Clinical trial results:
Open Randomized Multi-Center Study to Evaluate Safety and Efficacy of Low Molecular Weight Sulfated Dextran in Islet Transplantation.

Summary

EudraCT number	2008-001210-25
Trial protocol	SE
Global end of trial date	21 August 2014

Results information

Result version number	v1 (current)
This version publication date	15 November 2019
First version publication date	15 November 2019

Trial information

Trial identification

Sponsor protocol code	CIT-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00789308
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	National Institute of Allergy and Infectious Diseases, NIH
Sponsor organisation address	5601 Fishers Lane; Room 6B38, Rockville, United States, MD 20852
Public contact	Olle Korsgren, M.D., Ph.D., Division of Allergy, Immunology, and Transplantation National Institute of Allergy and Infectious, Olle.korsgren@igp.uu.se
Scientific contact	Nancy Bridges, MD, Division of Allergy, Immunology, and Transplantation National Institute of Allergy and Infectious, NBridges@niaid.nih.gov

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	26 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 August 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of Low Molecular Weight Dextran Sulfate (LMW-DS) to enhance engraftment and prevent IBMIR in islet transplantation to Type 1 diabetic subjects.

Protection of trial subjects:

Once the first islet transplantation was performed, subjects were required to perform periodic follow-up visits at days 1, 3, 7, 14, 21, 28, and 75, and at 6 and 12 months. The timing of all follow-up assessments will reset at the time of subsequent transplants. Clinical safety was monitored through routine physical examinations and appropriate laboratory assessments. Evaluations were to be made for sirolimus, cyclosporine and tacrolimus levels, as applicable. Immunosuppression levels were to be monitored from time of transplantation until the end of the study. Stopping rules for enrollment of subsequent patients were applied.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	11 July 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 14
Country: Number of subjects enrolled	Sweden: 25
Worldwide total number of subjects	39
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)	39
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first subject was enrolled on 11-Jul-2008 and the last subject was enrolled on 18-Jan-2012. All subjects had reached the primary endpoint by 17-Jan-2014. The last subject's last study visit was on 21-Aug-2014. The study was conducted in three (3) centers in Scandinavia (2 in Sweden, and 1 in Norway).

Pre-assignment

Screening details:

Eligible subjects (type 1 diabetes confirmed by absence of C-peptide and a history of at least one confirmed episode of severe hypoglycemia in the year prior to study entry) were placed on the transplant Waiting List and periodically re-tested for continued eligibility until a compatible islet donor preparation was made available.

Pre-assignment period milestones

Number of subjects started	39
Intermediate milestone: Number of subjects	Screening: 39
Intermediate milestone: Number of subjects	Waiting List: 29
Number of subjects completed	24

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Ineligible during Waiting List: 5
Reason: Number of subjects	Consent withdrawn by subject: 4
Reason: Number of subjects	screen failure: 6

Period 1

Period 1 title	Baseline/Randomization
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LMW-DS

Arm description:

Low Molecular Weight Sulfated Dextran (LMW-DS), 20 mg/mL
Subjects received LMW-DS prior, during and following the islet infusion

Arm type	Experimental
Investigational medicinal product name	LMW-DS
Investigational medicinal product code	
Other name	Low molecular weight dextran sulfate
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intraportal use, Intravenous bolus use

Dosage and administration details:

Prior islet infusion: Each subject received a bolus of LMW-DS (20 mg/mL) intraportally of 1.5 mg/kg body weight at 0 hour,
During islet infusion (Day 0): From 0-20 minutes, each subject received an infusion of LMW-DS (20 mg/mL) of 3 mg/kg added to the islet infusion and administered intraportally. From 20-32 minutes, each subject received an infusion of 0.7 mg/kg of LMW- DS added to the islet infusion "washing

solution” and administered intraportally,
Post-islet infusion: At 32 minutes, a continuous minutes intravenous infusion was initiated based on the subject’s APTT at 20 (optionally at 22 minutes) and adjusted to achieve the target APTT of 150±10 seconds. Subjects received LMW-DS for five (5) hours with close monitoring of APTT levels, i.e. at 10, 20, 22, 50, 90, 130 minutes and every 60 min thereafter (more often if necessary).

Arm title	State of the Art

Arm description:

Control Arm with Heparin given during and post islet infusion according to concentrations routinely used in clinical islet transplantation

Arm type	Active comparator
Investigational medicinal product name	Heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intraportal use

Dosage and administration details:

During islet infusion (Day 0): 70 U/kg body weight
Post-islet infusion: Continuous intraportal infusion of Heparin targeting an Activated Partial Thromboplastin Time (APTT) of 50±10 seconds, during five (5) hours
Heparin was given to subjects randomized to the “State of Art” arm according to concentrations routinely used in clinical islet transplantation.

Number of subjects in period 1[1]	LMW-DS	State of the Art
Started	10	14
Completed	10	14

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: The worldwide number enrolled corresponds to the number of subjects who consented participation in the study and were then screened for eligibility.
The number of subjects reported to be in the baseline period corresponds to the number of subjects who remained eligible during screening and waiting list period, and were randomised and exposed to one of the treatments.

Period 2

Period 2 title	75 days following first islet infusion
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LMW-DS

Arm description:

Low Molecular Weight Sulfated Dextran (LMW-DS), 20 mg/mL
Subjects received LMW-DS prior, during and following the islet infusion

Arm type	Experimental

Investigational medicinal product name	LMW-DS
Investigational medicinal product code	
Other name	Low molecular weight dextran sulfate
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous bolus use , Intraportal use

Dosage and administration details:

Prior islet infusion: Each subject received a bolus of LMW-DS (20 mg/mL) intraportally of 1.5 mg/kg body weight at 0 hour,
During islet infusion (Day 0): From 0-20 minutes, each subject received an infusion of LMW-DS (20 mg/mL) of 3 mg/kg added to the islet infusion and administered intraportally. From 20-32 minutes, each subject received an infusion of 0.7 mg/kg of LMW- DS added to the islet infusion "washing solution" and administered intraportally,
Post-islet infusion: At 32 minutes, a continuous minutes intravenous infusion was initiated based on the subject's APTT at 20 (optionally at 22 minutes) and adjusted to achieve the target APTT of 150±10 seconds. Subjects received LMW-DS for five (5) hours with close monitoring of APTT levels, i.e. at 10, 20, 22, 50, 90, 130 minutes and every 60 min thereafter (more often if necessary).

Arm title	State of the Art

Arm description:

Control Arm with Heparin given during and post islet infusion according to concentrations routinely used in clinical islet transplantation

Arm type	Active comparator
Investigational medicinal product name	Heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intraportal use

Dosage and administration details:

During islet infusion (Day 0): 70 U/kg body weight
Post-islet infusion: Continuous intraportal infusion of Heparin targeting an Activated Partial Thromboplastin Time (APTT) of 50±10 seconds, during five (5) hours
Heparin was given to subjects randomized to the "State of Art" arm according to concentrations routinely used in clinical islet transplantation.

Number of subjects in period 2	LMW-DS	State of the Art
Started	10	14
Completed	10	14

Baseline characteristics

Reporting groups	
Reporting group title	LMW-DS
Reporting group description:	
Low Molecular Weight Sulfated Dextran (LMW-DS), 20 mg/mL Subjects received LMW-DS prior, during and following the islet infusion	
Reporting group title	State of the Art
Reporting group description:	
Control Arm with Heparin given during and post islet infusion according to concentrations routinely used in clinical islet transplantation	

Reporting group values	LMW-DS	State of the Art	Total
Number of subjects	10	14	24
Age categorical Units: Subjects			
Adults (18-64 years)	10	14	24
Age continuous Units: years			
median	49.1	51.4	
full range (min-max)	27.5 to 59.7	36.7 to 63.8	-
Gender categorical Units: Subjects			
Female	6	8	14
Male	4	6	10
Race Units: Subjects			
White	2	0	2
Not reported	8	14	22
Ethnicity Units: Subjects			
Non-Hispanic / Non-Latino Origin	2	0	2
Not reported	8	14	22
Weight			
Lowest value observed for all subjects was imputed for missing values)			
Units: kilogram(s)			
median	73.3	66.8	
full range (min-max)	56 to 93	51 to 86	-
BMI			
body mass index			
Units: kilogram(s)/square meter			
median	25.3	22.4	
full range (min-max)	20.1 to 28.7	18.6 to 29.1	-
Duration of diabetes Units: years			
median	32.5	33	
full range (min-max)	18 to 49	16 to 46	-
C-peptide derived from MMTT_0 min			
C-peptide derived from MMTT at 0 min			

Units: nanogram(s)/millilitre			
median	0.05	0.05	
full range (min-max)	0.05 to 0.08	0.05 to 0.05	-
C-peptide derived from MMTT_60 min			
C-peptide derived from MMTT at 60 min			
Units: nanogram(s)/millilitre			
median	0.05	0.05	
full range (min-max)	0.05 to 0.29	0.05 to 0.06	-
C-peptide derived from MMTT_90 min			
C-peptide derived from MMTT at 90 min			
Units: nanogram(s)/millilitre			
median	0.05	0.05	
full range (min-max)	0.05 to 0.28	0.05 to 0.16	-

Subject analysis sets

Subject analysis set title	Intent-to-Treat Population (ITT) LMW-DS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All efficacy and safety analyses were based on a modified ITT principle: any subject who was randomized to LMW DS and received protocol driven therapy (LMW-DS or heparin) was analyzed as in the LMW-DS group despite protocol adherence

Subject analysis set title	Safety Population LMW-DS
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consisted of any subject who was randomized to LMW DS and in whom protocol-directed therapy was initiated. Subjects
in this population may not have received an islet transplant

Subject analysis set title	Intent-to-Treat Population (ITT) State of the Art
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All efficacy and safety analyses were based on a modified ITT principle: any subject who was randomized to State of the Art arm (i.e. heparin) and received protocol driven therapy (LMW-DS or heparin) was analyzed as in the State of the Art group despite protocol adherence.

Subject analysis set title	Safety Population State of the Art
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consisted of any subject who was randomized to State of the Art arm (i.e. heparin) and in whom protocol-directed therapy was initiated. Subjects
in this population may not have received an islet transplant

Reporting group values	Intent-to-Treat Population (ITT) LMW-DS	Safety Population LMW-DS	Intent-to-Treat Population (ITT) State of the Art
Number of subjects	9	10	12
Age categorical			
Units: Subjects			
Adults (18-64 years)	9	10	12
Age continuous			
Units: years			
median	51.1	49.1	51
full range (min-max)	27.5 to 59.7	27.5 to 59.7	36.7 to 63.8

Gender categorical Units: Subjects			
Female	6	6	7
Male	3	4	5
Race Units: Subjects			
White	2	2	0
Not reported	7	8	12
Ethnicity Units: Subjects			
Non-Hispanic / Non-Latino Origin	2	2	0
Not reported	7	8	12
Weight			
Lowest value observed for all subjects was imputed for missing values)			
Units: kilogram(s)			
median	66.5	73.3	66.8
full range (min-max)	56 to 93	56 to 93	51 to 86
BMI			
body mass index			
Units: kilogram(s)/square meter			
median	23.6	25.3	21.7
full range (min-max)	20.1 to 28.7	20.1 to 28.7	18.6 to 26
Duration of diabetes Units: years			
median	32	32.5	33.5
full range (min-max)	18 to 49	18 to 49	16 to 46
C-peptide derived from MMTT_0 min			
C-peptide derived from MMTT at 0 min			
Units: nanogram(s)/millilitre			
median	0.05	0.05	0.05
full range (min-max)	0.05 to 0.08	0.05 to 0.08	0.05 to 0.05
C-peptide derived from MMTT_60 min			
C-peptide derived from MMTT at 60 min			
Units: nanogram(s)/millilitre			
median	0.05	0.05	0.05
full range (min-max)	0.05 to 0.29	0.05 to 0.29	0.05 to 0.06
C-peptide derived from MMTT_90 min			
C-peptide derived from MMTT at 90 min			
Units: nanogram(s)/millilitre			
median	0.05	0.05	0.05
full range (min-max)	0.05 to 0.28	0.05 to 0.28	0.05 to 0.16

Reporting group values	Safety Population State of the Art		
Number of subjects	12		
Age categorical Units: Subjects			
Adults (18-64 years)	14		
Age continuous Units: years			
median	51.4		
full range (min-max)	36.7 to 63.8		

Gender categorical Units: Subjects			
Female	8		
Male	6		
Race Units: Subjects			
White	0		
Not reported	14		
Ethnicity Units: Subjects			
Non-Hispanic / Non-Latino Origin	0		
Not reported	14		
Weight			
Lowest value observed for all subjects was imputed for missing values)			
Units: kilogram(s)			
median	66.8		
full range (min-max)	51 to 86		
BMI			
body mass index			
Units: kilogram(s)/square meter			
median	22.4		
full range (min-max)	18.6 to 29.1		
Duration of diabetes Units: years			
median	33		
full range (min-max)	16 to 46		
C-peptide derived from MMTT_0 min			
C-peptide derived from MMTT at 0 min			
Units: nanogram(s)/millilitre			
median	0.05		
full range (min-max)	0.05 to 0.05		
C-peptide derived from MMTT_60 min			
C-peptide derived from MMTT at 60 min			
Units: nanogram(s)/millilitre			
median	0.05		
full range (min-max)	0.05 to 0.06		
C-peptide derived from MMTT_90 min			
C-peptide derived from MMTT at 90 min			
Units: nanogram(s)/millilitre			
median	0.05		
full range (min-max)	0.05 to 0.16		

End points

End points reporting groups

Reporting group title	LMW-DS
Reporting group description:	
Low Molecular Weight Sulfated Dextran (LMW-DS), 20 mg/mL Subjects received LMW-DS prior, during and following the islet infusion	
Reporting group title	State of the Art
Reporting group description:	
Control Arm with Heparin given during and post islet infusion according to concentrations routinely used in clinical islet transplantation	
Reporting group title	LMW-DS
Reporting group description:	
Low Molecular Weight Sulfated Dextran (LMW-DS), 20 mg/mL Subjects received LMW-DS prior, during and following the islet infusion	
Reporting group title	State of the Art
Reporting group description:	
Control Arm with Heparin given during and post islet infusion according to concentrations routinely used in clinical islet transplantation	
Subject analysis set title	Intent-to-Treat Population (ITT) LMW-DS
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All efficacy and safety analyses were based on a modified ITT principle: any subject who was randomized to LMW DS and received protocol driven therapy (LMW-DS or heparin) was analyzed as in the LMW-DS group despite protocol adherence	
Subject analysis set title	Safety Population LMW-DS
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population consisted of any subject who was randomized to LMW DS and in whom protocol-directed therapy was initiated. Subjects in this population may not have received an islet transplant	
Subject analysis set title	Intent-to-Treat Population (ITT) State of the Art
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All efficacy and safety analyses were based on a modified ITT principle: any subject who was randomized to State of the Art arm (i.e. heparin) and received protocol driven therapy (LMW-DS or heparin) was analyzed as in the State of the Art group despite protocol adherence.	
Subject analysis set title	Safety Population State of the Art
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population consisted of any subject who was randomized to State of the Art arm (i.e. heparin) and in whom protocol-directed therapy was initiated. Subjects in this population may not have received an islet transplant	

Primary: Primary Endpoint

End point title	Primary Endpoint
End point description:	
The level of stimulated C-peptide at 90-minutes derived from the mixed-meal tolerance test (MMTT) at 75±5 days following the first islet infusion. The ITT analysis set was used.	
End point type	Primary
End point timeframe:	
75±5 days following the first islet infusion	

End point values	Intent-to-Treat Population (ITT) LMW-DS	Intent-to-Treat Population (ITT) State of the Art		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	12		
Units: ng/mL				
arithmetic mean (confidence interval 95%)	1.333 (0.5487 to 2.1173)	1.5621 (0.7784 to 2.3458)		

Statistical analyses

Statistical analysis title	The difference in the means between the two arms

Statistical analysis description:

The difference in the means between the two treatment groups was used as the measure of efficacy.

Comparison groups	Intent-to-Treat Population (ITT) LMW-DS v Intent-to-Treat Population (ITT) State of the Art
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.6641 [2]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	0.6

Notes:

[1] - The primary analysis was based on an independent-samples two-sided t-test.

[2] - In order to declare a statistically significant difference it was necessary the overall p-value to be ≤0.05.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 75 and 365 days after initial transplant and 365 days after final transplant from baseline	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11

Reporting groups	
Reporting group title	LMW-DS (Baseline to 75 days after initial islet infusion)
Reporting group description: -	
Reporting group title	LMW-DS (Baseline to 365 days after initial islet infusion)
Reporting group description: -	
Reporting group title	LMW-DS (Baseline to 365 days after final islet infusion)
Reporting group description: -	
Reporting group title	SotA (Baseline to 75 days after initial islet infusion)
Reporting group description: -	
Reporting group title	SotA (Baseline to 365 days after initial islet infusion)
Reporting group description: -	
Reporting group title	SotA (Baseline to 365 days after final islet infusion)
Reporting group description: -	

Serious adverse events	LMW-DS (Baseline to 75 days after initial islet infusion)	LMW-DS (Baseline to 365 days after initial islet infusion)	LMW-DS (Baseline to 365 days after final islet infusion)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	6 / 10 (60.00%)	6 / 10 (60.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Procedural complication			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transplant failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Shoulder operation			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulocytopenia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Cytokine release syndrome			

subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transplant rejection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Lung infiltration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis norovirus			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	SotA (Baseline to 75 days after initial islet infusion)	SotA (Baseline to 365 days after initial islet infusion)	SotA (Baseline to 365 days after final islet infusion)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	4 / 14 (28.57%)	6 / 14 (42.86%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Procedural complication			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transplant failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Shoulder operation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Febrile neutropenia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulocytopenia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transplant rejection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Lung infiltration			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis norovirus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	LMW-DS (Baseline to 75 days after initial islet infusion)	LMW-DS (Baseline to 365 days after initial islet infusion)	LMW-DS (Baseline to 365 days after final islet infusion)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)	10 / 10 (100.00%)	10 / 10 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Multiple myeloma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin papilloma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Tendon operation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Catheter site pain			
subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	2 / 10 (20.00%)
occurrences (all)	1	2	2
Chest pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 10 (10.00%)	3 / 10 (30.00%)	3 / 10 (30.00%)
occurrences (all)	1	3	3
Feeling cold			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Non-cardiac chest pain			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	10 / 10 (100.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Lung infiltration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal blistering			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Rhinorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			

Depression			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nightmare			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood calcium decreased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Blood creatine increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	4	4
Blood magnesium decreased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	3 / 10 (30.00%)
occurrences (all)	1	1	3
Haemoglobin decreased			
subjects affected / exposed	1 / 10 (10.00%)	3 / 10 (30.00%)	3 / 10 (30.00%)
occurrences (all)	1	7	9
Hepatic enzyme increased			
subjects affected / exposed	3 / 10 (30.00%)	3 / 10 (30.00%)	3 / 10 (30.00%)
occurrences (all)	3	4	4
Neutrophil count decreased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	3	3
Serum ferritin decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Weight decreased			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	1 / 10 (10.00%)	3 / 10 (30.00%)	3 / 10 (30.00%)
occurrences (all)	1	3	3
White blood cell count increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
White blood cells urine			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye operation complication			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Scratch			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	10
Dysgeusia			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Formication			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	2 / 10 (20.00%)
occurrences (all)	2	2	2
Hypoaesthesia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Neuropathy peripheral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	2 / 10 (20.00%)	3 / 10 (30.00%)	3 / 10 (30.00%)
occurrences (all)	2	3	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Haemoglobinaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Lymphadenitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	2 / 10 (20.00%)
occurrences (all)	1	3	3

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Diabetic retinopathy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Macular oedema			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Retinopathy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	2	2	2
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Anal pruritus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Diabetic gastroparesis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Diarrhoea			

subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	2 / 10 (20.00%)
occurrences (all)	1	2	2
Food poisoning			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Gastritis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Gastrointestinal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Periodontitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	5 / 10 (50.00%)	5 / 10 (50.00%)
occurrences (all)	1	7	7
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	2	2	2
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	3 / 10 (30.00%)
occurrences (all)	1	2	3
Alopecia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Hirsutism			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Nail disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Rash pruritic			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Residual urine			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Fibromyalgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tendonitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Catheter related infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Cytomegalovirus infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Genital herpes			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	2 / 10 (20.00%)
occurrences (all)	3	5	5
Urinary tract infection bacterial			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	2	3
Viral infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	1	1	1

Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	1	1	1

Non-serious adverse events	SotA (Baseline to 75 days after initial islet infusion)	SotA (Baseline to 365 days after initial islet infusion)	SotA (Baseline to 365 days after final islet infusion)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	14 / 14 (100.00%)	14 / 14 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Multiple myeloma			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Skin papilloma			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Surgical and medical procedures			
Tendon operation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	3 / 14 (21.43%)	3 / 14 (21.43%)	3 / 14 (21.43%)
occurrences (all)	3	3	3
Catheter site pain			
subjects affected / exposed	1 / 14 (7.14%)	3 / 14 (21.43%)	3 / 14 (21.43%)
occurrences (all)	1	3	3
Chest pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	3 / 14 (21.43%)	3 / 14 (21.43%)	3 / 14 (21.43%)
occurrences (all)	3	3	3

Feeling cold			
subjects affected / exposed	0 / 14 (0.00%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	0	2	2
Non-cardiac chest pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Oedema peripheral			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Pyrexia			
subjects affected / exposed	2 / 14 (14.29%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	2	2	2
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	2 / 14 (14.29%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	2	2	2
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	1 / 14 (7.14%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	1	2	2
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	2	2
Lung infiltration			
subjects affected / exposed	0 / 14 (0.00%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	0	2	2
Oropharyngeal blistering			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	2	2

Rhinorrhoea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	2	2	2
Nightmare			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	2	2
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Blood calcium decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Blood creatine increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Blood magnesium decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Haemoglobin decreased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	2	2
Hepatic enzyme increased			
subjects affected / exposed	3 / 14 (21.43%)	3 / 14 (21.43%)	3 / 14 (21.43%)
occurrences (all)	4	4	4
Neutrophil count decreased			
subjects affected / exposed	2 / 14 (14.29%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	2	2	2
Serum ferritin decreased			

subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	2
Weight decreased			
subjects affected / exposed	2 / 14 (14.29%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	2	2	2
White blood cell count decreased			
subjects affected / exposed	2 / 14 (14.29%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	2	4	4
White blood cell count increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
White blood cells urine			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Eye operation complication			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Scratch			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Tachycardia			
subjects affected / exposed	1 / 14 (7.14%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	1	2	2
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Dizziness			

subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Dysgeusia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Formication			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Headache			
subjects affected / exposed	3 / 14 (21.43%)	4 / 14 (28.57%)	4 / 14 (28.57%)
occurrences (all)	4	5	5
Hypoaesthesia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Migraine			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Tremor			
subjects affected / exposed	2 / 14 (14.29%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	2	2	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	0	3	3
Haemoglobinaemia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Leukopenia			
subjects affected / exposed	1 / 14 (7.14%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	1	2	2
Lymphadenitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1

Neutropenia			
subjects affected / exposed	1 / 14 (7.14%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	1	4	4
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	2	2
Eye disorders			
Cataract			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Diabetic retinopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Macular oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Retinopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	2 / 14 (14.29%)	3 / 14 (21.43%)	3 / 14 (21.43%)
occurrences (all)	2	3	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	1	2	2
Abdominal pain upper			
subjects affected / exposed	1 / 14 (7.14%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	1	2	2
Anal pruritus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	0	2	2
Diabetic gastroparesis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Food poisoning			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	2 / 14 (14.29%)	2 / 14 (14.29%)	3 / 14 (21.43%)
occurrences (all)	2	2	3
Gastrointestinal pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Gingivitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	3 / 14 (21.43%)	4 / 14 (28.57%)	5 / 14 (35.71%)
occurrences (all)	3	4	5
Oral pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Periodontitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Alopecia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	0	2	2
Hirsutism			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Pruritus			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	2
Rash			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Rash pruritic			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	2	2
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Residual urine			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Fibromyalgia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Muscle spasms			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Myalgia			

subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Pain in extremity			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Tendonitis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Catheter related infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Cytomegalovirus infection			
subjects affected / exposed	0 / 14 (0.00%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	0	2	2
Genital herpes			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	3	3
Tooth infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Urinary tract infection bacterial			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Viral infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0
Metabolism and nutrition disorders Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2009	The amendment summary (i.e. Change Document) resulting in version 5.0 of the Clinical Study Protocol included the changes made to Version 3.0 (first effective/approved version) and also addressed comments and questions made to Version 4.0 by the Swedish Medical Products Agency. This amendment involved: • The removal of Part B from the study. The earlier version of the study (i.e. Version 3.0) included a 2-parted design (i.e. Part A and B). In contrast to Part A, Part B was designed to enroll T1D subjects who had undergone a renal transplantation (≥6 months prior enrolment) • Correction of the exclusion criterion regarding acceptable levels of panel-reactive anti-HLA antibodies (prior or current at the time of enrollment), i.e. exclusion criterion #10 • Changes in the study treatment regimen with: (a) clarification of the dosing and timing of control treatment, i.e. Heparin, in the "State of Art" arm; and (b) changes in the suggested induction immunosuppression therapy. I.e. (1) inclusion of rabbit ATG as therapy at initial transplantation, (2) exclusion of Daclizumab as Monoclonal Antibody IL-2 Receptor Blocker alternative, and (3) restriction of Basiliximab as therapy to be used in second or third transplantations (c) Clarification of dosing regimen of the suggested Calcineurin Inhibitors (i.e. Tacrolimus and Cyclosporine), and inclusion of anti-inflammatory therapy as part of the study treatment regimen. • Adjustment of the assessments performed during wait-list period and at baseline • Inclusion of definitions of "Partial Graft Function" and "Graft Failure" to support subsequent transplantations, and addition of time-window of eight (8) months since first transplantation as eligibility criterion for second and third transplants
13 July 2010	This amendment includes the changes included to Version 6.0 of the clinical study protocol, which was never implemented as the amendment was not approved in Sweden (only in Norway). The amendment included: • Modified definition requirements for 'whole islet graft function' based on the current trial experience • Clarified timing and criteria for second islet transplant for subjects who could experience graft failure. • Updated the risk of administration of Sirolimus, Etanercept, and MMF to reflect the current label • Included use of Basiliximab for induction of immunosuppression subjects who could not tolerate ATG • Increased dose and adjusted through levels of Tacrolimus and Cyclosporine for first, second, and third transplants to prevent graft rejection • A loading range was defined for Sirolimus
02 September 2010	The amendment summary resulting in version 7.0 of the Clinical Study Protocol (last version implemented) included the changes made to Version 5.0 (implemented) and Version 6.0 (never implemented as the amendment was not approved in Sweden). This amendment included changes in Section 7.4.2 (Criteria and Timing for Subsequent Islet Transplant) of the study protocol to enable the approval of subsequent transplantations in a timely fashion, once a pancreas was made available for production of isolated islets. This included clarification regarding: by whom and when approval decisions were made, the type of clinical information needed for decision-taking and the criteria for eligibility of subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
21 August 2014	The second planned interim analysis including 24 subjects who had reached Day 75 following the first islet transplant showed no safety concerns. On 07-May-2013, the DSMB advised NIH to stop enrollment and terminate the study early due to futility. Subjects already enrolled in the study continued with their assigned treatment unless the DSMB had any reason to recommend otherwise. The interruption date is the date for the last subject's last visit in the study.	-

Notes:

Limitations and caveats

None reported