SYNOPSIS

NAME OF THE SPONSOR: Dompé s.p.a. (Dompé)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:	*(FOR NATIONAL AUTHORITY USE ONLY)*
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Title of Study: A phase 2 multi-center, randomized, open-label, parallel assignment, pilot study to assess the efficacy and safety of reparixin following islet transplantation in patients with type 1 diabetes mellitus.

Investigators:

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Study Centers: 2 sites (1 in Italy and 1 in Germany). Only the Italian site recruited patients into the trial.

Publication (reference): Citro A et al. CXCR1/2 inhibition enhances pancreatic islet survival after transplantation. J Clin Invest 2012a 122:3647-3651c

Studied Period: 28 July 2010 (first patient in) to 30 April 2013 (last patient last visit)	**Phase of Development**: Phase 2

Objective: The objective of this clinical trial was to evaluate whether reparixin leads to improved transplant outcome as measured by glycemic control following infusion of pancreatic islets. The safety of reparixin in the specific clinical setting was also evaluated.

Methods: This was a phase 2, multi-center, randomized, open-label, parallel assignment, pilot study.

Originally, patients were randomly (1:1) assigned to receive either no additional experimental intervention (control group) or reparixin treatment (2.772 mg/kg body weight/hour intravenous [IV] continuous infusion for 7 days). Inclusion criteria restricted enrollment to patients who were expected to receive a single transplant with an islet mass (4000 to 7000 islet equivalent [IEQ]/kg body weight) in the lower range of the commonly accepted transplantable islet amount.

Due to preliminary results obtained in 7 patients, protocol REP0110 was amended to allow randomization

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to the reparixin treatment group only. Also, patients already treated with reparixin with a functioning graft were allowed to receive a second islet infusion. Follow-up was rescheduled to provide measurements up to 1 year after the second islet infusion. The schedule of post-transplant visits was re-set on the basis of the date of the second islet infusion, if any.

Number of Patients (planned and analyzed):

Planned: 10 patients undergoing intra-hepatic transplantation of pancreatic islets.

Actual: 9 patients were enrolled into the study (6 patients in the reparixin group and 3 patients in the control group).

Completed: 2 patients (both on r eparixin) completed the study as per protocol (12 months after the second transplant).

Analyzed: 9 patients (6 patients from the reparixin group and 3 patients from the control group) were analyzed for safety and efficacy.

Diagnosis and Main Criteria for Inclusion:

Patients aged 18 to 65 years with a clinical history of type 1 diabetes (T1D) with insulin dependence for ≥5 years and undetectable stimulated C-peptide levels in the 12 m onths before transplant who were eligible for pancreatic islet transplantation (planned intra-hepatic islets transplantation from non-living donor with brain death; planned first infusion of 4000 to 7000 IEQ/kg body weight), and who had given written informed consent were included. Patients were required to have an adequate renal reserve as per calculated creatinine clearance (CLcr) ≥60 mL/min (Cockcroft-Gault formula).

Patients were excluded if they were recipients of any previous transplant (except from the recipient of a previous pancreatic islet transplantation that had failed, were off immunosuppression for ≥1 year and had no anti-human leukocyte antigen [anti-HLA] antibodies); had a body mass index (BMI) of >30kg/m^2 or patient weight <45 kg; an insulin requirement of >1 international unit (IU)/kg/day; a glycated hemoglobin (HbA1c) of >11%. Patients with abnormal liver function tests (alanine aminotransferase [ALT]/aspartate aminotransferase [AST]) >3 times the upper limit of normal (ULN) and total bilirubin >3 mg/dL [>51.3 mol/L]); patients who had received chronic systemic steroids or who were treated with any antidiabetic medication other than insulin or with investigational agents within 4 weeks of transplant; who had hypersensitivity to ibuprofen or to more than 1 non-steroidal anti-inflammatory drug, or to sulfonamides, were excluded as well. Pregnant or breast-feeding women or males and females unwilling to use effective contraceptive measures were also excluded.

Test Product, Dose, Mode of Administration, and Batch Numbers:

Reparixin 33 mg/mL aqueous injectable solution. It was administered after dilution to 11 m g/mL as a continuous IV infusion into a (high flow) central vein at a dos e of 2.772 mg/kg body weight/hour. Batch numbers: PPD (expiration date PPD) and PPD (expiration date PPD).

Duration of Treatment:

7 days (168 hours) of continuous infusion at each islet transplant, starting approximately 12 hours (range between 6 and 16 hours) before islet infusion.

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Criteria for Evaluation:

Efficacy:

- The proportion of insulin-independent patients following a single-infusion islet cell transplantation (time frame: day 75 ± 5 post-transplant).

  Insulin-independence was defined as freedom from the need to take exogenous insulin for 14 or more consecutive days, with adequate glycemic control, as defined by:

  - HbA1c level of less than 7%;
  - glucose level after an overnight fast not exceeding 140 mg/dL (7.8 mmol/L) more than 3 times a week (based on measuring capillary glucose level a minimum of 7 times in a 7-day period);
  - glucose level not exceeding 2-hour postprandial levels of 180 mg/dL (10 mmol/L) more than 4 times a week (based on measuring capillary glucose level a minimum of 21 times in a 7-day period).
- The proportion of insulin-independent patients after islet cell transplantation (time frame: up to 1 year after the last transplant).
- Time to achieve insulin-independence after the transplant (time frame: up to 1 year after the last transplant). The time of insulin-independence attainment was defined as the time from transplant to the first day off insulin for 14 or more consecutive days.
- Total time of insulin-independence after the transplant (time frame: up to 1 year after the last transplant). The time to loss of insulin-independence was defined as the time from attainment of insulin-independence to the first day insulin was required for 14 or more consecutive days.
- Change in average daily insulin requirements (absolute and % decrease from pre-transplant levels) (time frame: Months 1, 3, 6, and 12 post-transplant). Daily insulin was averaged over the previous week.
- HbA1c (absolute and % decrease from pre-transplant levels) (time frame: Months 1, 3, 6, and 12 post-transplant).
- The proportion of patients free of severe hypoglycemic events (time frame: Months 1, 3, 6, and 12 post-transplant).
- The proportion of patients free of hypoglycemic events with reduced awareness (time frame: Months 1, 3, 6, and 12 post-transplant).
- Basal (fasting) and -10 to 120 minute time course of glucose, C-peptide, and insulin derived from the mixed meal tolerance test (MMTT) (time frame: Months 1, 3, 6, and 12 post-transplant).
- β-cell function as assessed by β-score and transplant estimated function (TEF) (time frame: Months 1, 3, 6, and 12 post-transplant).

Pharmacokinetics:

Plasma levels of reparixin (total and unbound) and its major metabolite, DF2243Y, at steady state conditions during the first treatment [time frame: Day 3 and Day 7 of first Investigational Product infusion (or anyway before the end of infusion)].

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Safety: Safety was assessed by monitoring the incidence and severity of adverse events (AEs) and serious AEs (SAEs) throughout the study up to 1 year after last transplant. The following were also performed at pre-transplant hospital admission and post-transplant hospital discharge: laboratory tests including hematology (hematocrit, hemoglobin, red blood cells, platelets, white blood cells, differential white blood cells count), and clinical chemistry (sodium, potassium, bicarbonate, serum creatinine, blood urea nitrogen, total bilirubin, ALT, AST, coagulation (prothrombin time [PT], partial thromboplastin time [PTT]), and vital signs (including blood pressure and heart rate). ALT/AST, PT/PTT, fibrin degradation products (XDP), and C-reactive protein (CRP) were all assessed daily up to Day 6/7 post-transplant; ALT/AST were also assessed at Month 1 and Month 3 post-transplant, up to or above 3 times the ULN.

Other: The following were exploratory endpoints:

- Time course of inflammatory chemokines/cytokines as assessed by serum levels of CXCL8 (CXC ligand 8 [formerly interleukin (IL)-8]), CXCL1, vascular endothelial growth factor (VEGF), interleukin 4 (IL-4), IL-6, IL-10, IL-12, and interferon-gamma [IFNγ] (time frame: 0, 6, 12, 24, 72, 120, and 168 hours after islet infusion).
- Autoantibodies (glutamic acid decarboxylase [GAD], protein tyrosine phosphatase [IA-2], insulin autoantibody [IAA], zinc transporter 8 [ZnT8]) (time frame: 0, Day 6/7, Months 1, 3, 6, and 12 post-transplant).
- Anti-HLA antibodies (time frame: 0, Day 6/7, Months 1, 3, 6, and 12 post-transplant).

Statistical Methods:

This study was exploratory in nature, so there was no data to provide a knowledgeable estimate of the effect size in the study. Therefore, no formal sample size calculation was performed and the study was arbitrarily sized at 10 patients (5 in each group).

The efficacy population consisted of all patients who received any study medication and the transplant, and was based on the treatment randomized, regardless of the treatment actually received. The safety population consisted of all patients who were randomized into the study. The safety population was used to present the demographic and baseline data, and all safety data.

For continuous parameters, mean, standard deviation (SD), standard error of the mean (SEM), median, minimum, maximum, and lower and upper 95% confidence limits for the mean were provided.

Efficacy:

All efficacy endpoints were presented using appropriate descriptive statistics, by treatment group. No inferential statistical testing was performed.

Safety:

Demographic and baseline characteristics were summarized for all patients in the safety population, by treatment group. Safety variables were presented for the safety population, by treatment group.

AEs were presented in terms of the incidence, severity, and relationship to the study drug, overall and by system organ class (SOC) and preferred term. SAEs were presented in the same way. Results for each laboratory test at screening and hospital discharge were assessed as being below the lower limit of the

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normal range (LLN), within the normal range, or above the ULN. Vital signs at each time point and the change in vital signs from screening were presented using descriptive statistics.

Exploratory Endpoints:

Inflammatory chemokines/cytokines (CXCL8, CXCL1, VEGF, IL-4, IL-6, IL-10, IL-12, and IFN γ) were measured 0, 6, 12, 24, 72, 120, and 168 hours after each islet infusion.

Autoantibodies (GAD, IA-2, IAA, and ZnT8) (time frame: 0, Day 6/7, Months 1, 3, 6, and 12 post-transplant) and anti-HLA antibodies (time frame: 0, Day 6/7, Months 1, 3, 6, and 12 post-transplant) were measured.

Autoantibody, anti-HLA antibodies, and chemokines/cytokines were presented using appropriate descriptive statistics, by treatment group.

Pharmacokinetics:

Plasma levels of reparixin (total and unbound) and its major metabolite, DF2243Y, were summarized using descriptive statistics.

Results:

Patient Disposition:

Of a total of 9 (100.0%) patients enrolled into the study (6 in the reparixin group and 3 in the control group). All 3 (100.0%) patients in the control group and 2 (33.3%) patients in the reparixin group were withdrawn between Day 45 and Day 80 after Transplant 1 due to graft loss. Four (66.7%) patients in the reparixin group received Transplant 2. Thereafter, 2 patients in the reparixin group completed the study as per protocol (observation up to Month 12 after Transplant 2), 1 patient was withdrawn at Month 6 after Transplant 2 due to graft loss. One patient was lost to follow-up (last visit was performed at Month 6 after Transplant 2). Nevertheless, this patient was followed up telephonically and by e-mail to monitor treatment progress and overall condition.

Efficacy Results:

Demographic and baseline characteristics of patients were comparable between the treatment and control groups.

After Transplant 1, none of the 9 patients in the study were insulin-independent at Day 75 (± 5 days post-transplant). After Transplant 2, 2 (50.0%) patients on reparixin were insulin-independent at Day 75 (± 5 days post-transplant); 1 patient reached insulin-independence 151 days after Transplant 2. Out of 3 patients who reached insulin independence, 2 (50.0%) patients maintained insulin-independence up to 1 year. The mean (SD) time to achieve insulin-independence was 66.3 (73.7) days with a range between 17 and 151 days. The mean (SD) total time of insulin-independence after Transplant 2 was 276 (96.2) days with a range between 208 and 344 days.

For Transplant 1 (patients on reparixin), the mean percentage decreases from pre-transplant in average insulin requirement were -41.9%, -50.3%, and -32.0% at Months 1, 3, and 6, respectively. For Transplant 1 (patients in the control group) the mean percentage increase in average insulin requirement was 16.4% at Month 1. For Transplant 2 (patients on reparixin), the mean percentage decreases from pre-transplant

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for average insulin requirement were -90.8%, -88.7%, -81.8%, and -100.0% at Months 1, 3, 6, and 12, respectively.

After both Transplant 1 and Transplant 2, for all patients at all time points, there were no severe hypoglycemic events and hypoglycemic events with reduced awareness recorded.

For Transplant 1 (patients on reparixin), the mean percentage decreases from pre-transplant in fasted HbA1c were -16.7%, -30.3%, and -19.7% at Months 1, 3, and 6, respectively. For Transplant 1 (patients in the control group), the mean percentage decrease from pre-transplant in fasted HbA1c was -11.2% at Month 1. For Transplant 2 (patients on reparixin), the mean percentage decreases from pre-transplant for fasted HbA1c were -32.8%, -32.2%, -31.6%, and -37.4% at Months 1, 3, 6, and 12, respectively.

For Transplant 1 (patients on reparixin), the mean C-Peptide AUC (derived from the MMTT) corrected by IEQ/kg values were 0.193, 0.366, 0.341 at Months 1, 3, and 6, respectively. For Transplant 1 (patients in the control group), the mean C-Peptide AUC (MMTT) corrected by IEQ/kg value was 0.044 at Month 1.

For Transplant 1 (patients on reparixin), the mean total calculated β-scores were 1.83, 3.75, and 1.67 at Months 1, 3, and 6, respectively. For Transplant 1 (patients in the control group), the mean total calculated β-score was 1.33 at Month 1. For Transplant 2 (patients on reparixin), the mean total calculated β-scores were 5.25, 4.75, 4.75, and 6.50 at Months 1, 3, 6, and 12, respectively.

For Transplant 1 (patients on reparixin), the mean values for TEF/IEQ were 111.9, 176.6, and 121.1 at Months 1, 3, and 6, respectively. For Transplant 1 (patients in the control group), the mean value for TEF/IEQ was 13.6 at Month 1. For Transplant 2 (patients on reparixin), the mean TEF/IEQ were 121.1, 119.4, 117.1, and 139.8 at Months 1, 3, 6, and 12, respectively.

Exploratory Results:

Given the small sample size of this study, it is difficult to come to any conclusions. Furthermore, the variability of pre-transplant values between the treatment and control groups precluded direct comparison of post-transplant data and clear findings.

After Transplant 1, there was an increase in the concentration of CXCL8, CXCL1 and IL-6 and a decrease in IFNγ, IL-10, and IL-12 concentrations in both the reparixin and control groups, whereas after Transplant 2 there was a reduction in the levels of all measured cytokines.

Comparison of the AUC values of the single variables for each patient in the first 168 hours after islet transplantation showed a possible trend towards an increase in CXCL8 levels in the reparixin group. Although this is quite predictable since reparixin is reported to inhibit CXCR2-mediated chemotaxis, due to the small sample size of the study, this finding needs to be confirmed in more patients. Furthermore, for the same reason, it remains to verify whether there is a correlation between the increased concentrations of CXCL8 and graft function 1 month after transplant.

There were no comparable GAD, IA-2, ZnT8 and IAA data for long-term values since all control group patients were withdrawal from the study at Month 1 after Transplant 1. From analysis of the data collected within the first month after Transplant 1, no significant changes in comparison to pre-transplant levels were found in all analyzed autoantibodies in both the reparixin and control patients.

Comparison of the individual autoantibody levels between pre-transplant and post-transplant time points

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showed a possible trend towards a transitory increase in GAD levels with a contemporary decrease in IAA levels in the reparixin patients who maintained graft function. Due to the small sample size of this study, however, these findings should be interpreted with caution.

Only 1 patient (number PPD) in the reparixin group was reported to be PPD during the study. At screening, discharge, and Month 1 this patient was PPD . Furthermore, at Month 1 after Transplant 1, the patient PPD . These findings suggested that this patient, although having received a transplant with favorable conditions for HLA matching, remained P . Indeed, the findings reflect the clinical course of the patient who, in being non-compliant with immunosuppressive therapy, developed PPD . There were no other reports throughout the study.

Pharmacokinetic Results:

Reparixin concentrations after Day 1 showed a higher variability (between patients) in the first 72 hours than from 145 to 168 hours after the start of infusion.

Reparixin concentrations (17.26 to 64.95 µg/mL) were similar to those obtained in healthy volunteers (C_{max}: min 24.49 to max 47.10 – mean [SD]: 35.16 (7.45) µg/mL; study REP0102) after administration of reparixin L–lysine salt (4.2 mg/kg/hour for 48 hours corresponding to 2.772 mg/kg/hour of reparixin).

Unbound reparixin concentrations in plasma were in the range (15.07 to 32.16 ng/mL) of those seen in healthy volunteers (C_{max} mean [SD] was 31.40 [9.84] ng/mL, study REP0102). Similarly, DF2243Y concentrations in plasma were in the range of those seen in healthy volunteers (C_{max} mean [SD] was 17.34 [3.19] ng/mL, study REP0102) for Patients 0102 and 0110 (range 10.18 to 12.54 µg/mL), while the concentrations appeared to be lower in other patients (range 4.38 to 7.93 µg/mL).

Due to an error in drug administration, Patient PPD received a 3-fold overdose of reparixin during Transplant 2 and was exposed to 8.316 mg/kg/hour of reparixin for 24.03 hours. Overexposure was confirmed by pharmacokinetic (PK) analysis.

Safety Results:

All 9 (100.0%) patients in the study had treatment-emergent adverse events (TEAEs). The most frequently reported TEAEs (by number of patients [percentage reporting]) were in the SOC of gastrointestinal disorders (7 [77.8%]), followed by the SOC of skin and subcutaneous tissue disorders (6 [66.7%]), and the SOCs of general disorders and administration site conditions and nervous system disorders (5 [55.6%] for both).

A higher number and percentage of patients on reparixin than in the control group reported TEAEs in the SOCs of gastrointestinal disorders (5 [83.3%] versus 2 [66.7%], respectively) and general disorders and administration site conditions (4 [66.7%] versus 1 [33.3%], respectively). An equal percentage of patients taking reparixin and in the control group reported TEAEs in the SOC of skin and subcutaneous tissue disorders (66.7% for both). A higher percentage of patients in the control group than on reparixin reported TEAEs in the SOC of nervous system disorders (66.7% versus 50.0%, respectively).

A total of 5 (83.3%) patients on reparixin had TEAEs with no relationship to study medication compared with all 3 (100%) patients in the control group. For patients on reparixin, the highest number and

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percentage of patients (6 out of 6 [100%]) had TEAEs with a possible relationship to study medication, followed by patients (5 out of 6 [83.3%]) who had TEAEs with an unlikely relationship to study medication. There were 11 reports of TEAEs with a highly probable relationship to study medication in 4 (66.7%) patients taking reparixin.

Overall, the highest number and percentage of patients (8 [88.9%]) had TEAEs of moderate severity. All 6 (100%) patients on reparixin had TEAEs of moderate severity compared with 2 out of 3 (66.7%) patients in the control group. The next highest number and percentage of patients (7 [77.8%]) had TEAEs of mild severity, with a higher number and percentage of patients on reparixin than in the control group reporting TEAEs of mild severity (5 out of 6 [83.3%] versus 2 out of 3 [66.7%], respectively). Overall, there were 10 severe TEAEs reported in 4 out of 9 (44.4%) patients, with a higher number and percentage of patients on reparixin than in the control group reporting severe TEAEs (3 out of 6 [50.0%] versus 1 out of 3 [33.3%], respectively).

There were 11 reports of SAEs in 3 (50.0%) patients taking reparixin compared with 1 report in 1 (33.3%) patient in the control group. For patients on reparixin, the highest number of reported SAEs was in the SOC of gastrointestinal disorders (6 reports in 3 [50.0%] patients). The SAE reported in 1 (33.3%) patient in the control group, was in the SOC of PPD disorders. The most frequently reported SAE (by preferred term) for patients taking reparixin was diarrhea (2 reports in 2 [33.3%] patients). All other SAEs for patients taking reparixin were reported 1 time in 1 patient. One patient (Patient PPD) on reparixin had 5 SAEs with a relationship to study medication considered highly probable (PPD). No other SAEs were considered to be drug-related.

No TEAEs led to withdrawal of patients from the study. No deaths or other significant AEs or TEAEs were reported during the study.

Clinical laboratory data (hematology, clinical chemistry, and coagulation results) and vital signs were comparable between the 2 groups. In general, the majority of laboratory values were within the normal ranges for both treatment and control groups at screening and hospital discharge. All changes in hematology and clinical chemistry values observed within the study period were considered by the Investigator not to be clinically relevant.

There were no clinically significant findings in PT/PTT, XDP, or CRP values for patients at any time points up to Day 7 post-transplant. After Transplant 1, CRP increased from day 1 post-transplant and returned to basal value by day 6. The increase was slightly lower in patients treated with reparixin than in patients from the control group.

After Transplant 1, ALT and AST increased in the early post-transplant days. Increases in both ALT and AST appeared to be delayed in reparixin as compared with the control group. Either similar or higher percentages of patients in the control group reached levels up to 3xULN as compared to patients in the reparixin group. At Month 1 (Transplant 1) the majority of patients (7 [77.8%] had ALT values below or within the normal range. At Month 1 (Transplant 1) all (100%) patients had AST values below or within the normal range.

Conclusions:

In this pilot study, a 7-day infusion of reparixin in 6 patients was compared to a control group of 3 patients

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that did not receive any experimental treatment; all 9 patients underwent islet transplantation. Four patients in the reparixin group received a second transplant.

Improved outcome was shown in the patients on reparixin, when glycemic control was measured by decreases from pre-transplant in mean daily insulin requirement and in mean percentage fasted HbA1c. Improved β-cell function was also shown by greater C-peptide AUC/IEQ/kg values in the patients on reparixin compared with patients from the control group. Similarly, mean values for TEF/IEQ in the patients on reparixin were greater than those from the control group.

Out of 4 patients on reparixin who received the second islet transplant, 3 reached insulin-independence which was maintained in 2 patients up to 12 months.

In conclusion, this study shows a clinical benefit of reparixin in terms of improved islet transplant outcomes, and provides a preliminary clinical proof of its potential in pancreatic islet transplantation in patients with type 1 diabetes.

Overall, reparixin was found to be safe and well-tolerated for patients in this study. The safety profile was in line with previous clinical experience and there were no safety issues that would preclude further development of reparixin in islet transplantation.

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