



Clinical trial results:

Effect of reparixin on long-term outcomes after pancreatic islet transplantation in type 1 diabetes mellitus patients. A non-interventional, monocentre study to extend up to 3 years the follow-up of patients treated with reparixin under protocol REP0110.

Summary

EudraCT number	2013-002244-86
Trial protocol	IT
Global end of trial date	23 March 2015

Results information

Result version number	v1 (current)
This version publication date	27 December 2020
First version publication date	27 December 2020

Trial information

Trial identification

Sponsor protocol code	REP0113
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dompé Farmaceutici S.p.A.
Sponsor organisation address	Via S.Lucia 6, Milan, Italy, 20122
Public contact	Clinical Trial Transparency Manager, Dompé Farmaceutici S.p.A., 0039 0258381, info@dompe.it
Scientific contact	Clinical Trial Transparency Manager, Dompé Farmaceutici S.p.A., 0039 0258381, info@dompe.it

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 March 2015
Global end of trial reached?	Yes
Global end of trial date	23 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this extension study is to evaluate whether treatment with reparixin at the time of islet transplantation improves long-term outcome of pancreatic islets allo-transplantation. This study extended the follow-up evaluation of efficacy and safety from 1 to 3 years post-transplant in patients treated with reparixin under protocol REP0110.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation (ICH) harmonised tripartite guidelines for Good Clinical Practice (ICH-GCP), and standard operating procedures (SOPs) for clinical investigation and documentation in force at Dompé.

Background therapy:

The following immunosuppression regimen was to be used in patients enrolled in the study:

Maintenance: Mycophenolate mofetil (MMF), administered orally at the dose of 1 g twice a day, starting on Day -1 of the first islet infusion;

Tacrolimus, administered orally starting on Day -1 of the first islet infusion at a dose of 0.087 mg/kg twice a day. Thereafter, dosing was to be targeted to blood trough levels of 8 to 10 ng/mL.

Administration continued up to Month 3 after the first transplant.

Rapamycin was to replace tacrolimus from Month 3 after the first transplant. It was to be administered orally at the starting dose of 0.1 mg/kg once a day, then targeted to a blood trough level of 10 to 12 ng/mL.

The immunosuppression strategy above could have been changed on the basis of clinical requirements, as per centre practice.

Evidence for comparator: -

Actual start date of recruitment	08 October 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	3
EEA total number of subjects	3

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

As per inclusion criteria, only 3 patients were potentially eligible for the extension study.

Pre-assignment

Screening details:

Criteria to be eligible for inclusion into this extended follow-up of the study REP0110

- functioning graft (stimulated serum C-peptide levels >0.3 ng/mL derived from the mixed meal tolerance test [MMTT]) at the last follow-up visit under REP0110
- compliance with the protocol procedures for the duration of the trial
- written informed consent

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Since the REP0110 study was not blinded, the extension study was conducted in an open fashion.

Arms

Arm title	No intervention patients
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Arm description:

REP0113 is an observational study, hence no products were to be administered.

Reparixin was administered in the interventional study REP0110, of which REP0113 is a follow-up.

Arm type	no intervention
Investigational medicinal product name	Reparixin
Investigational medicinal product code	
Other name	REP
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

REP0113 is an observational study, hence no products were to be administered.

Reparixin was administered in the interventional study REP0110, of which REP0113 is a follow-up.

Number of subjects in period 1	No intervention patients
Started	3
Completed	2
Not completed	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	No intervention patients
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Reporting group description:

REP0113 is an observational study, hence no products were to be administered.

Reparixin was administered in the interventional study REP0110, of which REP0113 is a follow-up.

Reporting group values	No intervention patients	Total	
Number of subjects	3	3	
Age categorical Units: Subjects			
Adults (18-64 years)	3	3	
Age continuous Units: years arithmetic mean standard deviation	46.67 ± 4.73	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	1	1	

End points

End points reporting groups

Reporting group title	No intervention patients
Reporting group description:	
REP0113 is an observational study, hence no products were to be administered.	
Reparixin was administered in the interventional study REP0110, of which REP0113 is a follow-up.	

Primary: The number of Insulin-independent Patients Following Islet Cell Transplantation

End point title	The number of Insulin-independent Patients Following Islet Cell Transplantation ^[1]
End point description:	
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).	
End point type	Primary
End point timeframe:	
Months 24, 36 after the last transplant	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Based on the inclusion criteria, only 3 patients were enrolled in this follow up trial. Hence, no statistical analysis have been calculated. Moreover, in this trial only patients who were treated with reparixin in the study REP0110 were enrolled, so no analysis between arms/treatments could be accomplished.

End point values	No intervention patients			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[2]			
Units: number of patients				
Month 24	1			
Month 36	0			

Notes:

[2] - n=3 at month 24
n=2 at month 36

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Total time of insulin independence up to 3 years after the last transplant

End point title	Total time of insulin independence up to 3 years after the last transplant
End point description:	
Total time of insulin-independence after the transplant. This was defined as the number of days between the onset and loss of insulin-independence and was calculated as the date of loss of insulin-independence minus the date of onset of insulin-independence.	

End point type	Other pre-specified
End point timeframe:	
Up to 3 years after the last transplant	

End point values	No intervention patients			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Number of days				
Patient X	917			
Patient Y	334			
Patient Z	489			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Absolute decrease in average daily insulin requirements from pre-transplant levels

End point title	Absolute decrease in average daily insulin requirements from pre-transplant levels
End point description:	
Daily insulin requirement was calculated as the average requirement over the previous week (seven days).	
End point type	Other pre-specified
End point timeframe:	
At months 24 and 36 from pre-transplant	

End point values	No intervention patients			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[3]			
Units: UI/kg/day				
number (not applicable)				
Month 24	0.61			
Month 36	0.50			

Notes:

[3] - n=3 at 24 months
n=2 at 36 months

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage decrease in average daily insulin requirements from pre-transplant levels

End point title	Percentage decrease in average daily insulin requirements from pre-transplant levels
End point description: Daily insulin requirement was calculated as the average requirement over the previous week (seven days).	
End point type	Other pre-specified
End point timeframe: At months 24 and 36 from pre-transplant	

End point values	No intervention patients			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[4]			
Units: Percentage decrease				
number (not applicable)				
Month 24	91.7			
Month 36	70.8			

Notes:

[4] - n=3 at month 24

n=2 at month 36

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Absolute decrease in fasted HbA1c from pre-transplant levels

End point title	Absolute decrease in fasted HbA1c from pre-transplant levels
End point description: The average pre-transplant value was taken as recorded on the CRFs.	
End point type	Other pre-specified
End point timeframe: At months 24 and 36 from pre-transplant levels	

End point values	No intervention patients			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[5]			
Units: Percentage of Hb				
number (not applicable)				
Month 24	3.50			
Month 36	3.10			

Notes:

[5] - n=3 at month 24

n=2 at month 36

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage decrease in Fasted HbA1c from pre-transplant levels

End point title	Percentage decrease in Fasted HbA1c from pre-transplant levels
End point description: The average pre-transplant daily insulin requirement was taken as recorded on the CRFs	
End point type	Other pre-specified
End point timeframe: At months 24 and 36 from pre-transplant levels	

End point values	No intervention patients			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[6]			
Units: Percentage decrease				
number (not applicable)				
Month 24	36.6			
Month 36	31.8			

Notes:

[6] - n=3 at month 24

n=2 at month 36

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The proportion of patients free of severe hypoglycaemic events

End point title	The proportion of patients free of severe hypoglycaemic events
End point description: A severe hypoglycemic event is defined as an event with one of the following symptoms: "memory loss, confusion, uncontrollable behavior, irrational 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 <54mg/dL or prompt recovery after oral carbohydrate, i.v. glucose, or glucagon administration.	
End point type	Other pre-specified
End point timeframe: At months 24 and 36 post-transplant	

End point values	No intervention patients			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[7]			
Units: percentage of patients				
number (not applicable)				
Month 24	66			
Month 36	100			

Notes:

[7] - n=3 at month 24
n=2 at month 36

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time profile (-10 to 120 Minutes Post-dose) of Glucose Derived From Mixed Meal Tolerance Test (MMTT)

End point title	Time profile (-10 to 120 Minutes Post-dose) of Glucose Derived From Mixed Meal Tolerance Test (MMTT)
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End point description:

Glucose level reflects the metabolic control. The MMTT was performed after an overnight fast, at baseline (within 1 week prior to randomization), and at each of the following timepoints. Only the value at 120 min after the MMTT administration is reported. See the attachment for data at each timepoint and for each of the two patients.

End point type	Other pre-specified
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End point timeframe:

At Months 24 and 36 after the last transplant

End point values	No intervention patients			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mg/dL				
number (not applicable)				
Patient X month 24	175.2			
Patient X Month 36	315.6			
Patient Z Month 24	105.6			
Patient Z Month 36	185.9			

Attachments (see zip file)	Time profile of glucose/Time profile (-10 to 120 min post dose)
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Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time profile (-10 to 120 Minutes Post-dose) of C-peptide Derived From Mixed Meal Tolerance Test (MMTT)

End point title	Time profile (-10 to 120 Minutes Post-dose) of C-peptide Derived From Mixed Meal Tolerance Test (MMTT)
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End point description:

C-peptide level is an indirect measure of pancreatic beta-cell function. The MMTT was performed after an overnight fast, at baseline (within 1 week prior to randomization), and at each of the above mentioned timepoints.

Only the value at 120 min after the MMTT administration is reported. See the attachment for data at each timepoint and for each of the two patients.

End point type	Other pre-specified
End point timeframe:	
At months 24 and 36 after the last transplant	

End point values	No intervention patients			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: ng/mL				
number (not applicable)				
Patient X Month 24	8.06			
Patient X Month 36	1.05			
Patient Z Month 24	8.02			
Patient Z Month 36	2.97			

Attachments (see zip file)	Time profile of C-peptide/Time profile (-10 to 120 min post
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Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time profile (-10 to 120 Minutes Post-dose) of Insulin Derived From Mixed Meal Tolerance Test (MMTT)

End point title	Time profile (-10 to 120 Minutes Post-dose) of Insulin Derived From Mixed Meal Tolerance Test (MMTT)
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End point description:

Insulin level is a direct measure of pancreatic beta-cell function. The MMTT was performed after an overnight fast, at baseline (within 1 week prior to randomization), and at each of the above mentioned timepoints.

Only the value at 120 min after the MMTT administration is reported. See the attachment for data at each timepoint and for each of the two patients.

End point type	Other pre-specified
End point timeframe:	
At months 24 and 36 after the last transplant.	

End point values	No intervention patients			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: MicroU/mL				
number (not applicable)				
Patient X at Month 24	67.1			
Patient X Month 36	24.7			
Patient Z Month 24	78.2			

Patient Z Month 36	25.9			
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Attachments (see zip file)	Time profile of insulin/Time profile (-10 to 120 min post dose)
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Statistical analyses

No statistical analyses for this end point

Other pre-specified: Beta-cell function as assessed by beta-score

End point title	Beta-cell function as assessed by beta-score
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End point description:

The beta-score provides a simple clinical scoring system that encompasses glycemic control, diabetes therapy, and endogenous insulin secretion that correlates well with physiological measures of beta-cell function. On this basis, it is suitable as an overall measure of beta-cell transplant function.

Beta score is a composite scoring system based on fasting plasma glucose values, HbA1c, insulin independence or use of insulin/OHAs, and the determination of stimulated C-peptide levels. Normal values are given a score of 2, intermediate values merit a score of 1, and clearly abnormal values garner no points. Thus, a perfect score is 8, and a score of 0 indicates absolute absence of beta-cell function.

End point type	Other pre-specified
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End point timeframe:

At months 24 and 36 after the last transplant

End point values	No intervention patients			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[8]			
Units: score				
number (not applicable)				
Month 24	6.0			
Month 36	4.5			

Notes:

[8] - n=3 at month 24

n=2 at month 36

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Beta-cell Function as Assessed by Transplant Estimated Function (TEF)

End point title	Beta-cell Function as Assessed by Transplant Estimated Function (TEF)
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End point description:

TEF estimates daily insulin secretion, it is simpler than the beta-score, and its performance against reference indexes of beta-cell secretion is in line with that exhibited by beta-score. TEF can be normalized to the number of transplanted islets and thereby provides a benchmarking tool to evaluate

the cost-effectiveness of the transplant.

TEF selects the two pivotal components of the beta-score (daily insulin requirement [DIR] and glycated hemoglobin [A1C]) and links them together through a simple description of how insulin supply influences the patient's glycemic control.

TEF represents the daily amount of insulin secreted by the beta-cells and can be derived as a linear combination of DIR and A1C:

$$\text{TEF} = a * \text{DIR} + b * \text{A1C} + c,$$

where $a = -1$, $b = 1/K$, K measures the sensitivity of the glycemic control to the insulin supply, and c is a constant depending on the pretransplant (pretx) DIR and A1C of the patient:

$$c = -a * \text{DIR}(\text{pretx}) - b * \text{A1C}(\text{pretx})$$

End point type	Other pre-specified
End point timeframe:	
At months 24 and 36 after the last transplant	

End point values	No intervention patients			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[9]			
Units: U/kg/24 h				
number (not applicable)				
Month 24	1.3			
Month 36	1.1			

Notes:

[9] - n= 3 at month 24

n=2 at month 36

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Throughout the follow up study

Adverse event reporting additional description:

Only the SAEs were recorded in the study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.0
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Reporting groups

Reporting group title	No intervention patients
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Reporting group description:

Only SAEs were recorded in the study, but no SAEs were reported.

Serious adverse events	No intervention patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	No intervention patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Only SAEs were recorded in the study, but no SAEs were reported.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Two the limitations of this trial:

- 1) the small number of subjects enrolled in the study (3),
- 2) the fact that these patients came all from the group treated with reparixin.

Notes: