacy of Reparixin in this population and the appropriateness of subsequent large-scale comparative Phase III clinical trials. In case early allograft dysfunction develops in ≥ 6 out of 39 patients in the group of the study drug, further study of Reparixin in this study population can be considered inappropriate.

The following statistical algorithm will be applied to the study:

<table>
<tr><th></th><th colspan="2">Experimental group</th><th>Control group</th></tr>
<tr><td rowspan="2">Stage 1</td><td colspan="2">22 patients
↙ ↘</td><td>22 patients</td></tr>
<tr><td>≥ 5 early graft dysfunctions (≥23%) → no efficacy (stop)</td><td>< 5 early graft dysfunctions (<23%) → potential efficacy (continue to Stage 2)</td><td>< 7 early graft dysfunctions (<32%) → potential study failure due to lack of power</td></tr>
<tr><td rowspan="2">Stage 2</td><td colspan="2">Up to 39 patients (total)
↙ ↘</td><td>Up to 39 patients (total)</td></tr>
<tr><td>≥ 6 early graft dysfunctions (≥15%) → no efficacy (stop)</td><td>< 6 early graft dysfunctions (13%) → potential efficacy</td><td>< 12 early graft dysfunctions (<31%) → potential study failure due to lack of power</td></tr>
</table>

9.6.2.2 Secondary efficacy analyses

Secondary assessment of the efficacy includes the following parameters:

- Primary nonfunction within 7 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.

All these parameters will be reported using appropriate descriptive statistics and 95% confidence intervals of difference between the Reparixin and control will be calculated

- 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 data for the treatment and control groups will be presented in a comparative table.
- 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 data for the treatment and control groups will be presented in a comparative table.
- 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 data for the treatment and control groups will be presented in a comparative table.
- 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 HBV, kidney function, score in scales of MELD, Child-

Turcotte-Pugh, etc.). The data for the treatment and control groups will be presented in a comparative table.

- Time for normalization of liver function parameters (ALT, AST and bilirubin levels, GGT, LDH, etc.) after OLT. The data will be presented with Kaplan-Meier curves.
- The incidence of hyperacute, acute and chronic liver allograft rejection (defined by histological evaluation). The data for the treatment and control groups will be presented in a comparative table.
- Mortality within 1 year after OLT. The data for the treatment and control groups will be presented in a comparative table.
- Graft survival at 1 year after OLT. The data for the treatment and control groups will be presented in a comparative table.

9.7 Safety analysis

Safety will be assessed on the basis of the analysis of the incidence of adverse events of different grade during 12 weeks and 1 year after OLT according to subjective complaints, physical examination, vital signs, laboratory tests (including liver and kidney function), ECG, vascular ultrasound of the liver and kidneys with Doppler sonography. The incidence of severe allograft dysfunction, which required extracorporeal detoxification and/or led to the death of the patient, will also be assessed. Data will be summarized and represented using descriptive statistics.

Number and percentage of patients with adverse events in each group will be presented in tabular form according to the class of organ systems and preferred term, relation to the investigational product and severity. Life and laboratory parameters will be presented using descriptive statistics.

9.8 PK analysis:

Plasma levels of reparixin (total and unbound) and its metabolites (DF2243Y and ibuprofen)will be summarized using descriptive statistics.

10 ADMINISTRATIVE PROCEDURES

10.1 Legal aspects

All information obtained during the conduct of the study will be regarded as confidential. An agreement for disclosure will be obtained in writing by the patient and will be included in a Patient Informed Consent Form. Patient's data collected during the study will be handled in accordance with applicable data protection laws and regulatory requirements.

Life and health of patients participating in the clinical study will be insured according to the legislation of the Russian Federation (article 44 of the Federal Law on Drugs Circulation No 61-FZ of April 12, 2010 and other statutes in force) and the Republic of Belarus.

The Sponsor is responsible for financing all clinical trial related activities.

All data obtained in this study is confidential information belonging to Sponsor of the Study. The Sponsor will publicly disclose the results of the study in accordance with legislative and regulatory requirements. Publication policy for Investigators and clinical sites will be specified in the clinical trial agreement.

10.2 Protocol Amendments

Changes to the Protocol will be implemented only when written amendments have been signed by all individuals who signed the protocol.

Any amendment will be sent to the appropriate IEC. No changes to the protocol will be implemented without documented approval of an amendment from the IEC which granted the original approval, except where necessary to eliminate an immediate hazard(s) to trial patient, or when the change(s) involves only logistical or administrative aspects of the trial. The changes to the protocol implemented to eliminate an immediate hazard to the trial patient and the proposed amendment, if appropriate, should be submitted to the IEC for review and approval as soon as possible.

Any written amendment will be sent to all recipients of the protocol and to the Competent Authorities.

10.3 Responsibilities of the Investigator

The Investigator shall conduct clinical trials in accordance with the requirements of this protocol, the Good Clinical Practice-International Conference on Harmonisation (GCP-ICH) regulations and the principles of the Helsinki Declaration, and in respect of local regulatory requirements [14].

The Investigator (or an authorized staff member) will be responsible for reporting any SAEs/SUSARs to the Local Ethics Committee and local institutions in accordance with local regulations and requirements.

The Investigator should permit monitoring and auditing by the Sponsor/CRO, and inspections by s appropriate regulatory authority(ies). Upon request of the Monitor, auditor, IEC, or regulatory authority, the Investigator/institution should make available for direct access all requested trial-related records.

The Investigator shall keep the originals of all signed during the study Patent Informed Consent Forms, as well as a full list of study subjects indicating the full name, given numbers, initials, date of birth, address and/or phone number to identify them if necessary. These documents shall not be copied for further transmission to the Sponsor.

The Investigator is obliged to ensure the safety of study materials, including supporting documentation and copies of the CRF and Investigator's File during at least 15 years after completion of the study or until the moment specified by the Sponsor.

10.4 CRF data entry

The Investigator shall transfer the data obtained during the clinical study from source documents into the CRF, as required. No data will be recorded directly in the CRF. CRF completion guidelines will be studied by the Investigator during the Investigators Meeting and/or during the Site Initiation Visit. If the Investigator delegates the authority to complete the CRF to other clinical site employees, their names, titles, signatures and initials shall be entered in the Site Personnel Signature and Delegation Form and provided to the Sponsor/CRO.

When a correction in CRF is made, there shall remain an audit trail, i.e. the data before and after the changes, reason (if applicable), date and initials of the one who makes changes shall be visible. The completed CRFs shall be signed by the Investigator.

The completed CRF pages will be checked during the monitoring visits and submitted to Data Management. In case of missing or contradictory data, queries will be raised (per patient) in order to obtain consistent data. The queries should be answered by the Principal Investigator (or an authorized staff member).

Upon study completion, original CRFs will be archived by the Sponsor, and copies of CRFs will be stored at clinical sites.

10.5 Data Monitoring Committee

An independent Data Monitoring Committee will be established to oversee study progress at regular intervals for the duration of the trial and make recommendations to the Sponsor on whether to continue, modify or stop the study. To contribute to enhancing the integrity of the trial, the DMC may also formulate recommendations to Dompé relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMC will operate independently of Dompé in accordance with a trial specific DMC Charter, and its members will not have connections to Dompé with the exception of the compensation to DMC members related to their activities. The DMC will report directly to Dompé who will convey the findings of the DMC to the investigators/CRO as applicable.

The DMC:

- Will be responsible for the ongoing review of efficacy data during the first recruitment stage and making appropriate recommendations regarding transition into stage 2 or stopping enrollment. In particular, the DMC will monitor the number of early graft dysfunctions to determine whether it is consistent with the expected rate.
- Will be responsible for the ongoing review of efficacy and other study related data throughout the trial to enable the assessment of the acceptability of safety in the context of emerging evidence about efficacy.

  Will be advisory to Dompé and make recommendations to Dompé regarding the continuation/early discontinuation of the trial and potential modifications to the design and conduct of the trial.

10.6 Monitoring procedures

The Investigator shall provide direct access to all source documents, CRFs and Site Investigator File to the Sponsor/CRO, IEC and regulatory authorities. Source documentation includes but is not limited to medical records, hospital records, laboratory records, notes, questionnaires, drug dispensing records, readings of automatic recording devices, verified and certified true copies or discharge reports, photographic negatives, microfilm or magnetic carriers,

X-rays, any entries relating to the patient, including data stored in the pharmacy, laboratories and instrumental diagnostics departments used in clinical study.

Monitoring will be conducted by PPD in accordance with its SOPs and Monitoring plan developed for this study.

10.7 Registration of data in the CRF

The CRO shall promptly inform the Sponsor about any issues related to early discontinuation of patients, interruption of the study drug infusion, early termination visit, and other important issues. The communication paths will be outlined in the Monitoring plan developed for this study.

10.8 Essential Document retention

The essential documents (source documents, the signed protocol, copies of the CRFs, Site Investigator File, Patient Informed Consent Forms from all patients who consented, etc.) shall be retained at clinical sites or another suitable archive with restricted access for at least 15 years after completion of the study or until the moment specified by the Sponsor.

The Investigator should inform the Sponsor/CRO of the storage location, and take measures to prevent accidental or premature destruction of these documents. The Sponsor shall be informed in case of transfer of documents to other authorities or to other storage location.

10.9 Ethical considerations

10.9.1 Independent Ethics Committee

Prior to the initiation of the clinical study all research centers will receive a written approval of the Independent Ethics Committees (IEC), in accordance with the Guidelines on Good Clinical Practice of the International Conference on Harmonization (ICH GCP), applicable laws and regulatory requirements. The following documents shall be provided to IEC for consideration: study protocol and amendments thereto, patient information sheet and informed consent form, written materials to be provided to the subjects of the research, current version of the Investigator's Brochure, information on safety of the study drug, scientific biography of the Investigator and the other required documents.

List of members of the IEC and the statement of compliance of its organization and operations with the principles of Good Clinical Practice and regulatory requirements shall be provided to the Sponsor/CRO.

10.9.2 Ethical performance of the clinical study

The study will be performed and monitored according to the Good Clinical Practice-International Conference on Harmonisation (GCP-ICH) regulations and conducted according to the principles of the Helsinki Declaration and any local regulatory requirements [14].

In addition to the other liabilities and responsibilities described in 10.2, the Investigator should permit monitoring and auditing by the Sponsor/CRO, and inspections by appropriate regulatory authority(ies). Upon request of the Monitor, auditor, IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

10.9.3 Informed Consent

Prior to the clinical study the Investigator shall obtain the written approval of IEC on Patient Informed Consent Form and any on other written information to be provided to the subjects of the study. The written approval of IEC and approved documents shall be stored in the Investigator Site File.

The process of obtaining of informed consent shall be held in accordance with the Guidelines on Good Clinical Practice of the International Conference on Harmonization (ICH GCP), the principles outlined in the Declaration of Helsinki and in accordance with applicable law and regulatory requiremets. Patient Informed Consent Form shall be personally signed and dated by the patient before the start of any study procedures in two original copies. One original copy of the signed form will be provided to the patient, and the other original copy of the signed Patient Informed Consent Form will be retained and filed in the Investigator Site File. The process of obtaining informed consent shall be described in detail in source documents, including the fact of patient's consent to participate in this clinical study and the date of signing a Patient Informed Consent Form.

10.9.4 Discontinuation of the study

Dompé farmaceutici s.p.a. reserves the right to stop the study at any time on the basis of new information regarding safety or efficacy, or if study progress is unsatisfactory, or for other valid administrative reasons.

After such a decision is made, the Investigator must inform all relevant persons e.g. study staff, potential patients etc. within 2 weeks. All delivered study materials must be collected and all CRFs completed to the extent possible.

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