1 TITLE PAGE

A PHASE 3, MULTICENTRE, RANDOMISED, DOUBLE-BLIND, PARALLEL ASSIGNMENT TRIAL TO ASSESS THE EFFICACY AND SAFETY OF REPARIXIN IN PANCREATIC ISLET TRANSPLANTATION.

Trial Drug:	Reparixin
Indication Studied:	Pancreatic Islet Transplant in Type 1 Diabetes Mellitus
Sponsor:	Dompé farmaceutici S.p.A (Dompé) Via Santa Lucia, 6-20122 Milan, Italy
Protocol Number:	REP0211
Investigational New Drug Number:	15,194
EudraCT Number:	2011-006201-10
Clinical Development Phase:	3
Trial Initiation Date:	05-Oct-2012
Trial Completion Date:	09-Dec-2016
Principal Investigator(s):	Lorenzo Piemonti, MD; Torbjorn Lundgren, MD, PhD; Prof. Gunnar Tufveson; Ehab Rafael, MD, PhD; Prof. James Shaw; Prof. Frantisek Saudek; Piotr Witkowski, MD, PhD; Federico Bertuzzi, MD; Bengt Gustafsson, MD, PhD
Sponsor Signatories:	Pier Adelchi Ruffini, MD Chief Medical Officer, Dompé Luisa Daffoncio Clinical Development Manager Tel. +39 02 58383246 Via Santa Lucia, 6-20122 Milan, Italy
Version:	Final 1.0
Date of Report:	9-Nov-17

This trial was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

CONFIDENTIAL

Part or all of the information in this report may be unpublished material. Accordingly, this report should be treated confidentially and restricted to its intended use. Should any portion of this unpublished material be desired for purposes of publication, authorization must be obtained from Dompé.

2 SYNOPSIS

NAME OF THE SPONSOR: Dompé	INDIVIDUAL TRIAL TABLE REFERRING TO PART OF THE DOSSIER: *to be filled in by sponsor*	*(FOR NATIONAL AUTHORITY USE ONLY)*
NAME OF FINISHED PRODUCT: Reparixin	VOLUME: *to be filled in by sponsor*	
NAME OF ACTIVE INGREDIENT: Reparixin	PAGE: *to be filled in by sponsor*	

Title of Trial: A phase 3, multicentre, randomised, double-blind, parallel assignment trial to assess the efficacy and safety of Reparixin in pancreatic islet transplantation.

Investigator(s): There were 9 investigators involved in the trial. The coordinating investigator was Lorenzo Piemonti, MD, San Raffaele Diabetes Research Institute (OSR-DRI), Milan, Italy.

Trial Centre(s): There were 9 sites in 5 countries in this trial.

Country	Number of Trial Sites	Site Contacts (Principal Investigator)	Assigned Site Number
Czech Republic	1	Prof. Frantisek Saudek	08
Italy	2	Lorenzo Piemonti, MD; Federico Bertuzzi, MD	01 10
Sweden	4	Torbjorn Lundgren, MD, PhD, Prof. Gunnar Tufveson, Ehab Rafael, MD, PhD Bengt Gustafsson, MD, PhD,	03 04 05 11
United Kingdom (UK)	1	Prof. James Shaw	06

NAME OF THE SPONSOR: Dompé	INDIVIDUAL TRIAL TABLE REFERRING TO PART OF THE DOSSIER: *to be filled in by sponsor*	*(FOR NATIONAL AUTHORITY USE ONLY)*
NAME OF FINISHED PRODUCT: Reparixin	VOLUME: *to be filled in by sponsor*	
NAME OF ACTIVE INGREDIENT: Reparixin	PAGE: *to be filled in by sponsor*	

United States of America (USA)	1	Piotr Witkowski, MD, PhD	09
Total	9		

Publication(s) (reference): None

Trial Period: 05-Oct-2012 to 09-Dec-2016	**Phase of Development**: 3

Objectives: The objective of this clinical trial was to assess whether Reparixin leads to improved transplant outcome as measured by glycaemic control following intra-hepatic infusion of pancreatic islets in Type 1 diabetes (T1D) subjects. The safety of Reparixin in the specific clinical setting was also evaluated.

Methodology: This was a phase 3, multicentre, double-blind, parallel-group, placebo-controlled, randomised, clinical trial designed to evaluate Reparixin versus placebo. Subjects were randomised to treatment groups on a 2:1 basis to receive either Reparixin for 7 days, starting approximately 12 hours (h) before each islet transplant, or matched placebo. Investigational Products (IP) were administered as an add-on treatment to the immunosuppressant regimen. The two groups were to be balanced within each centre. Subjects could receive up to 2 islet transplants. Each subject was to be involved in the trial for a 7-day hospital stay during each transplant and for a maximum of 3 post-transplant visits scheduled at 75±5 days after each islet infusion and 365±14 days after the last islet infusion.

Number of Subjects (Planned and Analysed): Planned: 42; Randomised: 51; Receiving 1st transplant: 46; Completed: 41; Analysed for efficacy: 46; Analysed for safety: 48

NAME OF THE SPONSOR: Dompé	INDIVIDUAL TRIAL TABLE REFERRING TO PART OF THE DOSSIER: *to be filled in by sponsor*	*(FOR NATIONAL AUTHORITY USE ONLY)*
NAME OF FINISHED PRODUCT: Reparixin	VOLUME: *to be filled in by sponsor*	
NAME OF ACTIVE INGREDIENT: Reparixin	PAGE: *to be filled in by sponsor*	
Diagnosis and Main Criteria for Inclusion: Criteria for inclusion were ages 18-70 years, inclusive, eligible for a pancreatic islet transplantation program (T1D with insulin-dependence for ≥5 years and undetectable (<0.3 ng/mL) stimulated C-peptide levels), and planned intrahepatic islet transplantation. Key exclusion criteria included recipients of any previous transplant, pre-transplant average daily insulin requirement >1 IU/kg/day, pre-transplant glycated haemoglobin (HbA1C) >11%, renal/hepatic dysfunction, hypersensitivity to ibuprofen and more than one medication belonging to the class of sulfonamides, and pregnant or breast-feeding women, subjects who receive treatment for a medical condition requiring chronic use of systemic steroids, and treatment with any anti-diabetic medication other than insulin within 4 weeks of transplant, apart from the glucagon like peptide-1 agonists (e.g. exenatide or liraglutide) which were to be discontinued at least 2 weeks prior to transplant. There were also exclusion criteria specific to the US, including but not limited to uncontrolled hyperlipidemia, macroalbuminuria, Graves' disease, and others.		
Test Product, Dose, Mode of Administration, and Batch Number(s): Reparixin, 2.772 mg/kg body weight/hour given by continuous intravenous infusion, Batch Number(s): 12REP01, 13REP01, 14REP01, 14REP02		
Duration of Treatment: 1 week after each transplantation		
Reference Therapy, Dose, Mode of Administration, and Batch Number(s): The reference therapy was the placebo, which was given with the same route, frequency, and total infusion time as Reparixin. The placebo group was given a commercially available physiological salt solution. Batch Number(s): 12C0801, 13A11 01, 14A17 03		

NAME OF THE SPONSOR: Dompé	INDIVIDUAL TRIAL TABLE REFERRING TO PART OF THE DOSSIER: *to be filled in by sponsor*	*(FOR NATIONAL AUTHORITY USE ONLY)*
NAME OF FINISHED PRODUCT: Reparixin	VOLUME: *to be filled in by sponsor*	
NAME OF ACTIVE INGREDIENT: Reparixin	PAGE: *to be filled in by sponsor*	

Criteria for Evaluation:

Efficacy:

Primary endpoint:
The primary endpoint was the area under the curve (AUC) for the serum C-peptide level during the 1st 2 h of a mixed meal tolerance test (MMTT), normalized by the number of Islet Equivalent (IEQ)/kg [time frame: Day 75±5 after the 1st islet infusion and Day 365±14 after the last islet infusion].

Secondary endpoints:
The proportion of insulin-independent subjects; the proportion of subjects who achieved and maintained an HbA1C <7.0% (or a reduction in HbA1C ≥2%) and were free of severe hypoglycaemic events after transplant, and HbA1C (%) (absolute and % decrease from pre-transplant levels); the proportion of subjects who were not allocated to a 2nd islet infusion because they were insulin independent after the 1st islet infusion; cumulative number of severe hypoglycaemic events after transplant; change in average daily insulin requirements (absolute and % decrease from pre-transplant levels); basal (fasting) and 0 to 120 min time course of glucose, C-peptide and insulin derived from the MMTT; β-cell function as assessed by β-score and transplant estimated function.

Safety:

Incidence and severity of adverse events (AE) and serious adverse events (SAE); standard laboratory tests including haematology, clinical chemistry, and coagulation; vital signs, i.e. blood

NAME OF THE SPONSOR: Dompé	INDIVIDUAL TRIAL TABLE REFERRING TO PART OF THE DOSSIER: *to be filled in by sponsor*	*(FOR NATIONAL AUTHORITY USE ONLY)*
NAME OF FINISHED PRODUCT: Reparixin	VOLUME: *to be filled in by sponsor*	
NAME OF ACTIVE INGREDIENT: Reparixin	PAGE: *to be filled in by sponsor*	

pressure and heart rate; alanine aminotransferase/aspartate aminotransferase, prothrombin time/partial thromboplastin time fibrin degradation products, C-reactive protein.

Other:

Auto-antibodies (GAD, IA-2, optional: ZnT8); Anti-HLA antibodies; time course of inflammatory chemokines as assessed by serum level of CXCL8, CCL2 (MCP-1), CCL3, CCL4, CXCL10 (IP-10), CXCL9 (MIG), IL-6, IL-10, ddPCR miR-375; time-course of coagulation/complement activation markers as assessed by blood level of C3a, sC5b-9, TAT, D-dimer, Hydroxynitrile Lyase, and Myeloperoxidase.

Statistical Methods:

The Enrolled Population consisted of all subjects screened for the trial. The Safety Population consisted of all subjects who were randomised and received the IP (either Reparixin or placebo) and was based on the treatment actually received. The Efficacy Population 1 consisted of all subjects who were randomised, received the IP (either Reparixin or placebo), and had a transplant (either one or two). Subjects who had an adjudicated condition that could have severely biased transplant outcome were excluded from the Efficacy Population 2.

The primary endpoint (AUC for the serum C-peptide level during the 1st 2 h of an MMTT) was analysed by analysis of variance (ANOVA), including terms for treatment, centre and treatment-by-centre interaction. All the AUC analyses were based on actual rather than scheduled timings and were calculated using the trapezoidal rule. For ease of interpretation, the AUC value

NAME OF THE SPONSOR: Dompé	INDIVIDUAL TRIAL TABLE REFERRING TO PART OF THE DOSSIER: *to be filled in by sponsor*	*(FOR NATIONAL AUTHORITY USE ONLY)*
NAME OF FINISHED PRODUCT: Reparixin	VOLUME: *to be filled in by sponsor*	
NAME OF ACTIVE INGREDIENT: Reparixin	PAGE: *to be filled in by sponsor*	

obtained was divided by the total time the scale was assessed for reporting purposes.

All secondary endpoints and the supportive analyses were considered as descriptive evidence of efficacy and were analysed without any procedures to account for multiple comparisons. AUC data at Day 75±5 after the 2nd islet infusion was analysed using the same model for the primary endpoint. The proportion of insulin-independent subjects, the proportion of subjects who achieved and maintained an HbA1C <7.0% and were free of severe hypoglycaemic events after transplant, the proportion of subjects who were not allocated to a 2nd islet infusion because they were off insulin after the 1st islet infusion, and the other secondary endpoints were tabulated.

All statistical tests performed were 2-tailed with significance determined by reference to the 5% significance level, unless otherwise stated. The null hypothesis at all times was the equality of the two treatments being compared. All comparisons between the treatments were, unless otherwise stated, reported with 95% confidence intervals for the difference.

Some endpoints were analysed by ANOVA including terms for treatment, centre and treatment-by-centre interaction. Analysis of covariance was also used. For the primary endpoint, treatment effect was compared using a two-sided 0.0025 level Student's t test estimated from the ANOVA model (statistical significance adjusted for one pivotal trial). Least squares adjusted mean values for each treatment group were presented, together with the difference in least squares means. As a sensitivity analysis, the primary efficacy endpoint was analysed including the Day 75 data from the 2nd transplant for those subjects who had more than one transplant, and also adding the Day 365 transplant 1 data for the subject who had their 2nd transplant more than a year after their 1st transplant.

NAME OF THE SPONSOR: Dompé	INDIVIDUAL TRIAL TABLE REFERRING TO PART OF THE DOSSIER: *to be filled in by sponsor*	*(FOR NATIONAL AUTHORITY USE ONLY)*
NAME OF FINISHED PRODUCT: Reparixin	VOLUME: *to be filled in by sponsor*	
NAME OF ACTIVE INGREDIENT: Reparixin	PAGE: *to be filled in by sponsor*	

Summary-Conclusions:

Subject Disposition:

A total of 51 subjects were randomised into the trial. Three of these subjects did not have a transplant and never received randomised medication. A total of 48 subjects, 29 in the Reparixin treatment group and 19 in the placebo treatment group, took trial medication and therefore were included in the Safety Population. Two of these subjects never proceeded to transplant. Therefore the Efficacy Population 1, which included all subjects who were randomised, received the IP and had at least 1 islet infusion, consisted of 46 subjects, 28 in the Reparixin group and 18 in the placebo group. The Efficacy Population 2 was defined as the Efficacy Population 1 with subjects who had an adjudicated condition that could have severely biased transplant outcome excluded and consisted of 44 subjects. The Per Protocol (PP) Population was defined as the Efficacy Population 2 with the exclusion of subjects who did not have additional major protocol violations and consisted of 43 subjects. A total of 33 subjects had a 2nd islet infusion, 18 in the Reparixin group and 15 in the placebo group, and 32 of these subjects received a 2nd dose of trial medication. A total of 5 subjects had IP discontinued due to an AE, 3 in the Reparixin treatment group and 2 in the placebo treatment group. These include one subject in the Reparixin group who withdrew from the trial due to an SAE, unrelated to IP administration.

The mean age of subjects at screening was 45.5 years. Of the 48 subjects in the Safety Population, 19 (39.6%) subjects were male and 29 (60.4%) subjects were female. All subjects were diagnosed with T1D and had a mean length of insulin-dependence of 26.9 years, with a median of 5.0 severe hypoglycaemic episodes in the past 6 months.

NAME OF THE SPONSOR: Dompé	INDIVIDUAL TRIAL TABLE REFERRING TO PART OF THE DOSSIER: *to be filled in by sponsor*	*(FOR NATIONAL AUTHORITY USE ONLY)*
NAME OF FINISHED PRODUCT: Reparixin	VOLUME: *to be filled in by sponsor*	
NAME OF ACTIVE INGREDIENT: Reparixin	PAGE: *to be filled in by sponsor*	

Efficacy:

- For the primary endpoint, there was no statistically significant difference between treatments for the Efficacy Population 1 at either Day 75 after the 1st islet transfusion (p=0.9863) or at Day 365 after the last islet transfusion (p=0.7115) for AUC for the serum C-peptide level during the 1st two hours of MMTT. Similar results were seen for the Efficacy Population 2.
- There were no statistically significant differences between treatment groups in either the Efficacy Population 1 or Efficacy Population 2 when examining the secondary endpoints proportion of insulin-independent subjects, subjects who achieved and maintained an HbA1C level <7.0% during the trial, cumulative number of severe hypoglycaemic events after transplant, change in average daily insulin requirements, HbA1C percentage, or 0 to 120 minute time courses of MMTT for glucose, C-peptide and insulin. At Day 75 following the 1st transplant, 5 (18.5%) subjects reported insulin independence in the Reparixin group compared to 1 (5.6%) subject in the placebo group. Similarly, 4 subjects, all in the Reparixin group, reached and maintained insulin-independence for up to 1 year after a single islet infusion and thus were not eligible to a 2nd islet infusion.
- There were no clear differences between treatment groups in either the Efficacy Population 1 or Efficacy Population 2 when assessing β-cell function or TEF/IEQ secondary endpoints, as the differences between treatment groups were not statistically significant. However, there was a statistically significant difference between treatment groups when examining TEF at some time points.

NAME OF THE SPONSOR: Dompé	INDIVIDUAL TRIAL TABLE REFERRING TO PART OF THE DOSSIER: *to be filled in by sponsor*	*(FOR NATIONAL AUTHORITY USE ONLY)*
NAME OF FINISHED PRODUCT: Reparixin	VOLUME: *to be filled in by sponsor*	
NAME OF ACTIVE INGREDIENT: Reparixin	PAGE: *to be filled in by sponsor*	

- No clear differences were apparent between treatment groups in the profile (quantity and distribution) of auto-antibodies, Anti-HLA antibodies, time courses of inflammatory chemokines/cytokines, miR-375, or time courses of coagulation/complement activity after the 1st or 2nd transplants. Greater rates of serum conversion were generally seen in the Reparixin treatment group and only the Reparixin treatment group had subjects with auto-antibody spreading.

Safety Results:

- No clear differences between treatment groups were observed for rates of TEAEs, severity of TEAEs, or rates of SAEs.
- A total of 48 subjects, 29 in the Reparixin treatment group and 19 in the placebo treatment group, received IP during the trial. A total of 18 subjects (62.1%) in the Reparixin treatment group received a 2nd IP infusion during the 2nd transplant compared to 15 subjects (78.9%) in the placebo treatment group.
- All subjects except 1 (subject **0803** in the placebo treatment group) reported at least one TEAE during the course of the trial.
- A total of 22 (45.8%) subjects, 14 (48.3%) in the Reparixin treatment group and 8 (42.1%) in the placebo treatment group, had a TEAE that was judged to be treatment related. A total of 72 TEAEs were judged to be possibly, probably, or highly probable to be treatment related.
- There were no deaths during the trial.
- There was 1 subject who withdrew from the trial due to an SAE.
- No clear differences were seen between treatment groups in AEs by SOCs or

NAME OF THE SPONSOR: Dompé	INDIVIDUAL TRIAL TABLE REFERRING TO PART OF THE DOSSIER: *to be filled in by sponsor*	*(FOR NATIONAL AUTHORITY USE ONLY)*
NAME OF FINISHED PRODUCT: Reparixin	VOLUME: *to be filled in by sponsor*	
NAME OF ACTIVE INGREDIENT: Reparixin	PAGE: *to be filled in by sponsor*	

Preferred Terms. The majority of subjects (38 subjects, 79.2%) had an event in the SOC of Gastrointestinal Disorders. The next most common SOC was Nervous System Disorders (20 subjects, 41.7%). The 3rd most common SOC was General Disorders and Administration Site Conditions (19 subjects, 39.6%).

- The most common treatment-related TEAE was nausea. The next most common treatment-related TEAE was headache. The 3rd most common treatment-related TEAE was vomiting.
- No clear differences were seen between treatment groups in any laboratory values (haematology, biochemistry, coagulation) or vital signs at screening and hospital discharge. Multiple subjects in both treatment groups reported abnormal, clinically significant haematology and biochemistry values after the 1st and 2nd islet infusions, when these values were normal or abnormal, not clinically significant upon hospital admission. There were 14 events, 7 in each treatment group, of laboratory abnormalities that were recorded as TEAEs within the Investigations SOC.
- There were no apparent differences between treatment groups in any post-transplant safety endpoint (ALT, AST, XDP, D-dimer, PT/INR, PTT/aPTT, or CRP).

NAME OF THE SPONSOR: Dompé	INDIVIDUAL TRIAL TABLE REFERRING TO PART OF THE DOSSIER: *to be filled in by sponsor*	*(FOR NATIONAL AUTHORITY USE ONLY)*
NAME OF FINISHED PRODUCT: Reparixin	VOLUME: *to be filled in by sponsor*	
NAME OF ACTIVE INGREDIENT: Reparixin	PAGE: *to be filled in by sponsor*	

Conclusion:

- This trial recruited subjects from a small population of T1D patients requiring a pancreatic islet transplant because of unstable glycaemia who were insulin dependent for 5 years or more. This limited the number of subjects eligible for enrolment and accordingly the sample size of the treatment groups. However, demographic and baseline characteristics of the subjects randomized in the trial reflect those of the general population of T1D patients eligible to an islet transplant.
- There were no statistically significant differences between Reparixin and the placebo in the primary efficacy endpoint, exploratory endpoints, and most secondary efficacy endpoints. The only statistically significant difference was in the secondary efficacy endpoint of β-cell function where the placebo treatment group had a significantly higher TEF than the Reparixin treatment group at some time points.
- The safety profiles of the two treatment groups were identical; there were no clear differences in any safety assessment or any clear differences in clinically significant laboratory findings. There were also no clear differences between treatment groups in the profile of auto-antibodies or inflammatory markers such as cytokines.
- The primary and secondary efficacy endpoints may not have been feasible or appropriate to detect differences between treatment groups. The sample size was based on feasibility and might not have been sufficient to detect treatment differences. Similarly, unbalanced patient distribution across sites and some site-specific differences in the population/procedures, including type of induction used for the 1st transplant, might have affected overall results.

NAME OF THE SPONSOR: Dompé	INDIVIDUAL TRIAL TABLE REFERRING TO PART OF THE DOSSIER: *to be filled in by sponsor*	*(FOR NATIONAL AUTHORITY USE ONLY)*
NAME OF FINISHED PRODUCT: Reparixin	VOLUME: *to be filled in by sponsor*	
NAME OF ACTIVE INGREDIENT: Reparixin	PAGE: *to be filled in by sponsor*	
Date of Report: Final 1.0, 9-Nov-17		