Clinical trial results:
A phase 3, multicenter, randomized, double-blind, parallel assignment study to assess the efficacy and safety of reparixin in pancreatic islet transplantation.

Summary

EudraCT number	2011-006201-10
Trial protocol	CZ GB SE IT
Global end of trial date	09 December 2016

Results information

Result version number	v1 (current)
This version publication date	28 April 2018
First version publication date	28 April 2018
Summary attachment (see zip file)	CSR summary report v 1.0 - 09 Nov 2017 (Dompe_REP0211_CSR_report-summary_v1.0_20171109.pdf)

Trial information

Trial identification

Sponsor protocol code	REP0211

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01817959
WHO universal trial number (UTN)	-
Other trial identifiers	IND - USA participated in the study: 15,194

Notes:

Sponsors

Sponsor organisation name	Dompé farmaceutici S.p.A
Sponsor organisation address	Via Santa Lucia, 6, Milan, Italy, 20122
Public contact	Project Development Direction, Dompe' spa, +39 0258383500, info@dompe.it
Scientific contact	Project Development Direction, Dompe' spa, +39 0258383500, 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	09 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this clinical trial is to assess whether reparixin leads to improved transplant outcome as measured by glycaemic control following intra-hepatic infusion of pancreatic islets in T1D patients. The safety of reparixin in the specific clinical setting will be also evaluated.

Protection of trial subjects:

There was a Data Monitoring Committee (DMC). There were 6 meetings from DMC committee.

The trial sites were monitored by WCT monitors according to ICH GCP guidelines and WCT SOPs. At each monitoring visit, progress of the trial was assessed and discussed with the investigator; completed CRFs were checked for completeness and accuracy and were compared to the original subject records and/or source documents; signed ICFs were inspected; and the trial supplies were examined.

Independent auditing was conducted by both Dompé and WCT's Quality Assurance Department according to the SOPs of both.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	51
EEA total number of subjects	39

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)	49
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Competitive recruitment was chosen to increase the speed of recruitment and to account for any difference in transplant rate among trial sites. However, each site was strongly encouraged to recruit the planned number of subjects in order to provide "within site" results for balanced treatment groups.

Pre-assignment

Screening details:

Potential study patients were identified whilst on the centre transplant waiting list. Consented patients (consent signed within 3 months prior to screening) underwent confirmatory screening for the study within maximum 3 days prior to the 1st transplant.
BP, HR, body weight (kg) and height (m) was be measured, blood samples were taken.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The trial was blinded to subjects, investigators, and sponsor. As the concentrated Reparixin solution has a pale yellow color compared with placebo, any pharmacist preparing the sterile i.v. bags with solutions for treatment could not be blinded. The solutions used for treatment were indistinguishable from each other once prepared.
Individual treatment codes were provided in sealed envelopes to the Pharmacist (or designee) and to the Investigator (one set each).

Arms

Are arms mutually exclusive?	Yes
Arm title	Reparixin arm

Arm description:

Patients received reparixin at a dose of 2.772 mg/kg body weight/hour for 7 days (168 hrs)

Arm type	Experimental
Investigational medicinal product name	Reparixin
Investigational medicinal product code	DF1681Y
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Reparixin at a dose of 2.772 mg/kg body weight/hour for 7 days (168 hrs)
The dosing solution (if reparixin, 11mg/mL) was administered as a continuous i.v. infusion into a (high flow) central vein, by an infusion pump adequate to provide reliable infusion rates, as per treatment schedule.
Infusion of the Investigational Product will start approximately 12hrs (allowed range 6-18hrs) before the anticipated time when each islet infusion is started. The Investigator will identify the time to start study drug administration.
The pump rate will be adjusted to provide an infusion rate of approximately 0.25mL/kg/hour. Actual infusion rate (mL/hour), adjusted to body weight

Arm title	Placebo

Arm description:

Patients received placebo for 7 days (168 hours) at the same flow rate (mL/kg body weight/hour) used for reparixin

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dosing solution of Placebo was administered as a continuous i.v. infusion into a (high flow) central vein at the same flow rate (mL/kg body weight/hour) used for reparixin; infusion was started approximately 12hrs (6-18hrs) before each pancreatic islet infusion and continued for 7 days (168 hours)

Number of subjects in period 1[1]	Reparixin arm	Placebo
Started	29	19
Completed	25	16
Not completed	4	3
Total withdrawals	4	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: There's a discrepancy on the total number of patients enrolled (51) and the ones who received IMP (48). There were 3 subject enrolled in the trial who withdrew prior to receiving the IMP for the study.

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	48	48	
Age categorical Units: Subjects			
Age 18- 70	48	48	
Gender categorical Units: Subjects			
Female	29	29	
Male	19	19	

End points

End points reporting groups

Reporting group title	Reparixin arm
Reporting group description:	
Patients received reparixin at a dose of 2.772 mg/kg body weight/hour for 7 days (168 hrs)	
Reporting group title	Placebo
Reporting group description:	
Patients received placebo for 7 days (168 hours) at the same flow rate (mL/kg body weight/hour) used for reparixin	

Primary: Area Under the Curve (AUC) for the serum C-peptide level during the first 2 hours of an MMTT, normalized by the number of Islet Equivalent (IEQ)/kg -Day 365+/-14 after the last islet infusion

End point title	Area Under the Curve (AUC) for the serum C-peptide level during the first 2 hours of an MMTT, normalized by the number of Islet Equivalent (IEQ)/kg -Day 365+/-14 after the last islet infusion

End point description:

The C-peptide AUC normalized by IEQ/kg will be analyzed at day 365+14 after the last islet infusion. Analysis of variance will be used, including terms for treatment, centre and treatment per centre interaction. The importance of the treatment by center interaction will be investigated but if this is not significant at the 10% level, this term will be excluded from the final model. If a center by treatment interaction is detected, alternative methods of presentation will be explored. Treatment effect will be compared using a two-sided 0.0025 level Student's t test (statistical significance adjusted for one pivotal trial).
Considering the nature of the variable, there are no reasonable substitutions of missing data that would not introduce a bias in the interpretation of the results. /-14 after the last islet infusion

End point type	Primary

End point timeframe:

Day 365+/-14 after the last islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	18		
Units: ng/ml				
arithmetic mean (standard error)	0.234 (± 0.05)	0.207 (± 0.033)		

Attachments (see zip file)	Table 14.2.1.1.doc

Statistical analyses

Statistical analysis title	Primary analysis model

Statistical analysis description:

The primary efficacy endpoint was analysed by analysis of variance (ANOVA) including terms for

treatment, centre and treatment-by-centre interaction. Centres that recruited less than four subjects were pooled and counted as a single centre for analysis purposes. If the treatment-by-centre interaction was not significant at the 10% level, the term was to be excluded from the final model. If the interaction term was significant at the 10% level, alternative methods of presentation were explored

Comparison groups	Reparixin arm v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05
Method	ANOVA

Primary: Area Under the Curve (AUC) for the serum C-peptide level during the first 2 hours of an MMTT, normalized by the number of Islet Equivalent (IEQ)/kg - Day 75+/-5 after the 1st islet infusion

End point title	Area Under the Curve (AUC) for the serum C-peptide level during the first 2 hours of an MMTT, normalized by the number of Islet Equivalent (IEQ)/kg - Day 75+/-5 after the 1st islet infusion

End point description:

The C-peptide AUC normalized by IEQ/kg will be analyzed at day 75+5 post the 1st islet infusion. Analysis of variance will be used, including terms for treatment, centre and treatment per centre interaction. The importance of the treatment by center interaction will be investigated but if this is not significant at the 10% level, this term will be excluded from the final model. If a center by treatment interaction is detected, alternative methods of presentation will be explored. Treatment effect will be compared using a two-sided 0.0025 level Student's t test (statistical significance adjusted for one pivotal trial).
Considering the nature of the variable, there are no reasonable substitutions of missing data that would not introduce a bias in the interpretation of the results. /-14 after the last islet infusion

End point type	Primary

End point timeframe:

Day 75+/-5 after the 1st islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	18		
Units: ng/ml				
arithmetic mean (standard error)	0.247 (± 0.042)	0.231 (± 0.049)		

Attachments (see zip file)	Table 14.2.1.1.doc

Statistical analyses

Statistical analysis title	Primary analysis model

Statistical analysis description:

The primary efficacy endpoint was analysed by analysis of variance (ANOVA) including terms for treatment, centre and treatment-by-centre interaction. Centres that recruited less than four subjects were pooled and counted as a single centre for analysis purposes. If the treatment-by-centre interaction

was not significant at the 10% level, the term was to be excluded from the final model. If the interaction term was significant at the 10% level, alternative methods of presentation were explored

Comparison groups	Reparixin arm v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05
Method	ANOVA

Secondary: The proportion of insulin-independent patients at timeframe day 365+14 after last islet infusion

End point title	The proportion of insulin-independent patients at timeframe day 365+14 after last islet infusion
End point description:	
The proportion of insulin-independent patients at timeframe day 365+14 after last islet infusion	
End point type	Secondary
End point timeframe:	
Day 365+14 after last islet infusion	

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	18		
Units: Subjects	8	5		

Attachments (see zip file)	Table 14.2.2.1.doc

Statistical analyses

Statistical analysis title	Fisher exact test
Comparison groups	Reparixin arm v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	≥ 0.05
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	4.93
Variability estimate	Standard deviation

Notes:

[1] - If a primary analysis model could not fit, a Fisher's exact test was used instead.

Secondary: The proportion of patients who achieve and maintain an HbA1c <7.0% (or o reduction in HbA1c > 2%) AND are free of severe hypoglycaemic events

End point title	The proportion of patients who achieve and maintain an HbA1c <7.0% (or o reduction in HbA1c > 2%) AND are free of severe hypoglycaemic events

End point description:

The proportion of patients who achieve and maintain an HbA1c <7.0% (or o reduction in HbA1c > 2%) AND are free of severe hypoglycaemic events at day 365+14 after the last islet infusion

End point type	Secondary

End point timeframe:

Day 365+14 after the last islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	18		
Units: Subjects	10	8		

Attachments (see zip file)	Table 14.2.3.1.doc

Statistical analyses

Statistical analysis title	Secondary analysis model

Statistical analysis description:

The data at Day 75±5 (both transplants) and Day 365±14 (last transplant) were analysed via logistic regression models with factors for treatment and pooled centre. The odds ratio for treatment effect were presented with the associated 95% CIs.

Comparison groups	Reparixin arm v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	2.66
Variability estimate	Standard deviation

Secondary: The number of patients not allocated to a 2nd infusion because insulin-independent after the 1st infusion

End point title	The number of patients not allocated to a 2nd infusion because insulin-independent after the 1st infusion

End point description:

The number of patients not allocated to a 2nd infusion because insulin-independent after the 1st infusion

End point type	Secondary

End point timeframe:

day 365+14 after the 1st islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	18		
Units: Subjects	4	0		

Attachments (see zip file)	Table 14.2.4.doc

Statistical analyses

Statistical analysis title	Fisher exact test

Statistical analysis description:

If a primary analysis model could not fit, a Fisher's exact test was used instead.

Comparison groups	Reparixin arm v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05
Method	Fisher exact
Parameter estimate	Yes/No
Point estimate	0.1383
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Secondary: Cumulative number of severe hypoglycaemic events

End point title	Cumulative number of severe hypoglycaemic events

End point description:

Cumulative number of severe hypoglycaemic events at day 365+14 after the last islet infusion

End point type	Secondary

End point timeframe:

day 365+14 after the last islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	18		
Units: Events	11	7		

Attachments (see zip file)	Table 14.2.5.1.doc

Statistical analyses

No statistical analyses for this end point

Secondary: Change in average daily insulin requirements (absolute and % decrease from pre-transplant levels)

End point title	Change in average daily insulin requirements (absolute and % decrease from pre-transplant levels)

End point description:

Change in average daily insulin requirements (absolute and % decrease from pre-transplant levels) at day 75+5 after the 1st and 2nd islet infusion and day 365+14 after last islet infusion

End point type	Secondary

End point timeframe:

day 75+5 after the 1st and 2nd islet infusion and day 365+14 after last islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[2]	18[3]		
Units: IU/kg/day	0	0		

Notes:

[2] - Multiple values, please check attached table for actual values

[3] - Multiple values, please check attached table for actual values

Attachments (see zip file)	Table 14.2.6.1.doc

Statistical analyses

Statistical analysis title	Secondary ANCOVA analysis

Statistical analysis description:

The data at Day 75±5 (both transplants) and Day 365±14 after the last islet infusion were analysed via analysis of covariance (ANCOVA) with factors for treatment and centre and pre-dose value as a covariate. Least squares adjusted mean values for each treatment group were presented, together with the difference in least squares means. The 95% CI for the difference in least square means were estimated using the mean square error from the ANCOVA.

Comparison groups	Reparixin arm v Placebo

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.042
upper limit	0.154
Variability estimate	Standard error of the mean

Secondary: HbA1c % (absolute and % decrease from pre-transplant levels)

End point title	HbA1c % (absolute and % decrease from pre-transplant levels)

End point description:

HbA1c % (absolute and % decrease from pre-transplant levels) at Day 75+5 after the 1st and 2nd islet infusion and day 365+14 after last islet infusion

End point type	Secondary

End point timeframe:

Day 75+5 after the 1st and 2nd islet infusion and day 365+14 after last islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[4]	18[5]		
Units: HbA1c %				
number (not applicable)	0	0		

Notes:

[4] - Multiple values, please check attached table for actual values

[5] - Multiple values, please check attached table for actual values

Attachments (see zip file)	Table 14.2.7.1.doc

Statistical analyses

Statistical analysis title	Secondary ANCOVA analysis

Statistical analysis description:

The data at Day 75±5 (both transplants) and Day 365±14 after the last islet infusion were analysed via analysis of covariance (ANCOVA) with factors for treatment and centre and pre-dose value as a covariate. Least squares adjusted mean values for each treatment group were presented, together with the difference in least squares means. The 95% CI for the difference in least square means were estimated using the mean square error from the ANCOVA.

Comparison groups	Reparixin arm v Placebo

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.93
Variability estimate	Standard error of the mean

Secondary: Basal (fasting) and 0 to 120 min time course of glucose, C-peptide and insulin derived from the MMTT

End point title	Basal (fasting) and 0 to 120 min time course of glucose, C-peptide and insulin derived from the MMTT

End point description:

Basal (fasting) and 0 to 120 min time course of glucose, C-peptide and insulin derived from the MMTT at 75+5 after the 1st and 2nd islet infusion and day 365+14 after last islet infusion

End point type	Secondary

End point timeframe:

Day 75+5 after the 1st and 2nd islet infusion and day 365+14 after last islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[6]	18[7]		
Units: IEQ/kg; ng/ml; minutes				
number (not applicable)	0	0		

Notes:

[6] - Multiple values, please check attached table for actual values

[7] - Multiple values, please check attached table for actual values

Attachments (see zip file)	Table 14.2.8.5.doc

Statistical analyses

No statistical analyses for this end point

Secondary: β-cell function as assessed by β-score and Transplant Estimated Function (TEF)

End point title	β-cell function as assessed by β-score and Transplant Estimated Function (TEF)

End point description:

β-cell function as assessed by β-score and Transplant Estimated Function (TEF) at day 75+5 after the 1st and 2nd islet infusion and day 365+14 after last islet infusion

End point type	Secondary

End point timeframe:

Day 75+5 after the 1st and 2nd islet infusion and day 365+14 after last islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[8]	18[9]		
Units: β-score and TEF				
number (not applicable)	0	0		

Notes:

[8] - Multiple values, please check attached table for actual values

[9] - Multiple values, please check attached table for actual values

Attachments (see zip file)	Table 14.2.11.1.doc

Statistical analyses

Statistical analysis title	Secondary analysis - ANOVA

Statistical analysis description:

beta cell function variables were analysed via ANOVA with factors for treatment and centre. Least squares adjusted mean values for each treatment group were presented, together with the difference in least squares means. The 95% CI for the difference in least square means were estimated using the mean square error from the ANOVA.

Comparison groups	Reparixin arm v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.97
upper limit	0.8
Variability estimate	Standard error of the mean

Secondary: The proportion of insulin-independent patients at timeframe day 75+5 after the 1st islet infusion

End point title	The proportion of insulin-independent patients at timeframe day 75+5 after the 1st islet infusion

End point description:

The proportion of insulin-independent patients at timeframe day 75+5 after the 1st islet infusion

End point type	Secondary

End point timeframe:

Day 75+5 after the 1st islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	18		
Units: Subjects	5	1		

Attachments (see zip file)	Table 14.2.2.1.doc

Statistical analyses

Statistical analysis title	Fisher exact test
Comparison groups	Reparixin arm v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	≥ 0.05
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	4.93
Variability estimate	Standard deviation

Notes:

[10] - If a primary analysis model could not fit, a Fisher's exact test was used instead.

Secondary: The proportion of insulin-independent patients at timeframe day 75+5 after the 2nd islet infusion

End point title	The proportion of insulin-independent patients at timeframe day 75+5 after the 2nd islet infusion

End point description:

The proportion of insulin-independent patients at timeframe day 75+5 after the 2nd islet infusion

End point type	Secondary

End point timeframe:

Day 75+5 after the 2nd islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	18		
Units: Subjects	5	8		

Attachments (see zip file)	Table 14.2.2.1.doc

Statistical analyses

Statistical analysis title	Fisher exact test
Comparison groups	Reparixin arm v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	≥ 0.05
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	4.93
Variability estimate	Standard deviation

Notes:

[11] - If a primary model could not fit, a Fisher's exact test was used instead

Other pre-specified: Incidence and severity of Adverse Events and Serious Adverse Events

End point title	Incidence and severity of Adverse Events and Serious Adverse Events

End point description:

Incidence and severity of Adverse Events and Serious Adverse Events throughout the study up to day 365+14 after last islet infusion.

All AEs will be coded using the most up-to-date version at the time of database lock of the MedDRA and will be presented by primary system organ class and preferred term. AEs will be presented in terms of the incidence, severity and relationship to the study drug, overall and by body system and preferred term. SAEs will be presented in the same way.

End point type	Other pre-specified

End point timeframe:

Throughout the study up to day 365+14 after last islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[12]	19[13]		
Units: Event	0	0		

Notes:

[12] - Multiple values, please check attached table for actual values

[13] - Multiple values, please check attached table for actual values

Attachments (see zip file)	Table 14.3.2.doc Table 14.3.5.doc

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Standard laboratory tests including hematology, clinical chemistry

End point title	Standard laboratory tests including hematology, clinical chemistry

End point description:

Standard laboratory tests including hematology, clinical chemistry at preinfusion hospital admission and post-infusion hospital discharge

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, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and coagulation (prothrombin time (PT), partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT))

Results for each laboratory test at screening and hospital discharge will be assessed as being below the lower limit of the normal range, within the normal range or above the upper limit of the normal range.

End point type	Other pre-specified

End point timeframe:

Preinfusion hospital admission and post-infusion hospital discharge

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[14]	19[15]		
Units: Various				
number (not applicable)	0	0		

Notes:

[14] - Multiple values, please check attached table for actual values

[15] - Multiple values, please check attached table for actual values

Attachments (see zip file)	Table 14.3.9.doc Table 14.3.10.doc Table 14.3.11.1.doc Table 14.3.11.2.doc Table 14.3.12.doc

Table 14.3.13.doc
Table 14.3.14.1.doc
Table 14.3.14.2.doc
Table 14.3.14.3.doc
Table 14.3.15.doc
Table 14.3.16.doc
Table 14.3.17.doc
Table 14.3.18.doc

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Vital signs

End point title	Vital signs

End point description:

Vital signs at each time point and the change in vital signs from screening will be presented using descriptive statistics

End point type	Other pre-specified

End point timeframe:

Pre-infusion hospital admission and post-infusion hospital discharge

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[16]	19[17]		
Units: Various				
number (not applicable)	0	0		

Notes:

[16] - Multiple values, please check attached table for actual values

[17] - Multiple values, please check attached table for actual values

Attachments (see zip file)	Table 14.3.19.doc
	Table 14.3.20.doc
	Table 14.3.21.doc

Statistical analyses

No statistical analyses for this end point

Other pre-specified: ALT/AST, PT/PTT, fibrin degradation products (XDPs) or D-dimer, C-reactive protein (CRP)

End point title	ALT/AST, PT/PTT, fibrin degradation products (XDPs) or D-dimer, C-reactive protein (CRP)

End point description:

ALT/AST, PT/PTT, XDP and CRP will be summarized for each of the 6 days post-transplant and (ALT/AST) for day 75+5 post-transplant. The proportion of patients with ALT/AST below or within

normal range, up to 3x ULN or above 3x ULN will also be presented.

End point type	Other pre-specified

End point timeframe:

All daily up to day 6 after the 1st and 2nd islet infusion; ALT/AST also on day 75+5 after the 1st and 2nd islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[18]	19[19]		
Units: Various				
number (not applicable)	0	0		

Notes:

[18] - Multiple values, please check attached table for actual values

[19] - Multiple values, please check attached table for actual values

Attachments (see zip file)	Table 14.3.9.doc Table 14.3.10.doc Table 14.3.11.1.doc Table 14.3.11.2.doc Table 14.3.12.doc Table 14.3.13.doc Table 14.3.14.1.doc Table 14.3.14.2.doc Table 14.3.14.3.doc Table 14.3.15.doc

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Auto-antibodies (GAD, IA-2, optional: ZnT8)

End point title	Auto-antibodies (GAD, IA-2, optional: ZnT8)

End point description:

Auto-antibody, anti-HLA antibodies, chemokines/cytokines and coagulation/complement activation markers will be presented using appropriate descriptive statistics, by treatment group.

End point type	Other pre-specified

End point timeframe:

Pre-infusion hospital admission, day 6/7 and day 75+5 after the 1st and 2nd islet infusion and day 365+14 after the last islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[20]	18[21]		
Units: Subjects	0	0		

Notes:

[20] - Multiple values, please check attached table for actual values

[21] - Multiple values, please check attached table for actual values

Attachments (see zip file)	Table 14.2.13.1.doc

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Anti-HLA antibodies

End point title	Anti-HLA antibodies

End point description:

Auto-antibody, anti-HLA antibodies, chemokines/cytokines and coagulation/complement activation markers will be presented using appropriate descriptive statistics, by treatment group.

End point type	Other pre-specified

End point timeframe:

Pre-infusion hospital admission, day 6/7 and day 75+5 after the 1st and 2nd islet infusion and day 365+14 after the last islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[22]	18[23]		
Units: Subjects	0	0		

Notes:

[22] - Multiple values, please check attached table for actual values

[23] - Multiple values, please check attached table for actual values

Attachments (see zip file)	Table 14.2.16.doc

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 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 & Time course of serum microRNA-375 (miR-375)

End point title	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 & Time course of serum microRNA-375 (miR-375)

End point description:

Auto-antibody, anti-HLA antibodies, chemokines/cytokines and coagulation/complement activation markers will be presented using appropriate descriptive statistics, by treatment group.

End point type	Other pre-specified

End point timeframe:

preinfusion hospital admission and 6, 12, 24, 72, 120 and 168hrs after the 1st and 2nd islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	18		
Units: Various				
number (not applicable)	9	7		

Attachments (see zip file)	Table 14.2.1.1.doc Table 14.2.18.doc Table 14.2.19.doc Table 14.2.20.doc Table 14.2.21.doc Table 14.2.22.doc Table 14.2.23.doc Table 14.2.24.doc Table 14.2.26.doc

Statistical analyses

Statistical analysis title	Exploratory ANCOVA analysis

Statistical analysis description:

For each of the above variables, the AUC0-168 after each transplant were analysed via ANCOVA of ranked transformed data with factors for treatment and centre and pre-transplant value as a covariate. The 95% Hodges-Lehmann CI for the difference between treatments were estimated using PROC NPAR1WAY in SAS using the Higher Level (HL) option. The within treatment distribution-free 95% CIs for the medians were estimated using the CIQUANTDF (alpha=.05) option within PROC UNIVARIATE in SAS.

Comparison groups	Reparixin arm v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.94
upper limit	5.55
Variability estimate	Standard error of the mean

Other pre-specified: Time-course of coagulation/complement activation markers as assessed by blood level of C3a, sC5b-9, Thrombin-antithrombin complexes (TAT), D-dimer (inclusive of markers of PMN/monocyte activation)

End point title	Time-course of coagulation/complement activation markers as assessed by blood level of C3a, sC5b-9, Thrombin-antithrombin complexes (TAT), D-dimer (inclusive of markers of PMN/monocyte activation)

End point description:

Auto-antibody, anti-HLA antibodies, chemokines/cytokines and coagulation/complement activation markers will be presented using appropriate descriptive statistics, by treatment group.

End point type	Other pre-specified

End point timeframe:

pre-infusion hospital admission and 1, 6, 12, 24, 72, 120 and 168hrs after the 1st and 2nd islet infusion

End point values	Reparixin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[24]	18[25]		
Units: Various				
number (not applicable)	0	0		

Notes:

[24] - Multiple values, please check attached table for actual values

[25] - Multiple values, please check attached table for actual values

Attachments (see zip file)	Table 14.2.27.doc Table 14.2.28.doc Table 14.2.29.doc Table 14.2.30.doc Table 14.2.31.doc Table 14.2.32.doc

Statistical analyses

Statistical analysis title	Exploratory ANCOVA analysis

Statistical analysis description:

For each of the above variables, the AUC0-168 after each transplant were analysed via ANCOVA of ranked transformed data with factors for treatment and centre and pre-transplant value as a covariate. The 95% Hodges-Lehmann CI for the difference between treatments were estimated using PROC NPAR1WAY in SAS using the HL option. The within treatment distribution-free 95% CIs for the medians were estimated using the CIQUANTDF (alpha=.05) option within PROC UNIVARIATE in SAS.

Comparison groups	Reparixin arm v Placebo

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-10.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.57
upper limit	19.95
Variability estimate	Standard error of the mean

Adverse events

Adverse events information

Timeframe for reporting adverse events:

- seven calendar days after becoming aware of the information if the event is fatal or life threatening; and
- fifteen calendar days after becoming aware of the information if the event is neither fatal nor life threatening

Adverse event reporting additional description:

Dompé was to submit a complete report in respect of ADR information that included an assessment of the importance and implication of any findings made within 8 days after having informed the Competent Authority.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Reparixin

Reporting group description:

Subjects who received Reparixin at a dose of 2.772 mg/kg body weight/hour for 7 days

Reporting group title	Placebo

Reporting group description:

Subjects who received Placebo at a dose of 2.772 mg/kg body weight/hour for 7 days

Serious adverse events	Reparixin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 29 (58.62%)	12 / 19 (63.16%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Implant site haemorrhage			

subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Puncture site haemorrhage			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Alloimmunisation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant rejection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
HLA marker trial positive			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panel-reactive antibody increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complications of transplant surgery			

subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Diabetic neuropathy			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 29 (6.90%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 29 (10.34%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 29 (6.90%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 29 (6.90%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	2 / 29 (6.90%)	2 / 19 (10.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 29 (3.45%)	3 / 19 (15.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	2 / 29 (6.90%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 29 (6.90%)	2 / 19 (10.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic haematoma			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Urinary retention			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Localised infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 29 (3.45%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ketosis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Reparixin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 29 (100.00%)	18 / 19 (94.74%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Dizziness			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 29 (3.45%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	3 / 29 (10.34%)	0 / 19 (0.00%)	
occurrences (all)	4	0	
Hypotension			
subjects affected / exposed	2 / 29 (6.90%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	1 / 29 (3.45%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Catheter site pain			
subjects affected / exposed	3 / 29 (10.34%)	2 / 19 (10.53%)	
occurrences (all)	4	2	
Chest discomfort			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Chills			

subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Generalised oedema			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Implant site haemorrhage			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	4 / 29 (13.79%)	1 / 19 (5.26%)	
occurrences (all)	5	1	
Peripheral swelling			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	3 / 29 (10.34%)	5 / 19 (26.32%)	
occurrences (all)	4	6	
Vessel puncture site erythema			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	2 / 29 (6.90%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Nasal congestion			
subjects affected / exposed	2 / 29 (6.90%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
Upper-airway cough syndrome			

subjects affected / exposed	1 / 29 (3.45%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Rhinorrhoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 29 (3.45%)	3 / 19 (15.79%)	
occurrences (all)	1	4	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	3 / 29 (10.34%)	0 / 19 (0.00%)	
occurrences (all)	3	0	
Blood potassium decreased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Blood pressure decreased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	1 / 29 (3.45%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Heart rate increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 29 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Liver function test increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Portal vein pressure increased			

subjects affected / exposed	2 / 29 (6.90%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Weight increased			
subjects affected / exposed	0 / 29 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Head injury			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Incision site pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Post procedural haematoma			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	3 / 29 (10.34%)	1 / 19 (5.26%)	
occurrences (all)	3	2	
Wound dehiscence			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Blood magnesium decreased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Bradycardia			

subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	2 / 29 (6.90%)	1 / 19 (5.26%)	
occurrences (all)	3	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	8 / 29 (27.59%)	7 / 19 (36.84%)	
occurrences (all)	11	9	
Migraine			
subjects affected / exposed	1 / 29 (3.45%)	2 / 19 (10.53%)	
occurrences (all)	1	2	
Syncope			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Emotional distress			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	1 / 29 (3.45%)	2 / 19 (10.53%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 29 (10.34%)	1 / 19 (5.26%)	
occurrences (all)	6	3	
Leukopenia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Neutropenia			

subjects affected / exposed	1 / 29 (3.45%)	2 / 19 (10.53%)	
occurrences (all)	1	2	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Vitreous floaters			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 29 (20.69%)	9 / 19 (47.37%)	
occurrences (all)	6	9	
Abdominal pain upper			
subjects affected / exposed	1 / 29 (3.45%)	2 / 19 (10.53%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	3 / 29 (10.34%)	0 / 19 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	5 / 29 (17.24%)	3 / 19 (15.79%)	
occurrences (all)	7	3	
Lip oedema			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Lip swelling			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	10 / 29 (34.48%)	10 / 19 (52.63%)	
occurrences (all)	15	15	
Peritoneal haemorrhage			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Stomatitis			

subjects affected / exposed	2 / 29 (6.90%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	6 / 29 (20.69%)	5 / 19 (26.32%)	
occurrences (all)	7	7	
Hepatobiliary disorders			
Hepatic haemorrhage			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 29 (3.45%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Erythema			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	2 / 29 (6.90%)	2 / 19 (10.53%)	
occurrences (all)	2	2	
Rash			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Skin exfoliation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	

Back pain			
subjects affected / exposed	2 / 29 (6.90%)	2 / 19 (10.53%)	
occurrences (all)	3	3	
Joint swelling			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	3 / 29 (10.34%)	1 / 19 (5.26%)	
occurrences (all)	3	1	
Neck pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 29 (3.45%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Infections and infestations			
Coccidioidomycosis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Fluid retention			
subjects affected / exposed	1 / 29 (3.45%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia			
subjects affected / exposed	3 / 29 (10.34%)	0 / 19 (0.00%)	
occurrences (all)	5	0	
Hypervolaemia			

subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	5 / 29 (17.24%)	3 / 19 (15.79%)	
occurrences (all)	6	5	
Hypokalaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2012	Protocol amendment 1: the wording for AEs and SAEs recording were corrected in protocol section 8.2 in order to clarify recording period and keep consistency with Appendix 4 of the protocol.
13 December 2013	Protocol version No. 2 dated 13 December 2013 included updates to: clinical data section, overall study design (study timelines), objectives and endpoints, exclusion criteria, investigation product section (other treatments), study procedure and assessments and finally administrative details It also included the changes introduced by previous amendment No. 1 and country-specific amendments No. 2 and 3. Country-specific amendment No. 2 created to address specific requirements from Swedish regulatory authority, is applicable to the Swedish sites only. Similarly, Amendment No. 3 issued upon specific requirements from the FDA, considering that islet allo-transplant is a research procedure in the US, is applicable to the US site only. Therefore, additional exclusion criteria and procedures, as well as stopping rules, are meant to comply with these specific IND requirements; consequently introduced by amendment no. 3, are applicable to the US site only. All country-specific procedures are clearly identified in the revised protocol (version No. 2 dated 13 December 2013). Some other minor corrections to the protocol and clarification with regard to some items were also included.

Notes:

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.

Sample size was based on feasibility and might have been too low to detect treatment differences. Similarly, unbalanced patient distribution across sites and site-specific differences in the population/procedures, might have affected overall results.

Notes: