16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan

Addendum to Statistical Analysis Plan

Statistical Analysis Plan

REP0112

A phase 2/3, multicenter, randomized, double-blind, placebo-controlled, parallel assignment study to assess the efficacy and safety of reparixin in pancreatic islet auto-transplantation.

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A phase 2/3, multicenter, randomized, double-blind, placebo-controlled, parallel assignment study to assess the efficacy and safety of reparixin in pancreatic islet auto-transplantation.

Protocol No: REP0112

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GLOSSARY OF ABBREVIATIONS

ADIR	Average Daily Insulin Requirements
AE	Adverse Event
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BP	Blood Pressure
CLcr	Calculated Creatinine Clearance (Cockcroft - Gault formula)
CRF	Case Report Form
CRO	Contract research organization
CRP	C-reactive Protein
DMC	Data Monitoring Committee
HbA1c	Glycated hemoglobin
HR	Heart Rate
Kg	Kilogram
IAT	Islet Auto-Transplantation
IEQ	Islet Equivalent
INR	International Normalized Ratio
ITT	Intent to Treat
MMTT	Mixed Meal Tolerance Test
NSAID	Non Steroidal Anti-inflammatory Drug
PK	Pharmacokinetic
PP	Per Protocol
PTT	Partial Thromboplastin Time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TEAE	Treatment emergent adverse event
ULN	Upper Limit of Normal
XDP	Fibrin Degradation Products

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 farmaceutici S.p.A (Dompé) Protocol REP0112.

The SAP will be finalized and approved by the sponsor in addition to the Project Manager and Statistician of the contract research organization appointed by Dompé prior to database lock.

1.2 Changes From Protocol

Not pertinent.

1.3 Changes From Previous Versions of SAP

Not pertinent.

2 STUDY OBJECTIVES

The objective of this clinical trial is to assess whether reparixin leads to improved transplant outcome as measured by the proportion of insulin-independent patients following islet auto-transplantation (IAT). The safety of reparixin in the specific clinical setting will also be evaluated.

3 STUDY DESIGN

3.1 Overview

The study will be a phase 2/3, multicenter, randomized, double-blind, placebo-controlled, parallel assignment pilot study.

The goal of this study is to reach a total of 100 adult patients who are randomized and receive IAT after total or completion pancreatectomy. Patients will be randomly (1:1) assigned to receive either reparixin [continuous intravenous infusion for 7 days (168 hours)], or matched placebo (control group), starting approximately 12 hours before islet infusion. The two groups will be balanced within each centre. All patients who are randomized and receive the investigational product (either reparixin or placebo) will be included in the intent to treat (ITT) analysis. Patients will be in the ITT analysis whether or not they receive IAT, because exclusions cannot be made for events occurring after randomization that could be influenced by the randomized assignment.

Recruitment will be competitive among the study sites, until the planned number of patients is enrolled. Competitive recruitment has been chosen to increase the speed of recruitment and to account for any difference in transplant rate among study sites. Each centre will enroll patients as rapidly as possible, up to a maximum of 40 patients (as per the randomization list).

Each patient will be involved in the study for at least a 7 day hospital stay during pancreatectomy followed by IAT, for all required measurements up to hospital discharge and for 2 post-transplant visits scheduled at Day 75 $\pm$ 14 days and Day 365 $\pm$ 14 days after the transplant.

3.2 Inclusion and Exclusion Criteria

To be eligible for inclusion into this study, each patient must fulfill ALL of the following inclusion criteria:

1. Patients eligible for an IAT following total (or completion) pancreatectomy.
2. Ages ≥ 18 years.
3. Patients willing and able to comply with the protocol procedures for the duration of the study, including scheduled follow-up visits and examinations.
4. Patients who have given written informed consent, prior to any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to their future medical care.

Patients who meet any of the following exclusion criteria are NOT eligible for participation in the study:

1. Recipients of a previous IAT (if completion pancreatectomy).
2. Patients undergoing total pancreatectomy due to either pancreatic cancer or pancreatic benign diseases other than chronic pancreatitis, including insulinomas, etc.
3. Patients with inadequate renal reserve as per calculated creatinine clearance (CLcr) < 60 mL/min according to the Cockcroft-Gault formula (1976).
4. Patients with hepatic dysfunction as defined by increased alanine aminotransferase/aspartate aminotransferase (ALT/AST) > 3 x upper limit of normal (ULN) **or** increased total bilirubin above the upper limit at local laboratory. Patients with Gilbert's syndrome (elevated unconjugated bilirubin levels in the absence of any evidence of hepatic or biliary tract disease) are not excluded.
5. Patients with a preoperative International Normalized Ratio (INR) > 1.5 or any known coagulopathy.
6. 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.
7. Concurrent sepsis (as per positive blood culture(s) and/or fever associated with other signs of systemic sepsis syndrome).
8. Treatment with systemic steroids in the 2 weeks prior to enrolment (except for the use of ≤5 mg prednisone daily or equivalent dose of hydrocortisone, for physiological replacement only) or with any immune modulators in the 4 weeks prior to enrolment.
9. Patients with pre-existing diabetes or evidence of impaired β-cells function, based on pre-operative fasting blood glucose >115 mg/dL and/or a HbA1c > 6.5%, or requiring treatment with any anti-diabetic medication (e.g. insulin, metformin, etc) within the 2 weeks prior to enrolment.
10. Use of any investigational agent in the 4 weeks prior to enrolment, including any anti-cytokine/chemokine agents.
11. Pregnant or breast-feeding women; unwillingness to use effective contraceptive measures (females and males). (NB: pregnancy should be avoided in patients or partners during the first month after completing the treatment with the investigational product; no other specific warnings are described, considering the treatment course of the investigational product, its pharmacokinetic (PK) profile, and the lack of significant adverse effects on mating performance and fertility in animal studies).

12. Patients with past or current history of alcohol abuse based on clinical history and/or past treatment for alcohol addiction.

13. Patients with evidence of pre-operative portal hypertension as per clinical history **and** abdominal/liver imaging by ultrasound techniques.

Sites will comply with any additional or more restrictive exclusion criteria locally accepted, as per centre practice.

3.3 Sample Size Considerations

The primary efficacy endpoint of the clinical trial is the proportion of insulin-independent patients following IAT at Day 365 ± 14 days after the transplant.

In the following considerations, statistical significance for this endpoint will be achieved if the Pearson Chi-square statistic yields a two sided p-value less than 0.05. The corresponding false positive error rate is (one-sided) 0.025. In addition, a 95% confidence interval for the difference of success (failure) rates between the reparixin and placebo groups will be provided based on the normal distribution approximation to the standardized difference in estimated success rates.

Based on published data from a retrospective series (Sutherland, 2012), it appears that the likelihood of achieving insulin independence at 12 month follow-up in the placebo control arm depends upon the number of IEQ/kg, with patients categorized in three groups:

- <2500 IEQ/kg: 13% insulin independence
- 2500-5000 IEQ/kg: 23% insulin independence
- >5000 IEQ/kg: 55% insulin independence

In their overall series, the yields were <2500 IEQ/kg in 36%, 2500-5000 IEQ/kg in 39% and >5000 IEQ/kg in 24% of patients. In the more recent series of 217 patients receiving IAT from 2006 to 2011, corresponding yields were <2500 IEQ/kg in 34%, 2500-5000 IEQ/kg in 42%, and >5000 IEQ/kg in 24%.

Initial focus is placed on the cohort that is in the range 2500-5000 IEQ/kg, since these participants will be the largest fraction of enrollees. It is anticipated that the percentage of such patients achieving insulin independence will be increased from 23% in the placebo control arm to 55% in the reparixin arm. Using standard statistical formulas based on the approximation of the binomial distribution by the normal distribution, the sample size of 44 patients per arm provides 90% power to detect a 23% versus 55% true difference when using a Pearson Chi-square statistic having the traditional (one-sided) 2.5% false positive error rate. Even accounting for the discreteness, the power should be in the 87% to 90% range. Furthermore, with 44 patients per arm, statistical significance (i.e., one-sided p=0.025) will be obtained if the estimated difference is 22.7% (10/44) versus 43.2% (19/44), which is an estimated 20.5% increase in percentage of patients achieving insulin independence. Hence, with 44 patients per arm, statistical significance is achieved with an estimated effect size that is clinically meaningful.

Even though the largest percentage of patients will be in the cohort receiving IEQ/kg in the range 2500-5000 IEQ/kg, the trial will also enroll participants in two additional strata: <2500 IEQ/kg and >5000 IEQ/kg. As noted above, we are presuming the middle strata would have an increase from 23% to 55% in percentage of patients achieving insulin independence. This is an odds ratio higher than 4. If we have an odds ratio of approximately 4.3 to 4.5 in the other 2 strata and if approximately 1/2 of the patients would be from the 2500-5000 IEQ/kg stratum, then only a modest increase of about 12 additional patients beyond the 88 patient sample size would be needed to maintain the statistical power of the trial. An increase in success rate from 13% to

40% in the <2500 IEQ/kg stratum would be an odds ratio of 4.4 and an increase in success rate from 55% to 84% in the >5000 IEQ/kg stratum would be an odds ratio of 4.3.

Based on these considerations, it is planned to enroll 100 patients in this trial who receive IAT, with the expectation that there will be approximately 5 others who do not receive IAT. Under such a plan, the trial would not be overpowered even if all participants were in the 2500-5000 IEQ/kg stratum since statistical significance (i.e., one-sided p=0.025) would be obtained with 52 patients per arm if the estimated difference is 23.1% (12/52) versus 42.3% (22/52), which is an estimated clinically significant 19.2% increase in percentage of patients achieving insulin independence.

The sample size of 100 to 105 patients also provides high statistical power for the key secondary endpoint, C-peptide area under the curve (AUC) (mixed meal tolerance test [MMTT]) normalized by IEQ/kg. Based on preliminary data reported from the ongoing pilot trial, Month 1 post transplant means and standard deviations for this endpoint are 1.92 ± 1.62 in the reparixin group and 0.44 ± 0.04 in the control group. With 52 patients in each treatment group, the trial will have greater than 95% power to detect a difference in means of at least 1.48 (the difference between a treated mean of 1.92 and a control mean of 0.44) assuming that the common standard deviation is 1.37 and using an 0.0025 two-sided significance level.

3.4 Randomization

Patients will be randomized in a 1:1 fashion to either reparixin or placebo.

The randomization list will be generated with a computer procedure by the method of random permuted blocks in which treatment (in blocks of 4) will be balanced within centres. A master randomization list will be generated, randomizing an excess of patients (a maximum of 40 for each site) to allow competitive recruitment within each centre.

The randomization list will be prepared by an independent statistician and provided to Dompé in a sealed envelope to prevent unblinding.

Similarly, individual treatment codes will be provided via a tamper-resistant system (either a sealed envelope or a scratch card). Such a system will definitely allow recognition of whether the code has been broken and guarantees detection of any code misuse. Individual treatment codes will be provided to:

- the Pharmacist (or designee) within each participating site for investigational product preparation;
- the Dompé Pharmacovigilance Department for safety procedures.

The investigators can request to an independent facility (either by telephone or web based system) an individual code in the event of an emergency only, where knowledge of the blinded treatment for that patient could influence further patient care. Any potential unauthorized code break and the reason behind it will be recorded.

The randomization codes will also be accessible to an independent statistician (liaison between the contract research organization [CRO] database and Data Monitoring Committee [DMC] biostatistician) who will generate the reports for the DMC evaluation.

The randomization code will be broken at study completion, i.e. when the last patient has completed his/her last follow-up visit (planned at 365 days after islet infusion), and once the database has been locked.

4 STUDY VARIABLES

4.1 Primary Variable

The proportion of insulin-independent patients at Day 365 ± 14 days following IAT.

For the purpose of this protocol, insulin-independence is defined as freedom from the need to take exogenous insulin for 14 or more consecutive days, with adequate glycemic control, as defined by:

- a glycated hemoglobin (HbA1c) level ≤6.5%;
- fingerstick fasting blood glucose not exceeding 126 mg/dL more than three times in the past week (based on a minimum of one daily measurement;
- a 2 hour post-prandial blood glucose not exceeding 180 mg/dL more than four times in the past week (based on a minimum of one daily measurement);
- a laboratory fasting glucose in the non-diabetic range (<126 mg/dL).

4.2 Secondary Variables

4.2.1 Efficacy Variables

- Area under the curve (AUC) for serum C-peptide level during the first 4 hours of a MMTT, normalized by the number of IEQ/kg, at Day 75 ± 14 days and at Day 365 ± 14 days after IAT.
- Average daily insulin requirement at Day 75 ± 14 days and at Day 365 ± 14 days after IAT.
  For the purpose of this protocol, daily insulin is reported as IU/kg and intake averaged over the previous week.
- Time course of glucose derived from the MMTT at Day 75 ± 14 days and at Day 365 ± 14 days after IAT. For each MMTT, there are 2 basal samples taken separately between -20 to 0 minutes before the meal followed by samples through 240 minutes after the meal.
- Time course of C-peptide derived from the MMTT at Day 75 ± 14 days and at Day 365 ± 14 days after IAT. For each MMTT, there are 2 basal samples taken separately between -20 to 0 minutes before the meal followed by samples through 240 minutes after the meal.
- Time course of insulin derived from the MMTT at Day 75 ± 14 days and at Day 365 ± 14 days after IAT. For each MMTT, there are 2 basal samples taken separately between -20 to 0 minutes before the meal followed by samples through 240 minutes after the meal.
- β-cell function as assessed by β-score at Day 75 ± 14 days and at Day 365 ± 14 days after IAT.
- The proportion of patients with HbA1c ≤ 6.5% at Day 365 ± 14 days after IAT.
- Cumulative number of severe hypoglycemic events from Day 75 ± 14 days to Day 365 ± 14 days after IAT.
  For the purpose of this protocol, a severe hypoglycemic event is defined as an event with one of the following symptoms: "memory loss, confusion, uncontrollable behavior, irrationale behavior, unusual difficulty in awakening, suspected seizure, seizure, loss of consciousness, or visual symptoms", in which the subject was unable to treat him/herself and which was associated with either a blood glucose level <54 mg/dL or prompt recovery after oral carbohydrate, i.v. glucose, or glucagon administration.
- The proportion of patients with HbA1c ≤ 6.5% at Day 365 ± 14 days after IAT **AND** free of severe hypoglycemic events from Day 75 ± 14 days to Day 365 ± 14 days after IAT, inclusive.

4.2.2 Safety Variables

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) throughout the study up to Day 365 ± 14 days after IAT.
- Standard laboratory tests including hematology (hematocrit, hemoglobin, red blood cells, platelets, white blood cells, differential white blood cells count), clinical chemistry (sodium, potassium, serum creatinine, blood urea nitrogen, total bilirubin, ALT, AST), and coagulation

(international normalized ratio [INR], partial thromboplastin time [PTT]) at pre-transplant hospital admission and post-transplant hospital discharge.

- Vital signs, i.e. systolic and diastolic blood pressure (BP) and heart rate (HR) at pre-transplant hospital admission and post-transplant hospital discharge.
- ALT, AST, INR, PTT, fibrin degradation products (XDPs), and C-reactive protein (CRP), all daily from Day 1 up to Day 7 after IAT; ALT and AST also on Day 75 ± 5 days after IAT.
- Weight loss from pre-transplant value at Day 75 ± 14 days and Day 365 ± 14 days after IAT.
- Serum level of albumin and pre-albumin, absolute and change from pre-transplant value, at Day 75 ± 14 days and Day 365 ± 14 days after IAT.
- Proportion of patients falling into one of the following levels of steatorrhea severity at Day 75 ± 14 days and Day 365 ± 14 days after IAT.

  For the purpose of this protocol, levels of steatorrhea severity (evaluated in the 4 weeks prior to Day 75 ± 14 days and Day 365 ± 14 days), are defined as:

  - No steatorrhea;
  - Steatorrhea few times per week;
  - Steatorrhea daily;
  - Stool incontinence.

- Proportion of patients falling into one of the following malnutrition risk levels according to pre-albumin level at Day 75 ± 14 days and Day 365 ± 14 days after IAT.

  For the purpose of this protocol, malnutrition risk levels are defined as (adapted from Bernstein, 1995):

  - Poor prognosis = pre-albumin level <5.0 mg/dL
  - Significant risk = pre-albumin level 5.0 to 10.9 mg/dL
  - Increased risk = pre-albumin level 11.0 to 15.0 mg/dL
  - Normal = pre-albumin level > 15.0 (up to 35.0) mg/dL

- Cumulative number of episodes of documented hypoglycemia (documented symptomatic; asymptomatic) from Day 75 ± 14 days to Day 365 ± 14 days after IAT.

  For the purpose of this protocol, the following definition applies (Diabetes Care, 2005):

  - Documented symptomatic hypoglycemia = An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤70 mg/dL.
  - Asymptomatic hypoglycemia = An event not accompanied by typical symptoms of hypoglycemia, but with a measured plasma glucose concentration ≤70 mg/dL.

- Cumulative number of diabetic ketoacidosis-related events from Day 75 ± 14 days to Day 365 ± 14 days after IAT.

  For the purpose of this protocol, a diabetic ketoacidosis event is defined as the presence of (Pediatrics, 2004):

  - Hyperglycemia (blood glucose >200 mg/dL);
  - pH <7.3 or HCO3 <15;
  - Ketones positive in the serum or urine.

4.2.3 Exploratory Variables

- Time course of inflammatory chemokines/cytokines as assessed by serum level of CXCL8, CCL2 (MCP-1), CCL3, CCL4, CXCL10 (IP-10), CXCL9 (MIG), IL-6, IL-10, INF-γ, TNF-α, and IL-1β at pre-infusion hospital admission (2 basal samples collected 6 to 24 hours apart with both samples obtained before surgery and before investigational product

administration is started) and 6, 12, 24, 72, 120, and 168 hours after the end of islet infusion.

- Proportion of patients who are randomized but do not receive IAT.
- Time course of serum microRNA-375 (miR-375) at pre-infusion hospital admission (sample will be obtained before surgery and before investigational product administration is started) and 6, 12, 24, 72, 120, and 168 hours after the end of islet infusion.

4.2.4 Pharmacokinetic Variables

- Plasma levels of reparixin (total and unbound) and relevant metabolites (DF2243Y and ibuprofen) at post-operative Days 1, 3, and 5 (steady state) in all patients; and just prior to, and then at 1, 3, 5, 6, 8, and 12 hours after termination of investigational product administration in a subset of at least 20-24 patients enrolled at Site 1 and Site 3.

Pharmacokinetic summarization and analysis will not be done by the CRO which is conducting summarization and analysis of the primary, secondary, and exploratory variables described in this SAP. Pharmacokinetic summarization and analysis will be described in a separate document and not discussed further in this SAP; pharmacokinetic data collected in the CRF will be listed.

5 DEFINITIONS AND DERIVED VARIABLES

Study Day Relative to Date of First Date of Investigational Product Administration: Day 1 will be defined as the first date on which infusion of investigational product is started. Positive study days will be counted forward from Day 1. Day -1 will be the date immediately preceding Day 1, and negative study days will be counted backward from Day -1.

Study Day Relative to Date of Islet Auto-Transplantation: Day 0 will be defined as the date on which islet are infused. Positive study days will be counted forward from Day 0. Day -1 will be the date immediately preceding Day 0, and negative study days will be counted backward from Day -1.

Visit Windows: For the per protocol population (see Section 6 of this SAP), data recorded at the Day 75 and Day 365 visits will be included in summarization and analysis only if the Day 75 and Day 365 visits fall within 14 days of the target study day relative to the date of IAT as indicated in the following table.

Visit	Target Study Day Relative to Date of IAT	Acceptable Range of Study Days Relative to IAT
Day 75	75	61 to 89
Day 365	365	351 to 379

Area Under the Curve (AUC) Normalized by the Number of IEQ/kg, C-peptide: When C-peptide values are below the limit of detection (0.05 ng/mL), a value of 0.05 ng/mL will be assumed in the calculation of area under the curve. Missing C-peptide values will be imputed via linear interpolation, and the average of the two basal samples (values, and mid-point of sample times) will be used as the first sample in the computation of the AUC. Once these rules have been applied to the data, AUC for C-peptide will be computed using the trapezoidal rule, and normalized by dividing the computed AUC value by the total IEQ/kg infused during IAT as recorded on Page 12 of the CRF. For ease of interpretation, the AUC value obtained will be divided by the total time the scale is assessed for reporting purposes. Computation of AUC will be based on actual collection times, unless actual collection time is missing, in which case the scheduled collection time will be used.

Other definitions and derived variables are found within the applicable subsections of Section 7, Statistical Methods.

6 ANALYSIS POPULATIONS

Five analysis populations will be identified and used in the summarization and analysis of data, namely all screened patients, all randomized patients, intent to treat, per protocol, and safety.

- All Screened Patients: This population will include all patients screened for participation in the trial.
- All Randomized Patients: This population will include all patients randomized to investigational product in the trial.
- Intent to Treat: This population will consist of all patients who are randomized and receive the investigational product (either reparixin or placebo). Summarization and analysis of this population will be based on randomized treatment, regardless of treatment actually received. Eligible patients will be included in this population whether or not they receive IAT, because exclusions cannot be made for events occurring after randomization that could be influenced by the randomized assignment.
- Per Protocol: This population will consist of all patients in the ITT population who meet all of the following criteria:
  - Received IAT
  - Completed 7 days of investigational product dosing
  - No major protocol violations, including violations of inclusion/exclusion criteria, errors in treatment assignment, use of prohibited medication, etc.
  - Visits occurring on Day 75 ± 14 days from IAT and Day 365 ± 14 days from IAT
  - Insulin-independence status recorded at Day 365 ± 14 days from IAT

  Further criteria for exclusion from the PP population may be identified during the data review meeting held prior to database lock.
- Safety: This population will consist of all randomized patients. Summarization and analysis of this population will be based on treatment actually received.

7 STATISTICAL METHODS

7.1 General Principles

The statistical package SAS® will be used to produce all summary tables, figures, and listings.

In general, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the number of patients, mean, standard deviation, median, minimum, and maximum. 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, and percentages will be rounded to one decimal. 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.

All data recorded in the CRF will be listed.

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

7.2 Missing Data

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.

Patients will be informed that they have the right at any time to withdraw from further participation in the study (*withdrawal of consent*), without prejudice to their medical care, and without being obliged to state their reasons. However, the term *withdrawal of consent* should be used only when the patient no longer wishes to participate in the trial and no longer authorizes the investigators to make efforts to continue to obtain his/her outcome data. Ideally, if patients withdraw their consent, it should be done in writing.

During the consent process, patients will be also educated about the scientific relevance of their continued participation as well as the deleterious effect that missing data will have on trial integrity.

It is important to distinguish reasons for stopping randomized treatment (i.e., for non-adherence), from reasons to stop follow-up (i.e., for non-retention). While there are many appropriate reasons to discontinue randomized treatment, the only reasons to discontinue follow-up would be death or withdrawal of consent. Patients who have discontinued the study treatment but have not withdrawn consent should be followed to ensure that primary and secondary outcome measures are assessed.

Investigators will be trained about the importance of patient retention and full data capture. Also, all reasonable attempts should be made by the investigators to emphasize continued patient's participation for the full duration of the trial. If a patient fails to return to the center for a scheduled visit, all reasonable attempts should be made to contact the patient. To minimize missing data, if a patient cannot refer to the site for a planned follow-up visit, the investigator will try to obtain any relevant information from the patients, including documents/lab results available from local medical care.

Handling of missing data will be addressed for each summarization and analysis of data, as applicable, in sections of this SAP which describe summarization and analysis of data.

Appropriate descriptive statistics will be produced to quantify the amount of missing data to allow comparison between the treatment groups.

7.3 Methods for Multiplicity Correction in Analyses

If the primary analysis of the primary endpoint leads to rejection of the null hypothesis, the null hypotheses for the following secondary endpoints will be tested in a conditional sequential manner. The sequence in which these secondary endpoints will be tested is as follows:

1. AUC for serum C-peptide level during the first 4 hours of a MMTT, normalized by the number of IEQ/kg, at Day 365 ± 14 days after IAT.
2. Average daily insulin requirement at Day 365 ± 14 days after IAT.
3. Time course of C-peptide derived from the MMTT at Day 365 ± 14 days after IAT.
4. β-cell function as assessed by β-score at Day 365 ± 14 days after IAT.
5. The proportion of patients with HbA1c ≤ 6.5% at Day 365 ± 14 days after IAT.

6. Cumulative number of severe hypoglycemic events from Day 75 ± 14 days to Day 365 ± 14 days after IAT.
7. The proportion of patients with HbA1c ≤ 6.5% at Day 365 ± 14 days after IAT **AND** free of severe hypoglycemic events from Day 75 ± 14 days to Day 365 ± 14 days after IAT, inclusive.

A null hypothesis will be rejected if and only if the primary analysis of that endpoint and all primary analyses of preceding primary and secondary endpoints result in a rejection of the respective null hypotheses. This procedure protects the family-wise false positive error rate at the overall one-sided 0.025 level.

7.4 Disposition, Baseline Data, Concomitant Medications, Drug Exposure

Summaries of disposition, baseline data, concomitant medications, and drug exposure will be produced using the screened, randomized, ITT, PP, and safety populations as noted in the following sections and will be presented by treatment group and overall.

7.4.1 Patient Disposition

The number of patients screened in total will be presented. The number of patients randomized and number and percentage of randomized patients who did not receive IAT, who were treated, who were included and treated/included and not treated/excluded from the safety population (with reason for exclusion [not randomized] presented as a percentage of patients screened in total only), who were included/excluded from the ITT population (with reason for exclusion), who were included/excluded from the PP population (with reason for exclusion), who completed the study, and who withdrew early from the study (with primary reason for early withdrawal) will be presented by treatment group and in total. The number and percentage of randomized patients who were included in the safety population will be summarized by treatment as received, or by treatment as randomized for those not treated. Fisher's exact test will be used to compare between treatment groups the proportion of randomized patients who did not receive IAT.

Screening data recorded for patients who do not proceed to transplant with study drug administration will be listed separately.

Patient disposition at each site will be presented by treatment group and in total, with the exception of there being no comparison between treatment groups of the proportion of randomized patients who did not receive IAT.

7.4.2 Protocol Deviations

Protocol deviations which exclude patients from the PP population (see Section 6 for definition) will be summarized by treatment group and in total. The number and percentage of ITT patients with at least one protocol deviation and with each type of protocol deviation (by classification and sub-classification) will be presented.

The summarization of protocol deviations will also be presented by site.

7.4.3 Demographic data

Demographic data will be presented for the ITT, PP, and safety populations. Summary statistics for age in years, height in centimeters, and weight in kilograms at screening, and gender, race, and ethnic origin will be presented by treatment group and in total.

7.4.4 Specific Clinical History

Specific clinical history data will be presented for the safety population. The number and percentage of safety patients with each type of pancreatectomy (total, completion), with each reason for pancreatectomy (chronic pancreatitis, recurrent acute pancreatitis), and with each

primary etiology of disease (hereditary or genetic disease, alcohol, sphincter of odi dysfunction, pancreas divisum, idiopathic or unknown, other) will be presented by treatment group and in total.

The number and percentage of patients who had a completion pancreatectomy who had previous IAT and who had each type of prior partial resection (whipple (head) resection, distal pancreatectomy) will be presented by treatment group and in total.

The summarization of specific clinical history will also be presented by site.

Other non-chronic pancreatitis etiology (which are reasons for exclusion from the study) will be presented in a data listing.

7.4.5 Significant Medical History

Significant medical history will be summarized for the safety population.

The number and percentage of patients reporting any significant medical history and any significant medical history which is ongoing at screening will be presented by treatment group and in total. In addition, the number and percentage of patients reporting an item of significant medical history (any and ongoing at screening) within each of the following 15 body systems will also be presented by treatment group and in total: general appearance; head, ears, eyes, nose and throat; cardiovascular; pulmonary; gastrointestinal; liver; renal; genitourinary; endocrine; immune/allergy; psychiatric; central nervous system; dermatologic; musculoskeletal; and other.

7.4.6 Concomitant Medications

Concomitant medications will be summarized for the safety population.

Concomitant medications will be those medications taken at or after the time of the start of investigational product. Medications will be coded to standardized therapeutic classes and preferred terms using the WHO Drug Dictionary version as specified in the Data Management Plan associated with this protocol.

The number and percentage of patients using at least one concomitant medication and using at least one concomitant medication within each therapeutic class and preferred term will be presented by treatment group and in total.

7.4.7 Investigational Product Exposure

Investigational product exposure will be summarized for the safety population.

The number and percentage of patients who did not receive investigational product (in total only), received continuous investigational product infusion, who completed investigational product infusion (7 days), and who prematurely and permanently discontinued investigational product (and by reason for premature and permanent discontinuation of investigational product) will be summarized by treatment group and in total.

Duration of investigational product infusion in hours, average rate of investigational product infusion in mL/hour, amount of investigational product infused in mL and in mg, and percentage of intended dose administered will be summarized descriptively by treatment group and in total.

- Duration of investigational product infusion in hours will be computed as the last infusion end date/time minus the first infusion start date/time plus 1 second and minus the total interruption time in hours, divided by 3,600 seconds per hour.
- Average rate of investigational product infusion to be summarized for a patient will be computed as the average of the infusion rates for all infusion bags which were started for the patient.
- Amount of investigational product infused in mL will be estimated for a given patient for each infusion bag as infusion rate in mL/hour multiplied by duration of investigational product infusion per bag (according to definition of investigational

product infusion in hours but on a per bag basis), and will be estimated in total as the sum over all infusion bags of the amount of investigational product infused.

- Amount of investigational product infused in mg will be estimated for a given patient for each infusion bag or over all infusion bags as the amount of investigational product infused in mL multiplied by 11.00 mg/mL (per Section 6.1.4 of the study protocol).
- Percentage of intended dose administered will be computed as duration of investigational product infusion in hours divided by 168 hours, multiplied by 100, which is derived as follows.

  Actual dose administered will be equal to:

  (2.772 mg/kg) x (body weight in kg) x (duration of infusion in hours)

  Intended dose will be equal to:

  (2.772 mg/kg) x (body weight in kg) x (168 hours)

  The percentage of intended dose administered will be computed as:

  (actual dose administered) / (intended dose) x 100%

  = (duration of infusion in hours) / (168 hours) X 100%

7.5 Efficacy Analyses

Summarization and analysis of efficacy parameters will be conducted for the ITT population (primary analysis) and PP population (secondary confirmatory analysis) by treatment group.

7.5.1 Primary Variable

The primary variable is the proportion of insulin-independent patients at Day 365 ± 14 days after IAT. The number and percentage of patients who are insulin-independent at Day 365 ± 14 days after IAT will be presented by treatment group overall and by IEQ/kg (<2500 IEQ/kg, 2500-5000 IEQ/kg, and >5000 IEQ/kg) infused at IAT.

The percentage of patients who are insulin-independent at Day 365 ± 14 days after IAT will also be presented graphically as a bar chart overall and by IEQ/kg group. Overall and within each IEQ/kg group there will be bars for reparixin and placebo.

Primary Analysis

The proportion of insulin-independent patients will be compared between treatment groups using the Cochran-Mantel-Haenszel test stratified by baseline IEQ/kg (<2500 IEQ/kg, 2500-5000 IEQ/kg, and >5000 IEQ/kg). The hypothesis to be tested is:

Null Hypothesis, H_0: $p_{reparixin} \leq p_{placebo}$ for all baseline IEQ/kg strata

Alternantive Hypothesis, H_A: $p_{reparixin} > p_{placebo}$ for at least one baseline IEQ/kg strata

The significance level used for statistical testing will be 2.5% and a one-sided test will be used. The 95% confidence interval for treatment proportions and the one-sided 95% confidence interval for the difference in treatment proportion between reparixin and placebo will be produced.

As a sensitivity analysis, the primary analysis will be repeated for the ITT population, dropping from the analysis any site with >20% of subjects not having data for the primary endpoint recorded; subjects will be considered to not have data recorded for the primary endpoint if they have discontinued the study prior to attending the Day 365 visit or if they have attended the Day 365 visit but did not have the primary endpoint recorded. The intent is to examine the sensitivity of the primary analysis to sites lacking a reasonable number of patients with data captured for the primary endpoint.

The relevance of the treatment-by-site interaction will be investigated using a logistic regression model which will include the main effect of treatment and IEQ/kg infused at IAT (<2500 IEQ/kg,

2500-5000 IEQ/kg, and >5000 IEQ/kg) and site as covariates. The analysis variable for treatment will be coded such that the reference treatment is placebo, the analysis variables for IEQ/kg infused at IAT will be coded such that the reference group is <2500 IEQ/kg, and the analysis variables for site will be coded such that the reference site is Site 1. The treatment-by-site interaction will be examined, and if not significant at the 0.10 α-level, will be removed from the model. The hypothesis to be examined is:

Null Hypothesis, H0: $\beta_{treatment} \leq 0$

Alternative Hypothesis, HA: $\beta_{treatment} > 0$

The treatment effect ($\beta_{treatment}$) will be declared significantly greater than 0 at the 0.025 α-level. A model parameter estimate and the corresponding standard error, p-value, and odds ratio with a one-sided 95% confidence interval will be presented for the treatment effect.

The logistic regression sensitivity analysis will also be performed for the ITT population, dropping from the analysis any site with >20% of subjects not having the primary endpoint recorded, using the same approach used for the sensitivity analysis of the primary endpoint.

As further sensitivity analysis, the primary endpoint analysis and the corresponding logistic regression analysis will be repeated including Site 01 only, which is the largest site with the greatest number of patients receiving IAT, having possibly the best treatment balance, having a high rate of primary endpoint data capture, and also being the site with the highest experience in the field and thus transplanting patients under highly reproducible surgical and clinical conditions. When performing the logistic regression analysis, site will no longer be considered a covariate in the model. The intent of these analyses is to examine the sensitivity of the primary analysis to the low enrollment/treatment balance, lesser experience level, and lower rates of retention which may be present at the other sites.

For both the primary and sensitivity analyses, patients who die or who discontinue before the primary endpoint assessment at Day 365 ± 14 days after IAT, or those who reach the Day 365 visit but have no primary endpoint assessment, will be treated as primary endpoint failures.

7.5.2 Secondary Variables

7.5.2.1 Area Under the Curve for C-peptide During First 4 Hours of a Mixed Meal Tolerance Test

C-peptide is to be collected at 9 time points (2 basal measurements and at 15, 30, 60, 90, 120, 180, and 240 minutes) during the first 4 hours of a mixed meal tolerance test on both Days 75 and 365 after IAT. For both Days 75 and 365, the area under the curve normalized by IEQ/kg infused during IAT will be computed as described in Section 5 of this SAP. AUC values at each day will be summarized descriptively by treatment group.

Analysis will be performed in two steps. First, the AUC normalized by IEQ/kg infused during IAT at each day will be compared between treatment groups using the t-test (two-sided tests at the 5% level of significance).

Second, the AUC normalized by IEQ/kg infused during IAT at the two days will be analyzed by a repeated measurements model using PROC MIXED within SAS®. The model will include fixed effect terms for site, time (Days 75 and 365), and treatment. Time 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 covariance 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-site interaction will be investigated and if the term is not significant at the 0.10 α-level, it will be excluded from the model. A logarithmic transformation of the data will be considered if found to be more suitable.

The adjusted least squares means and associated 95% confidence intervals will be estimated for each combination of day and treatment, and the adjusted least squares mean difference (reparixin minus placebo) and associated 95% confidence interval at each day will also be estimated. The treatment effect within each day will be tested using a two-sided test at the 5% level. The tests of the fixed effects in the model will also be presented.

7.5.2.2 Average Daily Insulin Requirements

The average daily insulin requirement (ADIR) will be computed by site personnel using data from the patient diary card and reported on Pages 24 and 24.1 for Days 75 and 365, respectively. ADIR values at each day will be summarized descriptively by treatment group.

ADIR will be analyzed in two steps as done for AUC of C-peptide. First, ADIR at each day will be compared between treatment groups using the t-test (two-sided tests at the 5% level of significance). Second, ADIR at Day 75 and Day 365 will be analyzed as repeated measures with a single repeated measurements model using PROC MIXED within SAS®. The model will include fixed effect terms for site, time (Days 75 and 365), and treatment. Time 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 covariance 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-site interaction will be investigated and if the term is not significant at the 0.10 α-level, it will be excluded from the model. A logarithmic transformation of the data will be considered if found to be more suitable.

The adjusted least squares means and associated 95% confidence intervals will be estimated for each combination of day and treatment, and the adjusted least squares mean difference (reparixin minus placebo) and associated 95% confidence interval at each day will also be estimated. The treatment effect within each day will be tested using a two-sided test at the 5% level. The tests of the fixed effects in the model will also be presented.

7.5.2.3 Time Course of Glucose, C-peptide, and Insulin

Glucose, C-peptide, and insulin are to be collected at 9 time points (2 basal measurements and at 15, 30, 60, 90, 120, 180, and 240 minutes) during the first 4 hours of a mixed meal tolerance test on both Days 75 and 365 after IAT.

The time course of each of these parameters at Days 75 and 365 will be analyzed separately with a repeated measurements model using PROC MIXED within SAS®. Each repeated measures model will include fixed effect terms for site, time (the average of 2 basal measurements at time 0 and at 15, 30, 60, 90, 120, 180, and 240 minutes), and treatment. Time 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 covariance 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-site interaction will be investigated and if the term is not significant at the 0.10 α-level, it will be excluded from the model. A logarithmic transformation of the data will be considered if found to be more suitable.

Separately for each day (Day 75 and Day 365), parameter values at each time point will be summarized descriptively by treatment group. The adjusted least squares means and associated 95% confidence intervals will be estimated for each combination of time and treatment, and the adjusted least squares mean difference (reparixin minus placebo) and associated 95% confidence interval at each time will also be estimated. The treatment effect within each time will be tested using a two-sided test at the 5% level. Adjusted least squares means for each treatment and the treatment effect, associated 95% confidence intervals, and a two-sided p-value testing treatment effect over all time points at the 5% level will also be presented. The tests of

the fixed effects in the model will also be presented. The time course of adjusted least squares means for each parameter will be plotted over time.

Separately for each day (Day 75 and Day 365), the peak (maximum) C-peptide and time to peak C-peptide value will be summarized descriptively. The time to peak value in minutes will be computed as the time of the peak value (HH:MM on a 24-hour clock) minus the end time of the mixed meal (HH:MM on a 24-hour clock) as recorded on the mixed meal tolerance test CRF.

7.5.2.4 β-cell Function (β Score)

The components of the β score and the total β score will be summarized descriptively at Day 75 ± 14 days and Day 365 ± 14 days after IAT. The Mann-Whitney U test will be used at each day (Days 75 and 365) in order to compare the distributions of the total β score of the two treatment groups. Testing will be two-sided at the 0.05 level of significance.

7.5.2.5 Proportion of Patients With HbA1c ≤6.5% at Day 365

HbA1c for Day 365 ± 14 days after IAT will be recorded on CRF Page 24.1 and this value will be used for summarization and analysis. The number and percentage of patients with HbA1c ≤6.5% at Day 365 ± 14 days after IAT, the 95% confidence interval for the proportion, the treatment effect (reparixin percentage minus placebo percentage), and the 95% confidence interval for the treatment effect will be presented by treatment group. The percentage of patients with HbA1c ≤6.5% at Day 365 ± 14 days after IAT will be compared between treatment groups using the Pearson chi-squared test (two-sided testing at the 0.05 level of significance). If assumptions regarding expected cell counts are not met, Yate's correction will be applied.

7.5.2.6 Cumulative Number of Severe Hypoglycemic Events From Day 75 to Day 365 After IAT

The cumulative number of severe hypoglycemic events from the Day 75 to Day 365 visits (as recorded on CRF Page 24.1) will be summarized descriptively by treatment group.

The effect of treatment on the rate of recurrent episodes of severe hypoglycaemia will be evaluated using an Andersen-Gill analysis with robust sandwich-type variance estimate. From the model, the estimated hazard ratio (reparixin versus placebo), associated 95% confidence interval, and a two-sided p-value assessing the significance of the hazard ratio (at the 5% level) will be presented.

7.5.2.7 Proportion of Patients With HbA1c ≤6.5% at Day 365 and Free of Severe Hypoglycemic Events From Day 75 Through Day 365

HbA1c for Day 365 ± 14 days after IAT and the number of severe hypoglycemic events from Day 75 through Day 365 will be recorded on CRF Page 24.1, and these values will be used for summarization and analysis. The number and percentage of patients with HbA1c ≤6.5% at Day 365 ± 14 days after IAT and who are free of severe hypoglycemic events from Day 75 ± 14 days to Day 365 ± 14 days after IAT, the 95% confidence interval for the proportion, the treatment effect (reparixin percentage minus placebo percentage), and the 95% confidence interval for the treatment effect will be presented by treatment group. The percentage of patients with HbA1c ≤6.5% at Day 365 ± 14 days after IAT and who are free of severe hypoglycemic events from Day 75 ± 14 days to Day 365 ± 14 days after IAT will be compared between treatment groups using the Pearson chi-squared test (two-sided testing at the 0.05 level of significance). If assumptions regarding expected cell counts are not met, Yate's correction will be applied.

7.6 Safety Analyses

The safety population will be used for the summarization and analysis of all safety data.

7.6.1 Adverse Events

All reported verbatim adverse event terms will be mapped to standard system organ classes and preferred terms using the MedDRA Dictionary as specified in the Data Management Plan for this protocol.

A treatment emergent adverse event (TEAE) is defined as any recorded adverse event which started on or after Day 1 of investigational product administration. If the start date of an adverse event is incomplete or missing, the event will be assumed to be a TEAE, unless the incomplete start date (month and/or year) or the stop date (complete or incomplete) clearly indicates that the event started prior to dosing.

The relationship of each adverse event to investigational product will be recorded as none, unlikely, possible, probable, or highly probable. If a relation is missing for an adverse event, the relation of the event to investigational product will conservatively be assumed to be highly probable for summarization.

The severity of each adverse event will be classified as mild, moderate, or severe. If the severity of an adverse event is missing, the severity of the event will conservatively be assumed to be severe for summarization.

Serious adverse events will be those events indicated as such on the CRF (a "Yes" response to "Serious").

An overview of TEAEs will summarize the number and percentage of patients and the number of events in the following categories: any TEAE, any TEAE by relationship to investigational product, any TEAE by severity, any serious TEAE, any serious TEAE by relationship to investigational product, any serious TEAE by severity, any TEAE resulting in early withdrawal from study, and death. For this overview, patients and events will be counted at each level of relationship to investigational product or severity at which an event is experienced (and not by worst relationship to investigational product and maximum severity).

The number and percentage of patients reporting at least one event and the number of events reported within system organ class and preferred term will be summarized by treatment group and in total for the following type of adverse events: TEAEs, TEAEs leading to discontinuation of the investigational product, TEAEs leading to early withdrawal from the study, serious TEAEs, serious TEAEs leading to discontinuation of the investigational product, and serious TEAEs leading to early withdrawal from the study. Patients will be counted only once within each system organ class and preferred term for which they experience at least one event.

A similar tabulation of these data, broken down further by relationship to investigational product, will be presented for TEAEs and serious TEAEs. Patients with multiple events within a particular system organ class or preferred term will be counted only under the category of their most related event within that system organ class or preferred term. Each category of relationship will be presented on a separate page or pages.

A similar tabulation of these data, broken down further by severity, will also be presented for TEAEs and serious TEAEs. Patients with multiple events within a particular system organ class or preferred term will be counted only under the category of their most severe event within that system organ class or preferred term. Each category of severity will be presented on a separate page or pages.

Listings will be presented by patient within treatment group for all adverse events, serious adverse events, adverse events leading to early withdrawal from the study, adverse events resulting in discontinuation of investigational product, and deaths.

7.6.2 Laboratory Data

7.6.2.1 Safety Laboratory Parameters

Safety laboratory parameters to be summarized include the following.

- Hematology: hematocrit, hemoglobin, platelets, red blood cells, white blood cells, and differential white blood cells count (neutrophils, lymphocytes, monocytes, eosinophils, basophils).

- Clinical chemistry: sodium, potassium, blood urea nitrogen, serum creatinine, total bilirubin, ALT, AST.
- Coagulation: activated partial thromboplastin time (aPTT) and international normalized ratio (INR).

Samples for safety laboratory parameters are taken at screening and hospital discharge. Each parameter will be summarized as the number and percentage of patients at each visit with out-of-range results and with out-of-range clinically significant (as reported by the investigator on the laboratory CRFs) results by treatment group and in total.

7.6.2.2 Post-transplant Safety Laboratory Parameters

Post-transplant safety laboratory parameters to be summarized include the following.

- AST, ALT, INR, PTT, fibrin degradation products, and C-reactive protein.

Samples for post-transplant safety laboratory parameters are taken at Days 1 through 7 post-transplant and on Day 75 ± 14 days for AST and ALT. Each parameter will be summarized descriptively at each applicable time point by treatment group and in total.

Change from baseline (screening) at each applicable follow-up time point will be summarized for AST and ALT by treatment group and in total. Change from baseline (screening) will be analyzed within a single repeated measurements model (for each of AST and ALT) using PROC MIXED within SAS®. The model will include fixed effect terms for site, time (Days 1 through 7 and 75), and treatment; the treatment by time interaction; the treatment by study site interaction if significant at the 0.10 α-level; baseline value as a covariate; and a random effect for patient. A compound symmetry covariance structure will be used to account for the multiple observations from the same patient.

The adjusted least squares means and associated 95% confidence intervals will be estimated for each combination of day and treatment, and the adjusted least squares mean difference (reparixin minus placebo) and associated 95% confidence interval at each day will also be estimated. The treatment effect within each day will be tested using a two-sided test at the 5% level. The tests of the fixed effects in the model will also be presented.

Observed values for all parameters will also be presented as box plots for each treatment group at each time point.

7.6.2.3 Albumin and Pre-albumin

Serum levels of albumin and pre-albumin are collected pre-transplant and on Day 75 ± 14 days and Day 365 ± 14 days. Each parameter will be summarized descriptively at each time point and change from pre-transplant to post-transplant time points (post-transplant value minus pre-transplant value) will be summarized descriptively by treatment group and in total.

Observed values will also be presented as box plots for each treatment group at each time point

7.6.3 Vital Signs

Vital signs, including systolic and diastolic blood pressure and heart rate, are measured at pre-transplant hospital admission (screening) and post-transplant hospital discharge. Each of these three parameters will be summarized descriptively at each time point and change from hospital admission to hospital discharge will be summarized descriptively by treatment group and in total.

Weight is collected at screening, Day 75, and Day 365. Observed values at each visit and change from screening to each follow-up visit will be summarized descriptively by treatment group and in total. Change from baseline (screening) will be analyzed as repeated measures with a single repeated measurements model using PROC MIXED within SAS®. The model will include fixed effect terms for site, time (Days 75 and 365), and treatment; the treatment by time interaction; the treatment by study site interaction if significant at the 0.10 α-level; baseline weight

as a covariate; and a random effect for patient. An appropriate covariance structure will be selected.

The adjusted least squares means and associated 95% confidence intervals will be estimated for each combination of day and treatment, and the adjusted least squares mean difference (reparixin minus placebo) and associated 95% confidence interval at each day will also be estimated. The treatment effect within each day will be tested using a two-sided test at the 5% level. The tests of the fixed effects in the model will also be presented.

7.6.4 Steatorrhea Severity

Summarization and analysis of steatorrhea severity will be performed separately at Day 75 and Day 365 after IAT by treatment group and in total. The number and percentage of patients in each steatorrhea severity category and the associated 95% confidence interval for the proportion of patients in each category will be presented.

7.6.5 Malnutrition Risk Level

Summarization and analysis of malnutrition risk level will be performed separately at Day 75 and Day 365 after IAT by treatment group and in total. The number and percentage of patients in each malnutrition risk level and the associated 95% confidence interval for the proportion of patients in each level will be presented.

7.6.6 Documented Hypoglycemic Episodes

The cumulative number of documented symptomatic hypoglycemic episodes and the cumulative number of asymptomatic hypoglycemia episodes occurring from Days 75 to 365 inclusive after IAT will be summarized descriptively by treatment group and in total. The cumulative number of episodes for a patient will be the number of episodes recorded on CRF Page 27.1. Treatment groups will be compared using a two-sided t-test or non-parametric Wilcoxon rank-sum test.

7.6.7 Diabetic Ketoacidosis-related Events

The cumulative number of diabetic ketoacidosis-related events occurring from Days 75 to 365 inclusive after IAT will be summarized descriptively by treatment group and in total. The cumulative number of diabetic ketoacidosis-related events for a patient will be the number of events recorded on CRF Page 27.1. Treatment groups will be compared using a two-sided t-test or non-parametric Wilcoxon rank-sum test.

7.7 Exploratory Analysis

The safety population will be used for the summarization and analysis of all exploratory data. Additional exploratory analyses beyond what is outlined below may be done.

7.7.1 Inflammatory Chemokines/Cytokines

Inflammatory chemokines/cytokines to be summarized include serum levels of CXCL8, CCL2 (MCP-1), CCL3, CCL4, CXCL10 (IP-10), CXCL9 (MIG), IL-6, IL-10, INF-γ, TNF-α, and IL-1β. Values are collected as 2 basal samples at pre-infusion hospital admission (6 to 24 hours apart) and at 6, 12, 24, 72, 120, and 168 hours after IAT.

Observed values at each time point and baseline (the average of the two basal samples) and change from baseline (follow-up value minus baseline value) at each post-transplant time point will be summarized descriptively by treatment group and in total.

Observed values will also be presented as box plots for each treatment group at each time point in order to graphically examine the time course of each parameter for each treatment group.

The relationship between inflammatory chemokines/cytokines response (including AUC, peak level, and maximum change from baseline) and exposure to reparixin may be explored graphically, with inflammatory chemokines/cytokine response plotted against total reparixin dose (in mg/kg) received.

- Area under the curve will be computed as follows. When parameter values are below the limit of detection, an appropriate value will be assumed in the calculation of area under the curve. Missing parameter values will be imputed via linear interpolation, and the average of the two basal samples (values, and mid-point of the sample times) will be used as the first sample in the computation of the AUC. Once these rules have been applied to the data, AUC for a parameter will be computed using the trapezoidal rule. For ease of interpretation, the AUC value obtained will be divided by the total time the scale is assessed for reporting purposes. Computation of AUC will be based on actual collection times, unless actual collection time is missing, in which case the scheduled collection time will be used.
- Peak level for any given inflammatory chemokine/cytokine parameter will be the maximum post-baseline value, where the baseline value will be the average of the two basal values.
- Maximum change from baseline for any given inflammatory chemokine/cytokine parameter will be the greatest change from baseline value, where change from baseline is computed as a post baseline value minus the baseline value and where baseline value is the average of the two basal values.

7.7.2 MicroRNA-375

MicroRNA-375 is collected pre-transplant and at 6, 12, 24, 72, 120, and 168 hours post-transplant.

Observed values at each time point and change from pre-transplant (follow-up value minus pre-transplant value) at each post-transplant time point will be summarized descriptively by treatment group and in total.

Observed values will also be presented as box plots for each treatment group at each time point in order to graphically examine the time course of MicroRNA-375 for each treatment group.

8 DATA MONITORING COMMITTEE

Safety and efficacy data will be reviewed on an ongoing basis by an independent DMC. Full details of the activities and responsibilities of the DMC are provided in the DMC Charter for the study.

The DMC will assess the safety and efficacy of the interventions during the trial and will monitor the overall conduct of the clinical trial. The DMC will provide recommendations to Dompé about stopping or continuing the trial. 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 review unblinded data. To this purpose, an independent statistician not affiliated with the conduct of the trial will liaise with the CRO statistician and will have access to those components of the database necessary to generate the reports for the DMC.
- Will be responsible for the ongoing (at least every 4 months) review of safety data throughout the trial. Primary among the safety data that will be reviewed are serious adverse events. In particular, the DMC will monitor the number of deaths for both arms of the study to assess whether mortality is consistent with historical data. The DMC also will give attention to post-surgical reoperation and clinically significant coagulation abnormalities (intra-abdominal as well as gastrointestinal hemorrhage have been reported to be the most common reasons for reoperation).
- Will review efficacy data in an ongoing manner to enable the assessment of the acceptability of safety in the context of emerging evidence about efficacy, i.e. measures of metabolic control and graft function.

- Will be advisory to Dompé and make recommendations to Dompé regarding the continuation of the trial and potential modifications to the design and conduct of the trial. These recommendations will be made in a manner to maintain confidentiality of emerging information about efficacy and safety, unless access to certain data is needed to enable Dompé to make decisions about the DMC recommendations. Dompé will be responsible for promptly reviewing the DMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in the study conduct are required

The independent statistician will use this SAP as a guideline for developing the outputs that are to be produced to facilitate DMC data review and deliberations.

9 INTERIM ANALYSES

Primary endpoint data will not be available until each patient reaches one year post randomization. Hence, it is expected that the majority of enrollment and treatment will be completed before meaningful evidence is available regarding treatment effect on the primary endpoint. Thus, traditional group sequential methods would have more limited utility in this setting.

The DMC will give careful consideration to the appropriateness of trial continuation if there is emerging evidence that reparixin is harmful. One component of this assessment will be the rate of unexpected deaths. Based on historical experiences from the published Minnesota series for 1977-2011 that includes 356 adults, 217 underwent pancreatectomy and IAT from 2006-2011. There was 1 unexpected death within 12 months of transplant. This translates to an estimated 0.5% rate.

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

- there are at least 2 unexpected deaths in the first 33 reparixin patients (an outcome with 1.2% chance if the true event rate is 0.5%);
- there are at least 3 unexpected deaths in reparixin patients at any time in the trial (an outcome with 0.2% chance in 50 reparixin patients if the true event rate is 0.5%).

In making any recommendations about termination, the totality of data will be considered, including the number of unexpected deaths in the control group, and the available evidence about efficacy and the overall safety profile.

The DMC will also give particular attention to clinically significant coagulation abnormalities, including but not limited to intra-abdominal or gastrointestinal hemorrhage. Early termination would be considered if the rate of clinically significant post-surgical complications that require reoperation reliably exceeds the rate expected currently in standard practice settings. Insights about that rate in standard practice settings will be provided by a literature review, and will include the publication for the Minnesota series, where intra-abdominal as well as gastrointestinal hemorrhage have been reported to be the most common reasons for reoperation (Sutherland, 2012).

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.

10 TABLES, FIGURES, AND LISTINGS FOR CLINICAL STUDY REPORT

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Table 14.2.2.1.A	Analysis of Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis	Intent to Treat Population Sensitivity Analysis
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Addendum to Statistical Analysis Plan

REP0112

A phase 2/3, multicenter, randomized, double-blind, placebo-controlled, parallel assignment study to assess the efficacy and safety of reparixin in pancreatic islet auto-transplantation.

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A phase 2/3, multicenter, randomized, double-blind, placebo-controlled, parallel assignment study to assess the efficacy and safety of reparixin in pancreatic islet auto-transplantation.

Protocol No: *REP0112*

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14 JUN 2018

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GLOSSARY OF ABBREVIATIONS

ADIR	Average Daily Insulin Requirements
AUC	Area Under the Curve
HbA1c	Glycated hemoglobin
Kg	Kilogram
IAT	Islet Auto-Transplantation
IEQ	Islet Equivalent
ITT	Intent to Treat
MMTT	Mixed Meal Tolerance Test
PP	Per Protocol
SAP	Statistical Analysis Plan

1 INTRODUCTION

This addendum to the statistical analysis plan (SAP) for Dompé farmaceutici S.p.A (Dompé) Protocol REP0112 describes the statistical methods to be used for analysis and reporting which are to be performed in addition to those described in the SAP.

The addendum to the SAP will be finalized and approved by the sponsor in addition to the statistician of the contract research organization appointed by Dompé prior to database lock.

2 DEFINITIONS AND DERIVED VARIABLES

Area Under the Curve (AUC), C-peptide: When C-peptide values are below the limit of detection (0.05 ng/mL), a value equal to the limit of detection will be assumed in the calculation of area under the curve. Missing C-peptide values will be imputed via linear interpolation, and the average of the two basal samples (values, and mid-point of sample times) will be used as the first sample in the computation of the AUC. Once these rules have been applied to the data, AUC for C-peptide will be computed using the trapezoidal rule. For ease of interpretation, the AUC value obtained will be divided by the total time the scale is assessed for reporting purposes. Computation of AUC will be based on actual collection times, unless actual collection time is missing, in which case the scheduled collection time will be used.

$AUC_{0\text{-}72H}$, miR-375: Missing miR-375 values will be imputed via linear interpolation. Once these rules have been applied to the data, $AUC_{0\text{-}72H}$ for miR-375 will be computed using the trapezoidal rule. Computation of $AUC_{0\text{-}72H}$ will be based on actual collection times, unless actual collection time is missing, in which case the scheduled collection time will be used.

Other definitions and derived variables are found within the applicable subsections of Section 3, Statistical Methods.

3 STATISTICAL METHODS

3.1 Methods for Multiplicity Correction in Analyses

All efficacy endpoints planned in this addendum are exploratory in nature and will be tested without a multiplicity correction being applied. In addition, all efficacy endpoints planned in the SAP will also be interpreted without the planned conditional sequential multiplicity correction being applied.

3.2 Efficacy Analyses

Summarization and analysis of efficacy parameters will be conducted for the ITT population (primary analysis) and PP population (secondary confirmatory analysis) by treatment group.

3.2.1 Primary Variable

The primary variable is the proportion of insulin-independent patients at Day 365 ± 14 days after IAT. In addition to the insulin-independence defined in the protocol, patients will be defined as being insulin-independent if the following criteria are satisfied:

- freedom from the need to take exogenous insulin for 14 or more consecutive days;
- a glycated hemoglobin (HbA1c) level ≤ 6.5%;
- a laboratory fasting glucose in the non-diabetic range (<126 mg/dL);
- a 90 minute blood glucose not exceeding 180 mg/dL from the MMTT. This measure is proposed as an alternative to finger-stick 2-hour post-prandial glucose on patient diary.

The same analyses defined in Section 7.5.1 of the SAP version 2.0 will be performed using the above insulin-independent definition.

In addition to the protocol and alternative insulin-independent definitions, the same analyses defined in Section 7.5.1 of the SAP version 2.0 will be run considering that Patient 0106 with sporadic and very low doses of insulin might be associated to "off insulin" criterion (freedom from the need to take exogenous insulin).

3.2.2 Secondary Variables

3.2.2.1 Area Under the Curve for C-peptide During First 4 Hours of a Mixed Meal Tolerance Test

C-peptide is to be collected at 9 time points (2 basal measurements and at 15, 30, 60, 90, 120, 180, and 240 minutes) during the first 4 hours of a mixed meal tolerance test on both Days 75 and 365 after IAT. For both Days 75 and 365, the AUC will be computed as described in Section 2. AUC values at each day will be summarized descriptively by treatment group, and analyzed as described in section 7.5.2.1 of the SAP version 2.0.

Change (absolute and percentage) in AUC values from Day 75 to Day 365 ($\Delta_{75\text{-}365}$) will be summarized descriptively by treatment group, and analyzed using a t-test to compare treatment groups (two-sided tests at the 5% level of significance) and using a general linear model which includes change in AUC as the response; treatment group and study site as fixed main effects; and the treatment by study site interaction if significant at the 0.10 α-level. Least squares means, standard errors, and associated 95% confidence intervals will be presented for each treatment group, along with the least square mean difference (reparixin minus placebo), standard error, associated 95% confidence interval, and p-value (two sided at the 5% level of significance). Data transformations will be considered, if appropriate.

Data will be plotted as a regression curve for $AUC_{0\text{-}240}$ versus IEQ/kg on days 75 and 365 after IAT by treatment group. The slope and intercept of the regression line and R^2 will be calculated and displayed on the figure. The p-value testing the slope for difference from zero will also be displayed. In addition, regression curve $AUC_{0\text{-}240}$ versus IEQ/kg will be plotted and analyzed only for patients receiving IEQ/kg ≤5000.

3.2.2.2 Average Daily Insulin Requirements

The average daily insulin requirement (ADIR) will be computed by site personnel using data from either the patient diary card or other appropriate source documents/information and reported on Pages 24 and 24.1 for Days 75 and 365, respectively.

In addition to the analyses described in Section 7.5.2.2 of SAP version 2.0, ADIR at Day 75 and Day 365 will be analyzed as repeated measures with a single repeated measurements model, as specified in the SAP, but also including IEQ/kg infused at IAT (<2500 IEQ/kg, 2500-5000 IEQ/kg, and >5000 IEQ/kg) as a fixed effect term. The importance of the treatment-by- IEQ/kg infused at IAT interaction will be investigated and if the term is not significant at the 0.10 α-level, it will be excluded from the model. If the addition of the IEQ/kg infused at IAT factors into the model cause the data to be too sparse for the model to converge, the repeated measures analysis will not be performed.

Summary statistics for ADIR at Day 75 and Day 365 will be provided for each IEQ/kg infused at IAT category (<2500 IEQ/kg, 2500-5000 IEQ/kg, and >5000 IEQ/kg) and treatment group. ADIR at Day 75 and Day 365 will be compared across treatment groups within each IEQ/kg infused at IAT category using a t-test.

3.2.2.3 Proportion of Patients With HbA1c ≤6.5% at Day 365

The percentage of patients with HbA1c ≤6.5% at Day 365 ± 14 days after IAT, as specified in Section 7.5.2.5 of SAP version 2.0, will also be compared between treatment groups using the Cochran-Mantel-Haenszel test stratified by baseline IEQ/kg (<2500 IEQ/kg, 2500-5000 IEQ/kg, and >5000 IEQ/kg). The hypothesis to be tested is:

Null Hypothesis, H_0: $p_{reparixin} \leq p_{placebo}$ for all baseline IEQ/kg strata

Alternative Hypothesis, H_A: $p_{reparixin} > p_{placebo}$ for at least one baseline IEQ/kg strata

The significance level used for statistical testing will be 2.5% and a one-sided test will be used. The 95% confidence interval for treatment proportions and the one-sided 95% confidence interval for the difference in treatment proportion between reparixin and placebo will be produced.

3.2.2.4 Proportion of Patients With HbA1c ≤7% at Day 365 and Free of Severe Hypoglycemic Events From Day 75 Through Day 365

The same analyses described in Section 7.5.2.7 of SAP version 2.0 will be used to analyze the proportion of patients with HbA1c ≤7% at Day 365 and free of severe hypoglycemic events from Day 75 through Day 365.

3.3 Exploratory Analysis

The safety population will be used for the summarization and analysis of all exploratory data.

3.3.1 Inflammatory Chemokines/Cytokines

Inflammatory chemokines/cytokines to be summarized include serum levels of CXCL8, CCL2 (MCP-1), CCL3, CCL4, CXCL10 (IP-10), CXCL9 (MIG), IL-6, IL-10, INF-γ, TNF-α, and IL-1β. Values are collected as 2 basal samples at pre-infusion hospital admission (6 to 24 hours apart) and at 6, 12, 24, 72, 120, and 168 hours after IAT. Mean values for each inflammatory chemokine/cytokine will be plotted for each sample time point by treatment group.

$AUC_{0\text{-}72H}$ will be computed as defined in Section 7.7.1 of SAP version 2.0. $AUC_{0\text{-}72H}$ for CCL2, IL-6 and IL-10 will be plotted versus IEQ as a regression curve for each treatment group. The slope and intercept of the regression line and R^2 will be calculated and displayed on the figure. The p-value testing the slope for difference from zero will also be displayed.

3.3.2 MicroRNA-375

MicroRNA-375 (miR-375) is collected pre-transplant and at 6, 12, 24, 72, 120, and 168 hours post-transplant. Mean miR-375 values will be plotted for each sample time point by treatment group. $AUC_{0\text{-}72H}$ for miR-375 will be calculated as specified in section 2 and plotted versus IEQ as a regression curve for each treatment group. The slope and intercept of the regression line and R^2 will be calculated and displayed on the figure. The p-value testing the slope for difference from zero will also be displayed.

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Table 14.2.16.2.1	Proportion of Patients With HbA1c ≤7.0% at Day 365 and Free of Severe Hypoglycemic Events From Day 75 to 365	Per Protocol Population

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Figure 14.4.1.2.1	Bar Chart of Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent	Per Protocol Population
Figure 14.4.1.1.2	Bar Chart of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation	Intent to Treat Population
Figure 14.4.1.2.2	Bar Chart of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation	Per Protocol Population
Figure 14.4.1.1.3	Bar Chart of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent	Intent to Treat Population
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Figure 14.4.4.3	Area Under the Curve for C-peptide at Day 75 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg	Intent to Treat Population
Figure 14.4.4.4	Area Under the Curve for C-peptide at Day 75 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg	Per Protocol Population
Figure 14.4.4.5	Area Under the Curve for C-peptide at Day 75 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg – Only Patients Receiving IEQ/kg ≤5000	Intent to Treat Population
Figure 14.4.4.6	Area Under the Curve for C-peptide at Day 75 During	Per Protocol Population

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Figure 14.4.5.3	Area Under the Curve for C-peptide at Day 365 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg	Intent to Treat Population
Figure 14.4.5.4	Area Under the Curve for C-peptide at Day 365 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg	Per Protocol Population
Figure 14.4.5.5	Area Under the Curve for C-peptide at Day 365 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg – Only Patients Receiving IEQ/kg ≤5000	Intent to Treat Population
Figure 14.4.5.6	Area Under the Curve for C-peptide at Day 365 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg – Only Patients Receiving IEQ/kg ≤5000	Per Protocol Population
Figure 14.4.11.1	Inflammatory Chemokines/ Cytokines, Plots of Mean Values Over Time	Safety Population
Figure 14.4.12.1	Area Under the Curve for CCL2, IL-6 and IL-10 During 72 Hours Following Transplant Versus IEQ, [Parameter Name]	Safety Population
Figure 14.4.15.1	miR-375, Plots of Mean Values over Time	Safety Population
Figure 14.4.15.2	Area Under the Curve for miR-375 During 72 Hours Following Transplant Versus IEQ	Safety Population

Section 16.2, Listings

Listing 16.2.6.1.1	Insulin Independence, Alternative Definition
Listing 16.2.6.3.3	Mixed Meal Tolerance Test, C-peptide Area Under the Curve (AUC), Alternative Computation
Listing 16.2.15.1	miR-375, Area Under the Curve (AUC)

Table 14.2.1.X Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation (IAT) – [Analysis Population]

	Reparixin (N = XX)			Placebo (N = XX)				Reparixin Minus Placebo	
	n	%	95% CI	n	%	95% CI	p-value	Estimate	95% CI
Insulin-independent at Day 365 Following Islet Auto-Transplantation [n (%)]									
Overall	XX	XXX.X	(XXX.X, XXX.X)	XX	XXX.X	(XXX.X, XXX.X)	0.XXX	XXX.X	(XXX.X, --)
<2500 IEQ/kg Infused at IAT	XX	XXX.X	(XXX.X, XXX.X)	XX	XXX.X	(XXX.X, XXX.X)			
2500-5000 IEQ/kg Infused at IAT	XX	XXX.X	(XXX.X, XXX.X)	XX	XXX.X	(XXX.X, XXX.X)			
>5000 IEQ/kg Infused at IAT	XX	XXX.X	(XXX.X, XXX.X)	XX	XXX.X	(XXX.X, XXX.X)			

Reference: 16.2.4.9, 16.2.6.1
Notes: p-value comparing proportion of insulin-independent patients at Day 365 following IAT between treatment groups using a Cochran-Mantel-Haenszel test controlling for IEQ/kg at baseline.

The following tables will be created from the above shell:

Table 14.2.1.1.1 Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent – Intent to Treat Population

- The "Notes" on this table will begin with the following sentence: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically."

Table 14.2.1.1.2 Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation – Intent to Treat Population

Table 14.2.1.1.3 Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent – Intent to Treat Population

- The "Notes" on this table will begin with the following sentence: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically."

Table 14.2.1.1.1.A Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent – Intent to Treat Population Sensitivity Analysis

- The "Notes" on this table will begin with the following sentences: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically. This sensitivity analysis excludes any site with >20% of subjects not having data for the primary endpoint recorded; subjects were considered to not have data recorded for the primary endpoint if they discontinued the study prior to attending the Day 365 visit or if they attended the Day 365 visit but did not have the primary endpoint recorded. Specific sites excluded were Sites XX, YY, and ZZ."

Table 14.2.1.1.2.A Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation – Intent to Treat Population Sensitivity Analysis

- The "Notes" on this table will begin with the following sentences: "This sensitivity analysis excludes any site with >20% of subjects not having data for the primary endpoint recorded; subjects were considered to not have data recorded for the primary endpoint if they discontinued the study prior to attending the Day 365 visit or if they attended the Day 365 visit but did not have the primary endpoint recorded. Specific sites excluded were Sites XX, YY, and ZZ."

Table 14.2.1.1.3.A Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent – Intent to Treat Population Sensitivity Analysis

- The "Notes" on this table will begin with the following sentences: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically. This sensitivity analysis excludes any site with >20% of subjects not having data for the primary endpoint recorded; subjects were considered to not have data recorded for the primary endpoint if they discontinued the study prior to attending the Day 365 visit or if they attended the Day 365 visit but did not have the primary endpoint recorded. Specific sites excluded were Sites XX, YY, and ZZ."

Table 14.2.1.1.1.B Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent – Intent to Treat Population Sensitivity Analysis, Site 01 Only

- The "Notes" on this table will begin with the following sentences: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically. This sensitivity analysis includes only Site 01."

Table 14.2.1.1.2.B Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation – Intent to Treat Population Sensitivity Analysis, Site 01 Only

- The "Notes" on this table will begin with the following sentence: "This sensitivity analysis includes only Site 01."

Table 14.2.1.1.3.B Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent – Intent to Treat Population Sensitivity Analysis, Site 01 Only

- The "Notes" on this table will begin with the following sentences: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically. This sensitivity analysis includes only Site 01."

Table 14.2.1.2.1 Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent – Per Protocol Population

- The "Notes" on this table will begin with the following sentence: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically."

Table 14.2.1.2.2 Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation – Per Protocol Population

Table 14.2.1.2.3 Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent – Per Protocol Population

- The "Notes" on this table will begin with the following sentence: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically."

Table 14.2.2.X Analysis of Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis – [Analysis Population]

Model Variable	Estimate of Beta	Standard Error of Beta	p-value	Odds Ratio	95% Confidence Interval for Odds Ratio
Reparixin	X.XXX	X.XXX	0.XXX	X.XXX	(X.XXX, --)
2,500 to 5,000 IEQ/kg Infused at IAT	X.XXX	X.XXX	0.XXX	X.XXX	(X.XXX, --)
>5,000 IEQ/kg Infused at IAT	X.XXX	X.XXX	0.XXX	X.XXX	(X.XXX, --)
Study Site 2	X.XXX	X.XXX	0.XXX	X.XXX	(X.XXX, --)
Study Site 3	X.XXX	X.XXX	0.XXX	X.XXX	(X.XXX, --)
Study Site 4	X.XXX	X.XXX	0.XXX	X.XXX	(X.XXX, --)
Study Site 5	X.XXX	X.XXX	0.XXX	X.XXX	(X.XXX, --)

Reference: 16.2.4.9, 16.2.6.1

Notes: Treatment groups compared using a logistic regression model with the main effect of treatment and IEQ/kg infused at IAT and study site as covariates. Odds of achieving insulin-independence at Day 365 following islet auto-transplantation are presented for reparixin relative to placebo; for patients with 2,500 to 5,000 IEQ/kg infused at IAT relative to patients with <2,500 IEQ/kg infused at IAT; for patients with >5,000 IEQ/kg infused at IAT relative to patients with <2,500 IEQ/kg infused at IAT; and for each study site versus Study Site 1.

The following tables will be created from the above shell:

Table 14.2.2.1.1 Analysis of Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis, With Patient 0106 Included as Insulin Independent – Intent to Treat Population

- The "Notes" on this table will begin with the following sentence: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically."

Table 14.2.2.1.2 Analysis of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis – Intent to Treat Population

Table 14.2.2.1.3 Analysis of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis, With Patient 0106 Included as Insulin Independent – Intent to Treat Population

- The "Notes" on this table will begin with the following sentence: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically."

Table 14.2.2.1.1.A Analysis of Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis, With Patient 0106 Included as Insulin Independent – Intent to Treat Population Sensitivity Analysis

- The "Notes" on this table will begin with the following sentences: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically. This sensitivity analysis excludes any site with >20% of subjects not having data for the primary endpoint recorded; subjects were considered to not have data recorded for the primary endpoint if they discontinued the study prior to attending the Day 365 visit or if they attended the Day 365 visit but did not have the primary endpoint recorded. Specific sites excluded were Sites XX, YY, and ZZ."

Table 14.2.2.1.2.A Analysis of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis – Intent to Treat Population Sensitivity Analysis

- The "Notes" on this table will begin with the following sentences: "This sensitivity analysis excludes any site with >20% of subjects not having data for the primary endpoint recorded; subjects were considered to not have data recorded for the primary endpoint if they discontinued the study prior to attending the Day 365 visit or if they attended the Day 365 visit but did not have the primary endpoint recorded. Specific sites excluded were Sites XX, YY, and ZZ."

Table 14.2.2.1.3.A Analysis of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis, With Patient 0106 Included as Insulin Independent – Intent to Treat Population Sensitivity Analysis

- The "Notes" on this table will begin with the following sentences: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically. This sensitivity analysis excludes any site with >20% of subjects not having data for the primary endpoint recorded; subjects were considered to not have data recorded for the primary endpoint if they discontinued the study prior to attending the Day 365 visit or if they attended the Day 365 visit but did not have the primary endpoint recorded. Specific sites excluded were Sites XX, YY, and ZZ."

Table 14.2.2.1.1.B Analysis of Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis, With Patient 0106 Included as Insulin Independent – Intent to Treat Population Sensitivity Analysis, Site 01 Only

- The "Notes" on this table will begin with the following sentences: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically. This sensitivity analysis includes only Site 01."

- The model notes in the table should read as follows: Treatment groups compared using a logistic regression model with the main effect of treatment and IEQ/kg infused at IAT as a covariate. Odds of achieving insulin-independence at Day 365 following islet auto-transplantation are presented for

reparixin relative to placebo; for patients with 2,500 to 5,000 IEQ/kg infused at IAT relative to patients with <2,500 IEQ/kg infused at IAT; and for patients with >5,000 IEQ/kg infused at IAT relative to patients with <2,500 IEQ/kg infused at IAT.

- The "Study Site X" rows will not appear in the table.

Table 14.2.2.1.2.B Analysis of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis – Intent to Treat Population Sensitivity Analysis, Site 01 Only

- The "Notes" on this table will begin with the following sentence: "This sensitivity analysis includes only Site 01."
- The model notes in the table should read as follows: Treatment groups compared using a logistic regression model with the main effect of treatment and IEQ/kg infused at IAT as a covariate. Odds of achieving insulin-independence at Day 365 following islet auto-transplantation are presented for reparixin relative to placebo; for patients with 2,500 to 5,000 IEQ/kg infused at IAT relative to patients with <2,500 IEQ/kg infused at IAT; and for patients with >5,000 IEQ/kg infused at IAT relative to patients with <2,500 IEQ/kg infused at IAT.
- The "Study Site X" rows will not appear in the table.

Table 14.2.2.1.3.B Analysis of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis, With Patient 0106 Included as Insulin Independent – Intent to Treat Population Sensitivity Analysis, Site 01 Only

- The "Notes" on this table will begin with the following sentences: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically. This sensitivity analysis includes only Site 01."
- The model notes in the table should read as follows: Treatment groups compared using a logistic regression model with the main effect of treatment and IEQ/kg infused at IAT as a covariate. Odds of achieving insulin-independence at Day 365 following islet auto-transplantation are presented for reparixin relative to placebo; for patients with 2,500 to 5,000 IEQ/kg infused at IAT relative to patients with <2,500 IEQ/kg infused at IAT; and for patients with >5,000 IEQ/kg infused at IAT relative to patients with <2,500 IEQ/kg infused at IAT.
- The "Study Site X" rows will not appear in the table.

Table 14.2.2.2.1 Analysis of Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis, With Patient 0106 Included as Insulin Independent – Per Protocol Population

- The "Notes" on this table will begin with the following sentence: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically."

Table 14.2.2.2.2 Analysis of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis – Per Protocol Population

Table 14.2.2.2.3 Analysis of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, Sensitivity Analysis, With Patient 0106 Included as Insulin Independent – Per Protocol Population

- The "Notes" on this table will begin with the following sentence: "Patient 0106 is considered off-insulin because of low doses of insulin administered sporadically."

Table 14.2.3.X Area Under the Curve for C-peptide (Alternate Computation) During First 4 Hours of a Mixed Meal Tolerance Test – [Analysis Population]

	Reparixin (N = XX)	Placebo (N = XX)
AUC at Day 75 [unit to be determined]		
N	XX	XX
Mean	XXX.XX	XXX.XX
SD	XXX.XXX	XXX.XXX
Median	XXX.XX	XXX.XX
Min	XXX.X	XXX.X
Max	XXX.X	XXX.X
p-value Comparing Treatments Using t-test	0.XXX	
LS Mean (SE)	XXX.XX (XX.XX)	XXX.XX (XX.XX)
95% CI for LS Mean	(XXX.XX, XXX.XX)	(XXX.XX, XXX.XX)
LS Mean Difference, Reparixin – Placebo (SE)	XXX.XX (XX.XX)	
95% CI for LS Mean Difference	(XXX.XX, XXX.XX)	
p-value	0.XXX	

Reference: 16.2.6.3.2
Note: AUC = Area Under the Curve, LS = Least Squares, SE = Standard Error, CI = Confidence Interval. Least squares means, standard errors, and confidence intervals come from a mixed repeated measures model which includes AUC as the response; treatment group, time, and study site as fixed main effects; the treatment by time interaction; the treatment by study site interaction if significant at the 0.10 α-level; patient as a random effect; and uses a [to be specified] covariance structure.

Table 14.2.3.X Area Under the Curve for Serum C-peptide (Alternate Computation) During First 4 Hours of a Mixed Meal Tolerance Test – [Analysis Population]

	Reparixin (N = XX)	Placebo (N = XX)
AUC at Day 365 [unit to be determined]		
N	XX	XX
Mean	XXX.XX	XXX.XX
SD	XXX.XXX	XXX.XXX
Median	XXX.XX	XXX.XX
Min	XXX.X	XXX.X
Max	XXX.X	XXX.X
p-value Comparing Treatments Using t-test	0.XXX	
LS Mean (SE)	XXX.XX (XX.XX)	XXX.XX (XX.XX)
95% CI for LS Mean	(XXX.XX, XXX.XX)	(XXX.XX, XXX.XX)
LS Mean Difference, Reparixin – Placebo (SE)	XXX.XX (XX.XX)	
95% CI for LS Mean Difference	(XXX.XX, XXX.XX)	
p-value	0.XXX	
Final Model p-values		
Treatment	0.XXX	
Time	0.XXX	
Study Site	0.XXX	
Treatment by Time Interaction	0.XXX	
Treatment by Study Site Interaction	0.XXX	
[only included in final model and displayed if significant at the 0.10 α-level]		

Reference: 16.2.6.3.2

Note: AUC = Area Under the Curve, LS = Least Squares, SE = Standard Error, CI = Confidence Interval. Least squares means, standard errors, and confidence intervals come from a mixed repeated measures model which includes AUC as the response; treatment group, time, and study site as fixed main effects; the treatment by time interaction; the treatment by study site interaction if significant at the 0.10 α-level; patient as a random effect; and uses a [to be specified] covariance structure.

The following tables will be created from the above shell:

Table 14.2.3.1.1 Area Under the Curve for C-peptide (Alternate Computation) During First 4 Hours of a Mixed Meal Tolerance Test – Intent to Treat Population

Table 14.2.3.2.1 Area Under the Curve for C-peptide (Alternate Computation) During First 4 Hours of a Mixed Meal Tolerance Test – Per Protocol Population

Table 14.2.3.3.X Change in Area Under the Curve for C-peptide (Alternate Computation) During First 4 Hours of a Mixed Meal Tolerance Test – [Analysis Population]

	Reparixin (N = XX)	Placebo (N = XX)
Change in AUC (Day 365 – Day 75) [unit to be determined]		
N	XX	XX
Mean	XXX.XX	XXX.XX
SD	XXX.XXX	XXX.XXX
Median	XXX.XX	XXX.XX
Min	XXX.X	XXX.X
Max	XXX.X	XXX.X
p-value Comparing Treatments Using t-test	0.XXX	
LS Mean (SE)	XXX.XX (XX.XX)	XXX.XX (XX.XX)
95% CI for LS Mean	(XXX.XX, XXX.XX)	(XXX.XX, XXX.XX)
LS Mean Difference, Reparixin – Placebo (SE)	XXX.XX (XX.XX)	
95% CI for LS Mean Difference	(XXX.XX, XXX.XX)	
p-value	0.XXX	
Final Model p-values		
Treatment	0.XXX	
Study Site	0.XXX	
Treatment by Study Site Interaction [only included in final model and displayed if significant at the 0.10 α-level]	0.XXX	

Page will be repeated for Percent Change in AUC (Day 365 – Day 75)

Reference: 16.2.6.3.2
Note: AUC = Area Under the Curve, LS = Least Squares, SE = Standard Error, CI = Confidence Interval. Least squares means, standard errors, and confidence intervals come from a general linear model which includes change in AUC as the response; treatment group and study site as fixed main effects; and the treatment by study site interaction if significant at the 0.10 α-level.

Table 14.2.3.3.1 Change in Area Under the Curve for C-peptide (Alternate Computation) During First 4 Hours of a Mixed Meal Tolerance Test – Intent to Treat Population

Table 14.2.3.3.2 Change in Area Under the Curve for C-peptide (Alternate Computation) During First 4 Hours of a Mixed Meal Tolerance Test – Per Protocol Population

Table 14.2.4.X Average Daily Insulin Requirements, Stratified by IEQ/kg – [Analysis Population]

	Reparixin (N = XX)	Placebo (N = XX)
Average Daily Insulin Requirement at Day 75 (IU/kg/day)		
<2500 IEQ/kg Infused at IAT		
N	XX	XX
Mean	X.XXX	X.XXX
SD	X.XXXX	X.XXXX
Median	X.XXX	X.XXX
Min	X.XX	X.XX
Max	X.XX	X.XX
p-value Comparing Treatments Using t-test	0.XXX	
LS Mean (SE)	X.XXX (X.XXXX)	X.XXX (X.XXXX)
95% CI for LS Mean	(X.XXX, X.XXX)	(X.XXX, X.XXX)
LS Mean Difference, Reparixin – Placebo (SE)	X.XXX (X.XXXX)	
95% CI for LS Mean Difference	(X.XXX, X.XXX)	
p-value	0.XXX	
2500-5000 IEQ/kg Infused at IAT		
N	XX	XX
Mean	X.XXX	X.XXX
SD	X.XXXX	X.XXXX
Median	X.XXX	X.XXX
Min	X.XX	X.XX
Max	X.XX	X.XX
p-value Comparing Treatments Using t-test	0.XXX	
LS Mean (SE)	X.XXX (X.XXXX)	X.XXX (X.XXXX)
95% CI for LS Mean	(X.XXX, X.XXX)	(X.XXX, X.XXX)
LS Mean Difference, Reparixin – Placebo (SE)	X.XXX (X.XXXX)	
95% CI for LS Mean Difference	(X.XXX, X.XXX)	
p-value	0.XXX	

>5000 IEQ/kg Infused at IAT		
N	XX	XX
Mean	X.XXX	X.XXX
SD	X.XXXX	X.XXXX
Median	X.XXX	X.XXX
Min	X.XX	X.XX
Max	X.XX	X.XX
p-value Comparing Treatments Using t-test	0.XXX	
LS Mean (SE)	X.XXX (X.XXXX)	X.XXX (X.XXXX)
95% CI for LS Mean	(X.XXX, X.XXX)	(X.XXX, X.XXX)
LS Mean Difference, Reparixin – Placebo (SE)	X.XXX (X.XXXX)	
95% CI for LS Mean Difference	(X.XXX, X.XXX)	
p-value	0.XXX	
Overall		
N	XX	XX
Mean	X.XXX	X.XXX
SD	X.XXXX	X.XXXX
Median	X.XXX	X.XXX
Min	X.XX	X.XX
Max	X.XX	X.XX
p-value Comparing Treatments Using t-test	0.XXX	
LS Mean (SE)	X.XXX (X.XXXX)	X.XXX (X.XXXX)
95% CI for LS Mean	(X.XXX, X.XXX)	(X.XXX, X.XXX)
LS Mean Difference, Reparixin – Placebo (SE)	X.XXX (X.XXXX)	
95% CI for LS Mean Difference	(X.XXX, X.XXX)	
p-value	0.XXX	

Reference: 16.2.6.1, 16.2.6.4

Note: LS = Least Squares, SE = Standard Error, CI = Confidence Interval. Least squares means, standard errors, and confidence intervals come from a mixed repeated measures model which includes average daily insulin requirement (IU/kg/day) as the response; treatment group, time, IEQ/kg infused at IAT, and study site as fixed main effects; the treatment by time interaction; the treatment by study site interaction and treatment by IEQ/kg infused at IAT interaction if significant at the 0.10 α-level; patient as a random effect; and uses a [to be specified] covariance structure.

Table 14.2.4.X Average Daily Insulin Requirements, Stratified by IEQ/kg – [Analysis Population]

	Reparixin (N = XX)	Placebo (N = XX)
Average Daily Insulin Requirement at Day 365 (IU/kg/day)		
<2500 IEQ/kg Infused at IAT		
N	XX	XX
Mean	X.XXX	X.XXX
SD	X.XXXX	X.XXXX
Median	X.XXX	X.XXX
Min	X.XX	X.XX
Max	X.XX	X.XX
p-value Comparing Treatments Using t-test	0.XXX	
LS Mean (SE)	X.XXX (X.XXXX)	X.XXX (X.XXXX)
95% CI for LS Mean	(X.XXX, X.XXX)	(X.XXX, X.XXX)
LS Mean Difference, Reparixin – Placebo (SE)	X.XXX (X.XXXX)	
95% CI for LS Mean Difference	(X.XXX, X.XXX)	
p-value	0.XXX	
2500-5000 IEQ/kg Infused at IAT		
N	XX	XX
Mean	X.XXX	X.XXX
SD	X.XXXX	X.XXXX
Median	X.XXX	X.XXX
Min	X.XX	X.XX
Max	X.XX	X.XX
p-value Comparing Treatments Using t-test	0.XXX	
LS Mean (SE)	X.XXX (X.XXXX)	X.XXX (X.XXXX)
95% CI for LS Mean	(X.XXX, X.XXX)	(X.XXX, X.XXX)
LS Mean Difference, Reparixin – Placebo (SE)	X.XXX (X.XXXX)	
95% CI for LS Mean Difference	(X.XXX, X.XXX)	
p-value	0.XXX	

>5000 IEQ/kg Infused at IAT		
N	XX	XX
Mean	X.XXX	X.XXX
SD	X.XXXX	X.XXXX
Median	X.XXX	X.XXX
Min	X.XX	X.XX
Max	X.XX	X.XX
p-value Comparing Treatments Using t-test	0.XXX	
LS Mean (SE)	X.XXX (X.XXXX)	X.XXX (X.XXXX)
95% CI for LS Mean	(X.XXX, X.XXX)	(X.XXX, X.XXX)
LS Mean Difference, Reparixin – Placebo (SE)	X.XXX (X.XXXX)	
95% CI for LS Mean Difference	(X.XXX, X.XXX)	
p-value	0.XXX	
Overall		
N	XX	XX
Mean	X.XXX	X.XXX
SD	X.XXXX	X.XXXX
Median	X.XXX	X.XXX
Min	X.XX	X.XX
Max	X.XX	X.XX
p-value Comparing Treatments Using t-test	0.XXX	
LS Mean (SE)	X.XXX (X.XXXX)	X.XXX (X.XXXX)
95% CI for LS Mean	(X.XXX, X.XXX)	(X.XXX, X.XXX)
LS Mean Difference, Reparixin – Placebo (SE)	X.XXX (X.XXXX)	
95% CI for LS Mean Difference	(X.XXX, X.XXX)	
p-value	0.XXX	
Final Model p-values		
Treatment	0.XXX	
Time	0.XXX	
Study Site	0.XXX	
IEQ/kg Infused at IAT	0.XXX	
Treatment by Time Interaction	0.XXX	

Treatment by Study Site Interaction [only included in final model and displayed if significant at the 0.10 α-level]	0.XXX
Treatment by IEQ/kg Infused at IAT Interaction [only included in final model and displayed if significant at the 0.10 α-level]	0.XXX

Reference: 16.2.6.1, 16.2.6.4
Note: LS = Least Squares, SE = Standard Error, CI = Confidence Interval. Least squares means, standard errors, and confidence intervals come from a mixed repeated measures model which includes average daily insulin requirement (IU/kg/day) as the response; treatment group, time, IEQ/kg infused at IAT, and study site as fixed main effects; the treatment by time interaction; the treatment by study site interaction and treatment by IEQ/kg infused at IAT interaction if significant at the 0.10 α-level; patient as a random effect; and uses a [to be specified] covariance structure.

The following tables will be created from the above shell:

Table 14.2.4.1.1 Average Daily Insulin Requirements, Stratified by IEQ/kg – Intent to Treat Population
Table 14.2.4.2.1 Average Daily Insulin Requirements, Stratified by IEQ/kg – Per Protocol Population

Table 14.2.14.X Proportion of Patients With HbA1c ≤6.5% at Day 365, Stratified by IEQ/kg – [Analysis Population]

	Reparixin (N = XX)			Placebo (N = XX)				Reparixin Minus Placebo	
	n	%	95% CI	n	%	95% CI	p-value	Estimate	95% CI
HbA1c ≤6.5% at Day 365 [n (%)]									
Overall	XX	XXX.X	(XXX.X, XXX.X)	XX	XXX.X	(XXX.X, XXX.X)	0.XXX	XXX.X	(XXX.X, --)
<2500 IEQ/kg Infused at IAT	XX	XXX.X	(XXX.X, XXX.X)	XX	XXX.X	(XXX.X, XXX.X)			
2500-5000 IEQ/kg Infused at IAT	XX	XXX.X	(XXX.X, XXX.X)	XX	XXX.X	(XXX.X, XXX.X)			
>5000 IEQ/kg Infused at IAT	XX	XXX.X	(XXX.X, XXX.X)	XX	XXX.X	(XXX.X, XXX.X)			

Reference: 16.2.6.2
Notes: p-value comparing proportion of patients with HbA1c ≤6.5% at Day 365 between treatment groups using a Cochran-Mantel-Haenszel test controlling for IEQ/kg at baseline.

The following tables will be created using the above shell:

Table 14.2.14.1.1Proportion of Patients With HbA1c ≤6.5% at Day 365, Stratified by IEQ/kg – Intent to Treat Population
Table 14.2.14.2.1Proportion of Patients With HbA1c ≤6.5% at Day 365, Stratified by IEQ/kg – Per Protocol Population

Table 14.2.16.X Proportion of Patients With HbA1c ≤7.0% at Day 365 and Free of Severe Hypoglycemic Events From Day 75 to 365 Inclusive – [Analysis Population]

	Reparixin (N = XX)	Placebo (N = XX)
HbA1c ≤7.0% at Day 365 and Free of Severe Hypoglycemic Events From Day 75 to 365 Inclusive [n (%)]		
n (%) of Patients	XX (XXX.X)	XX (XXX.X)
95% Confidence Interval for Proportion	(XXX.X, XXX.X)	(XXX.X, XXX.X)
Treatment Effect (Reparixin minus Placebo)	XXX.X	
95% Confidence Interval for Treatment Effect	(XXX.X, XXX.X)	
p-value	0.XXX	

Reference: 16.2.6.1, 16.2.6.2, 16.2.6.6
Note: p-value comparing treatment groups using the Pearson chi-squared test.

The following tables will be created from the above shell:

Table 14.2.16.1.1 Proportion of Patients With HbA1c ≤7.0% at Day 365 and Free of Severe Hypoglycemic Events From Day 75 to 365 Inclusive – Intent to Treat Population
Table 14.2.16.2.1 Proportion of Patients With HbA1c ≤7.0% at Day 365 and Free of Severe Hypoglycemic Events From Day 75 to 365 Inclusive – Per Protocol Population

Figure 14.4.1.X Bar Chart of Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation

Figure Type: Bar Chart

X-axis: Overall and IEQ/kg Infused at IAT (<2500 IEQ/kg, 2500-5000 IEQ/kg, >5000 IEQ/kg). Overall and within each IEQ/kg group there will be a bar chart with bars for reparixin and placebo appearing with different color fill and an accompanying legend.

Y-axis: Percentage of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation

The following figures will be created from the above details:

Figure 14.4.1.1.1 Bar Chart of Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent – Intent to Treat Population
Reference: 14.2.1.1.1, 16.2.4.9, 16.2.6.1

Figure 14.4.1.1.2 Bar Chart of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation – Intent to Treat Population
Reference: 14.2.1.1.2, 16.2.4.9, 16.2.6.1

Figure 14.4.1.1.3 Bar Chart of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent – Intent to Treat Population
Reference: 14.2.1.1.3, 16.2.4.9, 16.2.6.1

Figure 14.4.1.2.1 Bar Chart of Proportion of Insulin-independent Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent – Per Protocol Population
Reference: 14.2.1.2.1, 16.2.4.9, 16.2.6.1

Figure 14.4.1.2.2 Bar Chart of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation – Per Protocol Population
Reference: 14.2.1.2.2, 16.2.4.9, 16.2.6.1

Figure 14.4.1.2.3 Bar Chart of Proportion of Insulin-independent (Alternate Definition) Patients at Day 365 Following Islet Auto-Transplantation, With Patient 0106 Included as Insulin Independent – Per Protocol Population
Reference: 14.2.1.2.3, 16.2.4.9, 16.2.6.1

Figure 14.4.X.X Area Under the Curve for C-peptide at Day 75 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg – [Analysis Population]

X-axis: IEQ/kg

Y-axis: Area Under the Curve (unit to be determined)

Data will be plotted as a regression curve for AUC versus IEQ/kg on days 75 and 365 after IAT by treatment group. The slope and intercept of the regression line and R^2 will be calculated and displayed on the figure. The p-value testing the slope for difference from zero will also be displayed.

The following figures will be created from the above details:

Figure 14.4.4.3 Area Under the Curve for C-peptide at Day 75 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg – Intent to Treat Population
Reference: 16.2.6.3.2

Figure 14.4.4.4 Area Under the Curve for C-peptide at Day 75 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg – Per Protocol Population
Reference: 16.2.6.3.2

Figure 14.4.4.5 Area Under the Curve for C-peptide at Day 75 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg – Only Patients Receiving IEQ/kg ≤5000 – Intent to Treat Population
Reference: 16.2.6.3.2

Figure 14.4.4.6 Area Under the Curve for C-peptide at Day 75 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg – Only Patients Receiving IEQ/kg ≤5000 – Per Protocol Population
Reference: 16.2.6.3.2

Figure 14.4.5.3 Area Under the Curve for C-peptide at Day 365 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg – Intent to Treat Population
Reference: 16.2.6.3.2

Figure 14.4.5.4 Area Under the Curve for C-peptide at Day 365 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg – Per Protocol Population
Reference: 16.2.6.3.2

Figure 14.4.5.5 Area Under the Curve for C-peptide at Day 365 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg – Only Patients Receiving IEQ/kg ≤5000 – Intent to Treat Population
Reference: 16.2.6.3.2

Figure 14.4.5.6 Area Under the Curve for C-peptide at Day 365 During First 4 Hours of a Mixed Meal Tolerance Test and Not Corrected for IEQ/kg Versus IEQ/kg – Only Patients Receiving IEQ/kg ≤5000 – Per Protocol Population
Reference: 16.2.6.3.2

Figure 14.4.12.1 Area Under the Curve for CCL2, IL-6 and IL-10 During 72 Hours Following Transplant Versus IEQ, [Parameter Name] – Safety Population
Reference: 16.2.14

Programming note, this figure is versus IEQ, not IEQ/kg.

Figure 14.4.15.2 Area Under the Curve for miR-375 During 72 Hours Following Transplant Versus IEQ – Safety Population
Reference: 16.2.15

Programming note, this figure is versus IEQ, not IEQ/kg.

Figure 14.4.11.1 Inflammatory Chemokines / Cytokines, Plots of Mean Values Over Time – Safety Population

X-axis: Time Point (Basal, 6 Hours Post, 12 Hours Post, 24 Hours Post, 72 Hours Post, 120 Hours Post, and 168 Hours Post)

Y-axis: Parameter (unit), mean ± standard error

Reference: 14.3.12, 16.2.13

Notes: Plots for mean values ± standard error bars will be presented for each treatment group at each time point (where "Basal" is the single baseline which is the average of the two basal values). Each treatment group will be in a different color with an accompanying legend. Separate pages will be created for CXCL8 (pg/mL), CCL2 (MCP-1) (pg/mL), CCL3 (pg/mL), CCL4 (pg/mL), CXCL10 (IP-10) (pg/mL), CXCL9 (MIG) (pg/mL), IL-6 (pg/mL), IL-10 (pg/mL), INF-γ (pg/mL), TNF-α (pg/mL), and IL- 1β (pg/mL).

Figure 14.4.15.1 miR-375, Plots of Mean Values Over Time – Safety Population

X-axis: Time Point (Pre-transplant 1, 6 Hours Post, 12 Hours Post, 24 Hours Post, 72 Hours Post, 120 Hours Post, and 168 Hours Post)

Y-axis: miR-375 (copies/mL), mean ± standard error

Reference: 14.3.13, 16.2.15

Notes: Plots for mean values ± standard error will be presented for each treatment group at each time point. Each treatment group will be in a different color with an accompanying legend.

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Listing 16.2.6.1.1 Insulin Independence, Alternative Definition

Treatment: Reparixin or Placebo

Patient Number	Visit	Date (Day) of Visit	Insulin Ind, Alternative Definition
XXXX	Day 365	DDMMMYYYY (XXX)	Yes
XXXX	Day 365	DDMMMYYYY (XXX)	Yes
XXXX	Day 365	DDMMMYYYY (XXX)	Yes
	.		
	.		
	.		

Reference: CRF Page 24 and 24.1 and listings 16.2.6.2, 16.2.6.3.1 and 16.2.6.4.
Notes: Ind = Independent. Alternative definition: freedom from the need to take exogenous insulin for 14 or more consecutive days; a glycated hemoglobin (HbA1c) level ≤ 6.5%; a laboratory fasting glucose in the non-diabetic range (<126 mg/dL); and a 90 minute blood glucose not exceeding 180 mg/dL from the MMTT. This measure is proposed as an alternative to finger-stick 2-hour post-prandial glucose on patient diary.

Listing 16.2.6.3.3Mixed Meal Tolerance Test, C-peptide Area Under the Curve (AUC), Alternative Computation

Treatment: Reparixin or Placebo

Patient Number	IEQ/kg Infused During IAT	Visit	Mixed Meal Administration Date (Day)	End Time	Time Point	Sample Time	C-peptide (ng/mL)	Area Under the Curve (unit)
XXXX	XXXXX	Day XXX	DDMMMYYYY (XXX)	HH:MM	Basal 1	HH:MM	X.XX	XXX.X
					Basal 2	HH:MM	X.XX	
					Basal	HH:MM	X.XX	
					15 min	HH:MM	X.XX	
					30 min	HH:MM	X.XX	
					60 min	HH:MM **	X.XX **	
					90 min	HH:MM	X.XX	
					120 min	HH:MM **	X.XX	
					180 min	HH:MM	X.XX	
					240 min	HH:MM	X.XX	
		.						
		.						
		.						

Reference: CRF Pages 12, 25, and 25.1.
Notes: All times are on a 24-hour clock. IAT = Islet Auto-transplantation. For C-peptide values below the limit of detection (0.05ng/mL), a value of 0.05 ng/mL is assumed in the calculation of AUC. Missing C-peptide values are imputed via linear interpolation, and the average of the two basal samples (values, and mid-point of sample times) is used as the first sample in the computation of the AUC. AUC is computed using the trapezoidal rule. For ease of interpretation, the AUC value is also divided by the total time the scale is assessed. Computation of AUC is based on actual collection times, unless actual collection time is missing, in which case the scheduled collection time will be used. ** = Imputed value.

Listing 16.2.15.1 miR-375, Area Under the Curve (AUC)

Treatment: Reparixin or Placebo

Patient Number	Sample Date (Day) Time	miR-375 (serum copies/mL)	Area Under the Curve (unit)
XXXX	Pre-transplant 1 DDMMMYYYY (XXX) HH:MM	XXXXXX	XXXXXX
	Pre-transplant 2 DDMMMYYYY (XXX) HH:MM	XXXXXX	
	6 Hours Post-transplant DDMMMYYYY (XXX) HH:MM	XXXXXX **	
	. . .		

Reference: CRF Page 402.
Notes: All times are on a 24-hour clock. Missing miR-375 values are imputed via linear interpolation. Once these rules have been applied to the data, AUC0-72H for miR-375 will be computed using the trapezoidal rule. Computation of AUC0-72H will be based on actual collection times, unless actual collection time is missing, in which case the scheduled collection time will be used. ** = Imputed value.