PPD

Statistical Analysis Plan Approval Sheet

REP0104

A phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel group study of repertaxin in the prevention of primary graft dysfunction after lung transplantation.

Month 1

Author(s): PPD / PPD
Version number: 1.1 (Final)

The undersigned have reviewed this and find it to be consistent with the study requirements as it applies to their respective function:

PPD

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Month 1

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CONFIDENTIAL

Version Number	Author
1.0	PPD
1.1	

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemical Classification
BAL	Bronchoalveolar Lavage
BOS	Bronchiolitis Obliterans Syndrome
BP	Blood Pressure
CMV	Cytomegalovirus
CO	Cardiac Output
CRF	Case Report Form
CSR	Clinical Study Report
CVP	Right Atrial Pressure
CXCL8	CXC ligand 8 [formerly interleukin (IL)-8]
DMC	Data Monitoring Committee
Dompé	Dompé pha.r.ma s.p.a
FEV_1	Forced Expiratory Volume in One Second
FiO_2	Fraction of Inspired Oxygen
FVC	Forced Vital Capacity
HR	Heart Rate
i.v.	Intravenous
ICU	Intensive Care Unit
ITT	Intention-To-Treat
mmHg	Millimeters mercury
PPD	PPD
PA	Pulmonary Artery
PaO_2	Partial Pressure of Arterial Oxygen
PCWP	Partial Capillary Wedge Pressure
PGD	Primary Graft Dysfunction
PK	Pharmacokinetic
PMN	Polymorphonuclear Leukocyte
PP	Per Protocol
PT	Prothrombin Time
PVR	Pulmonary Vascular Resistance
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SOC	System Organ Class
SVR	Systemic Vascular Resistance

1 INTRODUCTION

1.1 General

This statistical analysis plan (SAP) describes the statistical methods to be used during the analysis and reporting of data collected under Dompé pha.r.ma s.p.a. (Dompé) Protocol REP0104.

The study is split into two phases: screening to one month post-transplant and greater than one month to 12 months post-transplant. This SAP applies to all outputs, in-text or post-text, produced for inclusion in the clinical study report (CSR) for the Month 1 analyses. A separate SAP will be produced for the Month 12 analyses. This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the revised protocol dated 30 August 2005; the CRF dated 01 March 2005 and the amended pages relating to the 30 August protocol amendment. Any further changes to the protocol or CRF may necessitate updates to the SAP.

At the time of writing this version of the SAP, approximately 60 patients have been randomized into the study.

The analysis plan will be finalized and approved by the sponsor and PPD prior to database lock.

1.2 Changes from Protocol

None.

1.3 Changes from previous versions of SAP

For the primary analysis, the covariance matrix for the final model was wrongly defined as the matrix with the highest value for the Akaike's Information Criterion. The selection criterion has been changed to the matrix with the lowest value for the Akaike's Information Criterion.

2 STUDY OBJECTIVES

To evaluate whether CXCL8 inhibition with repertaxin leads to reduced severity of primary graft dysfunction (PGD), as the result of improved functional and clinical outcomes in lung transplantation patients.

The safety of repertaxin in the specific clinical setting will also be evaluated.

The ability of repertaxin to reduce target cells (PMN) infiltration into the graft will be evaluated to confirm its mechanism of action. Plasma levels of repertaxin and its major metabolite will be measured at steady state conditions to provide population pharmacokinetic (PK) profile in this clinical setting.

3 STUDY DESIGN

3.1 Overview

This is a phase 2, multi-center, randomized, double blind, placebo-controlled, parallel group study of repertaxin in the prevention of PGD after lung transplantation. The study will involve 100

patients undergoing single or bilateral lung transplant who will be randomized to receive either repertaxin or placebo via continuous intravenous (i.v.) infusion administered over 48 hours. Patients randomized into the study who do not go on to receive study drug or lung transplant will be replaced therefore the total number of patients randomized may exceed 100. Patients will be followed for 12 months post-transplant but the majority of study assessments are performed during the intensive care unit (ICU) and hospital stay immediately after surgery.

Patients will be selected for entry into the study from those listed on the center's lung transplant waiting list. Inclusion/exclusion criteria (as listed in protocol sections 5.1 and 5.2), disease history, extrapulmonary site of infection, significant medical history, vital signs, renal and hepatic function, laboratory safety tests and donor information will all be assessed prior to randomization to ensure patient eligibility.

The lung transplant surgery will be performed according to the center's standard practice. The study drug infusion will start approximately 2 hours before the anticipated time of reperfusion of the first allograft. A loading dose will be administered for the first 30 minutes, followed by a maintenance dose for the remaining 47.5 hours of administration.

After completion of surgery, patients will be admitted to an ICU and blood gases (PaO_2, FiO_2 and PaO_2/FiO_2 ratio) will be measured on admission (time 0) and at 24, 48 and 72 hours post ICU admission or until extubation whichever occurs earlier. Chest x-rays, renal and hepatic function and PK sampling will be measured at defined time points within the 72 hours following ICU admission. Vital signs (BP and HR) and cardiopulmonary measurements will be assessed at defined time points within the 5 days post ICU admission or until ICU discharge (or PA catheter removed) whichever occurs earlier. Further patient assessments are made at ICU discharge and hospital discharge.

Patients will return to the center at least 30 days after the transplant for the Month 1 assessment and at 24-28 weeks and 50-54 weeks post transplant for the Month 6 and Month 12 assessments respectively. Once data up to and including the Month 1 assessment has been collected, entered and cleaned, the Month 1 database will be locked, the study will be unblinded and the primary analysis of safety and efficacy data will be performed. Data collected during the open phase of the study i.e. at Months 6 and 12 will be presented in an eddendum to the main CSR.

An independent Data Monitoring Committee (DMC) has been established to ensure patient safety, to consider patient risks against the potential for meeting trial objectives, and to provide recommendations to Dompé with respect to the conduct and analysis of the trial. PPD will be responsible for providing the DMC statistician with listings of data relating to disposition (randomization, completion and withdrawal), demography, adverse events (AEs) and occurrence of clinically diagnosed PGD. Full details of the responsibilities of the DMC are provided in the DMC Charter.

3.2 Sample Size Considerations

Under the following assumptions:

1. A single primary endpoint – PaO_2/FiO_2 ratio
2. One primary comparison: repertaxin versus placebo at 24 hours post ICU admission (H_0: $\mu_R = \mu_P$; H_1: $\mu_R > \mu_P$).
3. A one-sided two group t-test of statistical significance
4. α-level or probability of Type I error associated with the test of 0.05
5. A placebo mean of 315 mmHg
6. A common standard deviation of 137 mmHg
7. A sample size of 50 in each group

the study has 81% power to detect a difference in means of 70 mmHg (μ_R = 385 mmHg) and 56% power to detect a difference in means of 50 mmHg (μ_R = 365 mmHg). The data for assumptions 5 and 6 is taken from the results of 700 lung transplant operations at the Washington University. However, there are currently no data available to provide an estimate of the treatment effect size for this study.

3.3 Randomization

Prior to surgery, patients who meet all the entry criteria and who provide written informed consent will be randomized to receive either repertaxin or placebo according to a 1:1 randomization.

A master randomization list was prepared for 352 patients (44 at each of 8 centers) by Insight Statistical Consulting on behalf of PPD . A dummy randomization was reviewed by statisticians at both PPD and Dompé prior to production of the final version. Since each patient should only ever require a single drug pack, the randomization number is identical to the patient number.

The randomization number is assigned sequentially at each site as patients are found to be eligible for entry to the study and are enrolled. Patients who are enrolled to replace patients who withdraw from the study prior to study drug infusion or lung transplantation will be issued a new randomization/patient number.

If a patient is allocated a randomization number and either the transplant does not happen or the study drug is not administered, the relevant drug box should be annulled to avoid its re-use with another patient.

4 STUDY VARIABLES AND COVARIATES

4.1 Primary variable

The primary variable within the study is PaO_2/FiO_2 ratio measured at ICU admission (time 0) and 24 hours post ICU admission.

4.2 Secondary variables

4.2.1 Efficacy

- Time profile of PaO_2/FiO_2 ratio measured ICU admission and at 24, 48 and 72 hours post ICU admission or until extubated whichever occurs earlier.
- PGD score
- Time to freedom from mechanical ventilation
- Duration of ICU stay
- ICU mortality
- Mortality in the first 30 days post-transplant
- FEV_1 and FVC at Months 1, 6 and 12 post-transplant
- BOS score at Months 6 and 12 post-transplant
- Cumulative acute rejection episodes at months 6 and 12 post-transplant
- Patient survival rate evaluated at Months 6 and 12 post-transplant

4.2.2 Safety

- Study drug dosing
- Incidence of adverse events
- Incidence of clinically significant results and shifts (relative to normal ranges) in hematology, clinical chemistry and coagulation test results
- Incidence of concomitant medication use
- Vital signs
- Cardiopulmonary measurements

4.3 Predetermined Covariates and Prognostic Factors

- Type of transplant (single or double)

Data recorded only at Months 6 and 12 will not be covered within this document but will be discussed in the Month 12 SAP.

Data for PMN count in bronchoalveolar lavage (BAL) and plasma levels of repertaxin and its major metabolite DF2243Y will not be analyzed PPD These data will be provided in separate stand alone reports by the responsible laboratories. These reports will be included as appendices to the CSR.

5 DEFINITIONS

Time 0
This is defined as date and time of ICU admission.

Month 1
This is defined as 30-35 days after date of lung transplant.

Month 6
This is defined as 24 – 28 weeks (168 – 196 days) after date of lung transplant.

Month 12
This is defined as 50 – 54 weeks (350 – 378 days) after date of lung transplant.

Age
The integer age of the patient will be derived relative to the date of the screening visit using the following SAS code:
age = INTCK('YEAR', dob, dos) – ((MONTH(dos) < MONTH(dob)) OR
(MONTH(dos) = MONTH(dob) AND DAY(dos) < DAY(dob))) ;
where dob = date of birth and dos = date of screening visit.

Transplant type
This is defined as either single or double where a single transplant is defined as a single left lung or a single right lung and a double transplant is defined as a bilateral sequential lung or an en-bloc double lung.

Duration of cold ischemia
This is the interval in hours between onset of organ ischemic time (date and time of cross-clamp on donor organ) and the removal of the donor organ from cold storage and is derived as:
(Date/time of organ removal from cold storage – date/time of cross clamp on donor organ)/3600

Duration of warm ischemia
This is the interval in hours between removal of donor organ from cold storage and the start of reperfusion or vascular de-clamping of the allograft and is derived as:
(Date/time of start of reperfusion – date/time of organ removal from cold storage)/3600

Duration of cold and warm ischemia
This is the interval in hours between onset of organ ischemic time and the start of reperfusion and is derived as:
(Date/time of start of reperfusion – date/time of cross clamp on donor organ)/3600

Time to freedom from mechanical ventilation
This will be measured in hours and will be derived as:

(date/time of extubation – date/time of ICU admission)/3600. The result will be rounded to the nearest integer.

Duration of ICU stay
This is the interval in hours between ICU admission and ICU discharge and will be derived as: (date/time of ICU discharge – date/time of ICU admission)/3600. The result will be rounded to the nearest integer.

PGD Score
This is graded as an integer between 0 and 3 according to the following definitions:

Grade 0	no radiographic infiltrates
Grade 1	$PaO_2/FiO_2 \geq 300$ mmHg + radiographic infiltrates consistent with pulmonary oedema
Grade 2	200 mmHg $\leq PaO_2/FiO_2 < 300$ mmHg + radiographic infiltrates consistent with pulmonary oedema
Grade 3	$PaO_2/FiO_2 < 200$ mmHg + radiographic infiltrates consistent with pulmonary oedema

Duration of study drug infusion
This is measured in hours and derived as follows:
(date/time of termination of infusion – date/time of start of infusion)/3600.

The duration should be adjusted for documented interruptions of at least one hour or cumulative interruptions of at least 2 hours. The CRF does not provide a place to record interruptions so the clock times of infusion interruptions and infusion re-start will be provided via filenotes where applicable.

Amount of study drug infused
This is measured in milliliters and will be derived as the sum of each of the dosing intervals multiplied by the relevant infusion rate. Assuming that dosing is performed per protocol, the formula will be:
(date/time of dose switch - date/time of start of infusion)/3600 × infusion rate for loading dose
+
(date/time of bag switch – date/time of dose switch)/3600 × infusion rate for maintenance dose
+
(date/time of end of infusion – date/time of bag switch)/3600 × infusion rate for bag 2.

If the dose switch is not performed then it will be:
(date/time of bag switch - date/time of start of infusion)/3600 × infusion rate for loading dose
+
(date/time of end of infusion – date/time of bag switch)/3600 × infusion rate for bag 2.

If the bag switch is not performed then it will be:
date/time of dose switch - date/time of start of infusion)/3600 × infusion rate for loading dose
+
(date/time of end of infusion – date/time of dose switch)/3600 × infusion rate for maintenance dose.

If neither the dose switch nor the bag switch are performed then the formula will be:
(date/time of end of infusion – date/time of start of infusion)/3600 × infusion rate for loading dose.

For repertaxin, the amount of study drug in milligrams will be derived as 12.65 × total volume transfused in milliliters.

Treatment-emergent adverse events

Treatment-emergent adverse events are those which first occur or increase in severity after the first dose of study drug. Adverse events with a start date greater than or equal to the start date of study drug infusion will be considered to be treatment emergent. If the onset date is missing then the event will be assumed to be treatment-emergent. If the start date is partial and only the month and year are populated then all events starting in the same month as the study drug infusion will be assumed to be treatment-emergent. If the start date is partial and only the year is populated then all events starting in the same year as the study drug infusion will be assumed to be treatment-emergent.

Systemic Vascular Resistance (SVR)
This is measured in dyn·s·cm-5 and is derived as:
80 × (MAP – CVP)/CO where MAP = mean arterial pressure = DBP + (SBP – DBP)/3.

Pulmonary Vascular Resistance (PVR)
This is measured in dyn·s·cm-5 and is derived as:
80 × (MPAP – PCWP)/CO
where MPAP = mean pulmonary arterial pressure
= systolic PA pressure + (2 × diastolic PA pressure)/3.

BOS Score
This is an integer between 0 and 3 based on FEV_1 categories defined as follows:

BOS 0	FEV_1 ≥80% of baseline value
BOS 1	FEV_1 66-80% of baseline value
BOS 2	FEV_1 51-65% of baseline value
BOS 3	FEV_1 ≤50% of baseline value

The baseline value will be defined as per center practice as the best FEV_1 value following surgery.

6 ANALYSIS POPULATIONS

The primary analysis of the primary efficacy variable will be presented for the intention-to-treat (ITT) population. A secondary confirmatory analysis will be performed using the per protocol (PP) population.

6.1 Intention-to-treat (ITT)

The ITT population will consist of all randomized patients who received any study medication and a lung transplant. Patients will be analyzed according to the treatment randomized regardless of which treatment was actually received.

6.2 Per protocol (PP)

The PP population will consist of all patients in the ITT population who do not meet any of the following criteria:

- Started study drug infusion after reperfusion i.e. after vascular de-clamping of the first allograft
- Received study drug infusion for less than 24 hours
- Missing data for PaO_2/FiO_2 ratio at both time 0 and 24 hours post ICU admission while on mechanical ventilation
- Received Orthoclone OKT3 or Campath induction immunosuppression at time of transplant. This will be recorded in the Month 1 Concomitant Medication pages if used.

Further criteria for exclusion from the PP population may be identified during the data review meeting held prior to database lock.

6.3 Safety

The safety population will consist of all patients who received any study medication and will be based on the treatment actually received.

7 INTERIM ANALYSES

No formal interim analyses of efficacy are planned for this study. However, safety data will be reviewed on an ongoing basis by a DMC. Full details of the activities and responsibilities of the DMC are provided in the study DMC charter.

8 DATA REVIEW

8.1 Data handling and Transfer

The data from this study will be entered, verified and cleaned by the Data Management group at PPD in accordance with the study data handling manual and data clarification policies. The data will be provided to the statistician as SAS datasets. The preferred term and system organ classification (SOC) from the relevant version of the MedDRA dictionary will be provided for all adverse events. The ATC group and sub-group from the relevant version of the WHO-DRUG dictionary will be provided for all prior and concomitant medications.

8.2 Data Review Meeting

Programming of analysis datasets, tables, figures and listings will be ongoing during the data management of the study. When the Month 1 database is considered clean by data management, a set of blinded listings (using a dummy randomization) will be produced and distributed to the study team for review. A meeting will be held to review any data values requiring investigation or correction and also protocol deviations. Once all data issues have been resolved, the Month 1 data will be locked. Treatment code unblinding and the full run of outputs will then take place.

9 STATISTICAL METHODS

9.1 General Principles

The statistical package SAS (Version 8.1) will be used to produce all summary tables, graphs and listings. 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. Minima and maxima will usually be reported to the same level of accuracy as the raw data; means, medians and standard deviations will be presented to one further decimal place; standard errors (if presented) will be presented to 2 decimal places more than the raw data. 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.

All data recorded in the CRF will be listed.

9.2 Patient Disposition

The number and percentage of patients screened, randomized and treated in the study will be presented, together with the number and percentage of patients who withdrew from the study prematurely prior to Month 1 and a breakdown of the corresponding reasons for withdrawal. The number and percentage of patients included in each of the ITT, PP and safety analysis populations will also be included. Screening data recorded for patients who do not proceed to transplant with study drug administration will be listed separately in the report. The exact format of the listings will be discussed with Dompé when the total number of patients randomized but not treated/transplanted is known.

A tabulation of the number and percentage of patients randomized at each center will be presented.

All data relating to study completion or withdrawal and inclusion in the analysis populations will also be listed.

9.3 Protocol deviations

Protocol deviations which exclude patients from the ITT or PP populations (see Sections 6.1 and 6.2 for definitions) will be summarized by treatment group.

9.4 Demographic and Baseline Characteristics

Summaries of baseline data will be produced using the safety population and will be presented by treatment group and overall. Data for parameters measured at screening that are also measured at subsequent time points post-randomization (e.g. vital signs, renal and hepatic function) will not be presented in this section. All baseline data will also be listed.

9.4.1 Demographic data

Summary statistics for age (see Section 5 for definition of derivation), height and weight at screening will be presented, together with frequency counts and percentages for ethnic origin, race and gender.

9.4.2 Recipient Information

Frequency counts and percentages will be presented for transplant procedure type, reasons for transplant, medical condition and CMV status. A footnote will be added to the table to clarify that multiple reasons for transplant may be indicated. Data relating to extra respiratory tract of infection will also be included. Frequency counts and percentages will be presented for blood culture results, fever and other signs of systemic sepsis syndrome.

9.4.3 Significant Medical History

The total number of patients reporting any significant medical history and the total number of patients reporting significant occurrences ongoing at screening will be presented. In addition, the number and percentage of patients reporting an item of significant medical history within each of the following 15 body systems will also be presented: General Appearance; Head, Ears, Eyes, Nose and Throat; Cardiovascular; Pulmonary; Gastrointestinal; Liver; Renal; Genitourinary; Endocrine; Immune/Allergy; Psychiatric; Central Nervous System; Dermatologic; Musculoskeletal; Other.

9.4.4 Donor Information

Summary statistics will be presented for the age of the donor, together with frequency counts and percentages of the gender of the donor, whether the donor was a brain dead heart beating donor and a breakdown of the reasons for brain death. If multiple reasons are provided than a footnote should be added to the table explaining that the number of reasons given will exceed the number of patients. The number and percentage of donors whose transplant organ was flushed will be presented by type of solution (Perfadex or other) and category of flush (anterograde, retrograde, additional) and the number and percentage of donors whose transplant organ was stored in either Perfadex or other solution will also be presented.

9.4.5 Transplantation

The data for first and second allograft will be presented separately. For each allograft, the following data will be presented: summary statistics for the duration of cold ischemia, the duration of warm ischemia and the duration of both cold and warm ischemia (see section 5 for definitions) will be presented, together with frequency counts and percentages for the number of patients who had cardiopulmonary bypass performed. All other data relating to transplant will be listed only.

9.5 Efficacy analyses

9.5.1 Primary Variable

The PaO_2/FiO_2 ratio will be analyzed at two time points: 0 hours (time of ICU admission) and 24 hours after ICU admission. These analyses will be performed using both the ITT and PP populations with the ITT analysis considered as the primary result. As this is not a pivotal study and the contrast estimates will be obtained from a repeated measurements model fitted for data at both time points, adjustments for multiplicity are not considered necessary.

Primary analysis

The ratio at the two time points will be analyzed using a repeated measurements model using PROC MIXED within SAS®. The model will include fixed effect terms for center, time point and treatment. Time point will be specified as a repeated measurement. In order to select an appropriate matrix for the observations within each patient, 3 models will be fitted using the compound symmetry, Huynh-Feldt and unstructured structures. The matrix for the final model will be selected using Akaike's Information Criterion where the lowest value indicates the best fit. Type III sums of squares from the mixed procedure within SAS® will be used to assess the significance of individual terms within the model using the selected matrix structure. The importance of the treatment-by-center interaction will be investigated but if the term is not significant at the 10% level, it will be excluded from subsequent models. If there are insufficient data within each center and treatment combination to allow estimation of effects, centers will be pooled based on similar surgical practices.

The adjusted least squares means will be estimated for each combination of time point and treatment. The treatment effect within each time point will be compared using a one sided test at the 5% level. Missing data will be excluded. The primary analysis will be performed for the ITT population.

The tests of the fixed effects will be presented, together with the estimated least squares means and summary statistics of the raw PaO_2/FiO_2 ratio for each of the two treatments at each time point. The estimated treatment difference between repertaxin and placebo at each time point will be presented together with the corresponding 95% confidence interval. The confidence interval will be generated using α=0.10 and the lower limit will be replaced by $-\infty$.

Sensitivity Analyses

The primary analysis will be repeated using the PP population.

The primary analysis will be repeated using a two-sided test at the 5% level.

The primary analysis will be repeated using the last observation carried forward (LOCF) method to substitute a missing PaO_2/FiO_2 ratio for patients extubated within 24 hours after ICU submission. For patients who died within 24 hours of ICU admission a ratio of 0 will be used at the 24 hour time point. Data for patients with a ratio missing for any other reason will not be substituted.

The primary analysis will be performed including the type of transplant (single or double) as a fixed effect covariate whose importance will be assessed at the 5% level. The interaction term for type of transplant and treatment will also be fitted but if this is not significant at the 10% level it will be excluded from the final model. The randomization has not been stratified by the type of transplant and therefore this analysis will only be performed if there are sufficient data within each treatment, center and type of transplant combination.

In summary, the following presentations of PaO_2/FiO_2 ratio at time 0 and 24 hours will be produced:
Repeated Measurements Analysis using a one-sided test for the ITT population with missing data excluded.
Repeated Measurements Analysis using a one-sided test for the PP population with missing data excluded.

Repeated Measurements Analysis using a two-sided test for the ITT population with missing data excluded.
Repeated Measurements Analysis using a one-sided test for the ITT population with substitution of missing data.
Repeated Measurements Analysis using a one-sided test for the ITT population including type of transplant but with missing data excluded.
Repeated Measurements Analysis using a one-sided test for the PP population including type of transplant but with missing data excluded.

Additional exploratory analyses may be performed to further investigate the robustness of the primary efficacy data.

9.5.2 Secondary Variables

9.5.2.1 PaO_2/FiO_2 ratio at 48 hours and 72 hours after ICU admission
These data will be analyzed as described for the primary analysis using a one-sided test at the 5% level and with missing data excluded. A further analysis including type of transplant again using a one-sided test at the 5% level and with missing data excluded will also be performed provided there are sufficient data recorded. Both these analyses will be performed on the ITT and PP analysis populations.

9.5.2.2 PGD score
Analysis of PGD score will be performed separately at time 0 and at 24, 48 and 72 hours after ICU admission. Two analyses, using Cochran-Mantel-Haenszel statistics from PROC FREQ within SAS, will be performed at each time point. The first will use type of transplant (single or double) as a stratification factor and will use the following SAS code:

```
Proc freq data=data1 (where=(time=x)) noprint ;
  table tran_typ*PGD*treat/cmh out=ct_typ ;
  output out=cmhtype cmh ;
run ;
```

As the randomization did not include type of transplant it is possible that that there will be insufficient data within each of the cells to perform the analysis. This will be assessed after the Month 1 database lock.

The second analysis will use center as a stratification factor.

Both analyses will be performed for both the ITT and PP populations. For each analysis, the number and percentage of patients within each table cell will be presented, together with the second of the threa p-values provided by PROC FREQ (labeled as Row Mean Scores Differ), and the corresponding Mantel-Haenzsel odds ratio and the associated 95% confidence interval.

9.5.2.3 Time to freedom from mechanical ventilation
Time to freedom from mechanical ventilation will be derived as described in Section 5. Kaplan-Meier summary statistics and plots will be used to illustrate time to freedom from mechanical ventilation for each treatment group. The analysis will be performed using PROC LIFETEST within SAS:

```
proc lifetest plots=(s, ls, lls) data=data2 method=km outsurv=estimates ;
   time freetime*censor(1) ;
   strata treatment ;
   ods output ProductLimitEstimates=file1 ;
run ;
```

Patients who die while still on mechanical ventilation will be censored at the time of death.

The risk set and number of events occurring within each 12-hour interval will be presented together with the event probability and standard error. The estimated difference in event probability and corresponding 95% confidence interval will also be presented together with the log-rank and Wilcoxon tests for differences between treatments.

The analysis will also be performed by treatment and type of transplant.

Both analyses will be presented for both the ITT and PP populations.

9.5.2.4 Duration of ICU stay
The duration of ICU stay will be derived as described in Section 5. This duration is equivalent to time to ICU discharge. The duration of ICU stay will be analyzed as described for time to freedom from mechanical ventilation.

9.5.2.5 Mortality
Frequency counts and percentages for the number of patients who die while in ICU and also the number and percentage of patients who die within the first 30 days post-transplant (derived as latest date of reperfusion + 30) will be presented by treatment group. This table will be presented for the ITT population only.

9.5.2.6 Pulmonary Function Tests
Summary statistics for FEV_1 and FVC measured at Month 1 will be presented for the ITT population by treatment group and also for each treatment group and transplant type combinations.

9.5.2.7 Acute Rejection Episodes
The number and percentage of patients reporting at least one acute rejection episode up to and including Month 1 will be reported by treatment group and also by treatment group and transplant type. The total number of episodes will also be reported for each treatment group and each treatment group and transplant type combination. This summary will be presented for the ITT population only.

9.6 Safety analyses

9.6.1 Extent of Study Drug Exposure
Summary statistics for duration of study drug infusion and amount of study drug infused (see Section 5 for definition) will be presented by treatment group.

9.6.2 Adverse events
A summary of treatment-emergent adverse events (see Section 5 for definition) reported between start of infusion and the Month 1 visit, including the total number of events reported, the number and percentage of patients reporting at least one adverse event, the number and percentage of patients withdrawing prematurely due to an adverse event, the number and percentage of patients with at least one serious adverse event and the number and percentage of deaths, will be presented by treatment. In addition, a summary of the event by each category of drug relationship will be presented for adverse events and also for serious adverse events.

A breakdown of the number and percentage of patients reporting each adverse event, categorized by body system and preferred term coded according to the MedDRA dictionary, will be presented. Note that counting will be of patients not events and patients are only counted once within each preferred term.

A further tabulation of these data, broken down by relationship to study drug, will be presented. Patients with multiple events within a particular body system or preferred term will be counted under the category of their most drug-related event within that body system or preferred term.

Relationship to study drug is categorized as none, unlikely, possible, probable and highly probable as recorded on the CRF. Each category of relationship will be presented on a separate page.

A summary of events reported, broken down by severity (mild, moderate, severe, life threatening), will also be provided. Patients with multiple events within a particular body system or preferred term will be counted under the category of their most severe event within that body system or preferred term. Each category of severity will be presented on a separate page.

A summary of adverse events leading to premature withdrawal will be provided, grouped by body system and preferred term.

All adverse events recorded on the CRF will be listed.

9.6.3 Serious Adverse Events

A breakdown of the number and percentage of patients reporting each serious adverse event (SAE) between the start of infusion and the Month 1 visit, categorized by body system and preferred term coded according to the MedDRA dictionary, will be presented.

A further tabulation of these data, broken down by relationship to study drug, will be presented. Patients with multiple SAEs within a particular body system or preferred term will be counted under the category of their most drug-related SAE within that body system or preferred term. Relationship to study drug is categorized as none, unlikely, possible, probable and highly probable as recorded on the CRF. Each category of relationship will be presented on a separate page.

A summary of SAEs reported, broken down by severity (mild, moderate, severe, life threatening), will also be provided. Patients with multiple SAEs within a particular body system or preferred term will be counted under the category of their most severe SAE within that body system or preferred term. Each category of severity will be presented on a separate page.

A summary of SAEs leading to premature withdrawal will be provided, grouped by body system and preferred term.

9.6.4 Laboratory data

Samples for safety laboratory tests for hematology, clinical chemistry and coagulation are taken at Screening and hospital discharge. The following parameters will be included in the summary data presentations:
Hematology: hematocrit, hemoglobin, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils
Clinical chemistry: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine
Coagulation: activated partial thromboplastin time (APTT), prothrombin time (PT), INR
Note: patients will either have a value for PT or INR at each time point.

Results for each parameter at screening and hospital discharge will be assessed as being below the lower limit of the normal range, within the normal range or above the upper limit of the normal range. The number and percentage of patients with out-of-range results and the number and percentage of patients with clinically significant out-of-range results will be presented for each parameter at each time point, together with the number of patients with results for that parameter and time point. Shifts in laboratory parameters during the hospital stay will also be presented for each parameter.

Creatinine clearance is calculated using Cockcroft-Gault formula at Screening and at 12, 24 and 36 hours post ICU admission for the assessment of renal and hepatic function during the study.

These data are used for assessment of patient during the study conduct phase and will be listed only.

9.6.5 Concomitant Medications

All medications reported in the CRF as being taken prior to the Month 1 visit, categorized by medication group and subgroup according to WHO DRUG, will be summarized. The number and percentage of patients using at least one medication within each medication group and subgroup will be presented.

9.6.6 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital signs

Vital signs, including systolic and diastolic blood pressure and heart rate, are measured at Screening, ICU admission, every 12 hours post ICU admission until 120 hours post ICU admission or until ICU discharge or PA catheter removed whichever occurs earliest. Summary statistics for each of these three parameters will be presented by treatment group at each time point. Summary statistics for the change from screening to each post-screening time point will also be presented.

Cardiopulmonary measurements

Cardiopulmonary measurements consist of CVP, PCWP, CO and PA Pressure (systolic/diastolic) and are measured at ICU admission, every 12 hours post ICU admission until 120 hours post ICU admission or until ICU discharge or PA catheter removed whichever occurs earliest. These data will be summarized by treatment group at each time point. Summary statistics for the derived variables SVR and PVR (see Section 5 for definitions) will also be provided.

10 VALIDATION

All summary tables and figures will be validated by independent programming within SAS. Any numerical discrepancies will be resolved prior to finalization of the tables and figures. All outputs will have the following checks performed:

- Titles and footnotes are correct
- No errors or warnings in SAS log file
- Expected number of observations in dataset used for final output
- Matches the specifications documented in this plan

11 LIST OF TABLES, FIGURES AND LISTINGS FOR MONTH 1 REPORT

Output numbering may be further sub-divided in order to allow for logical presentation of the data.

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1.5	Recipient Information (Safety Population)
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12 DATA PRESENTATION

All outputs will be produced using the following settings:

Orientation	Margins	Font	Headers	Footers
Landscape	Top: 1in/2.54cm Bottom: 1in/2.54cm Left: 0.5in/1.27cm Right: 0.5in/1.27cm	SAS Monospace 8pt	(Centered) Protocol Number Table/Listing Number and title	(Left) Path and Filename Creation date

Titles will be as follows:

Dompé pha.r.ma s.p.a. Protocol REP0104

Table tabno tabtitle

13 TABLE SHELLS

Tables 2.1.x and 2.2.x Repeated Measurements Analysis

Tests of Fixed Effects

Source	NDF	DDF	Type III F	P
Center	x	x	x.xx	0.xxxx
Time	x	x	x.xx	0.xxxx
Treatment	x	x	x.xx	0.xxxx
Center-by-treatment	x	x	x.xx	0.xxxx

Summary Statistics

		Repertaxin	Placebo
Time=0	Least Squares Mean	xx.xx	xx.xx
	Mean	xx.xx	xx.xx
	SD	xx.xx	xx.xx
	Median	xx.xx	xx.xx
	Range	(xx.x; xx.x)	(xx.x; xx.x)
	N	x	x
Time=24	Least Squares Mean	xx.xx	xx.xx
	Mean	xx.xx	xx.xx
	SD	xx.xx	xx.xx
	Median	xx.xx	xx.xx
	Range	(xx.x; xx.x)	(xx.x; xx.x)
	N	x	x

Treatment Comparison

Time	Comparison	Difference between Means	SE of difference	95% confidence interval	P-value
0	Repertaxin - Placebo	x.xxx	x.xxx	(-x.xx, x.xx)	0.xxxx
24	Repertaxin - Placebo	x.xxx	x.xxx	(-x.xx, x.xx)	0.xxxx

Table 2.3.x Analysis of PGD Score

	Repertaxin N=		Placebo N=		Odds Ratio [1]	95% CI for Odds Ratio	P-value [2]
	N	%	N	%			
Grade 0	xx	xx	xx	xx	x.xx	(x.xx, x.xx)	0.xxx
Grade 1	xx	xx	xx	xx			
Grade 2	xx	xx	xx	xx			
Grade 3	xx	xx	xx	xx			

[1] Odds ratio is Repertaxin:Placebo
[2] The p-value is obtained from a Cochran-Mantel-Haenszel test of the treatment difference.

Table 2.4.x Time to Freedom from Mechanical Ventilation

	Repertaxin N=				Placebo N=					
TIME POINT	Number of Patients Remaining	Cumulative Number of Events	Event Probability	S.E.	Number of Patients Remaining	Cumulative Number of Events	Event Probability	S.E.	Difference in Event Prob.	95% CI for Difference
24 hrs										
48 hrs										
72 hrs										
96 hrs										
etc										
Censored (N)	xx				xx				Chi-sq statistic	P-value
Log-rank										

Examples of adverse event presentations

Table 3.2.1.1 Summary of Treatment-Emergent Adverse Events (TEAEs)

	Treatment	
	Repertaxin	Placebo
Total number of TEAEs	XX	XX
Number of Patients with:		
At least one TEAE	XX (XX%)	XX (XX%)
Withdrawing prematurely due to TEAE	XX (XX%)	XX (XX%)
At least one Serious TEAE	XX (XX%)	XX (XX%)
TEAE leading to death	XX (XX%)	XX (XX%)
TEAEs - Most Serious Relationship to Study Drug		
Unrelated	XX (XX%)	XX (XX%)
Unlikely	XX (XX%)	XX (XX%)
Possible	XX (XX%)	XX (XX%)
Probable	XX (XX%)	XX (XX%)
Highly Probable	XX (XX%)	XX (XX%)
Serious TEAEs - Most Serious Relationship to Study Drug		
Unrelated	XX (XX%)	XX (XX%)
Unlikely	XX (XX%)	XX (XX%)
Possible	XX (XX%)	XX (XX%)
Probable	XX (XX%)	XX (XX%)
Highly Probable	XX (XX%)	XX (XX%)

Table 9.2.1.2 Treatment-Emergent Adverse Events by Body System and Preferred Term

MedDRA Body System & Preferred Term	Treatment	
	Repertaxin	Placebo
PAIN	XX (XX%)	XX (XX%)
Pain- other	XX (XX%)	XX (XX%)
Bone Pain	XX (XX%)	XX (XX%)
Abdominal	XX (XX%)	XX (XX%)
Headache	XX (XX%)	XX (XX%)
Chest pain	XX (XX%)	XX (XX%)
GASTROINTESTINAL	XX (XX%)	XX (XX%)
Constipation	XX (XX%)	XX (XX%)
Nausea	XX (XX%)	XX (XX%)
Anorexia	XX (XX%)	XX (XX%)
Vomiting	XX (XX%)	XX (XX%)
Diarrhea	XX (XX%)	XX (XX%)