11 EFFICACY EVALUATION

11.1 Data Sets Analysed

Twenty-one (21) of the 24 subjects enrolled into Protocol CIT-01 were included in the analysis of the Primary Endpoint: nine (9) of 10 enrolled subjects in the LMW DS (experiental) treatment arm and 12 of 14 enrolled subjects in the Heparin (control) arm.

The three (3) subjects who received the first islet infusion had missing primary endpoint due to the following reasons:

- Subject 07-003 (LMW-DS) had an acute graft failure at Day 58, therefore MMTT not done. This is not a Major Deviation.
- Subject 07-016 (Heparin) did not tolerate MMTT at any visits (reported as a major deviation).
- Subject 11-003 (Heparin) missed Day 75 visit (reported as a major deviation).

All 24 enrolled subjects were included in the safety analysis.

11.2 Demographic and Other Baseline Characteristics

Table 11.1 presents the demographic and baseline characteristics of the 24 subjects enrolled in Protocol CIT-01.

No statistical difference was observed between the two treatment arms at baseline (see Section 14.1).

Table 14.1.10 displays the demographic and baseline characteristics for randomized subjects by center. Table 14.1.11 lists the demographic and baseline characteristics by subject.

Table 14.1.12 displays the baseline immunity characteristics for randomized subjects.

Table 14.1.13 displays the physical and medical history for randomized subects at baseline and Table 14.1.14 displays the data by center.

Table 14.1.15, Table 14.1.16 and Table 14.1.17 display the concomitants medications by WHO DD, ATC code and subject, respectively.

Table 11.1 Demographics Variable Analysis

	LMW-DS	Heparin	Total
Total	10	14	24
Gender			
Male	4	6	10
Female	6	8	14
Race			
Unknown*	8	14	22
White	2	0	2
Ethnicity			
Non-Hispanic / Non-Latino Origin	2	0	2
Unknown/Not Reported*	8	14	22
Age			
Number missing	0	0	
Mean (SD)	47.4 (10.1)	51.8 (8.9)	
Median	49.1	51.4	
Minimum – Maximum	27.5 – 59.7	36.7 - 63.8	
Weight			
Number missing	0	0	
Mean (SD)	74.2 (13.7)	66.5 (11.7)	
Median	73.3	66.8	
Minimum – Maximum	56.0 – 93.0	51.0 – 86.0	
BMI			
Number missing	0	0	
Mean (SD)	24.9 (3.3)	22.8 (2.9)	
Median	25.3	22.4	
Minimum – Maximum	20.1 – 28.7	18.6 – 29.1	
Duration of Diabetes			
Number missing	0	0	
Mean (SD)	33.0 (8.5)	33.6 (8.5)	
Median	32.5	33.0	
Minimum – Maximum	18.0 – 49.0	16.0 – 46.0	

Source: Table 14.1.9

* Not documented as protocol deviations during the study

11.2.1 Baseline Metabolic Data

Table 14.1.18 and Table 14.1.19 display the insulin requirements by units per kg of body weight and by total units, respectively, at baseline (i.e. prior initial transplant), respectively.

Table 14.1.20 displays the glycemic control by means of HbA1c at baseline.

Table 14.1.21 and Table 14.1.22 display the glycemic lability by means of MAGE (in mmol/L) and LI (in mmol/L2/hr wk 1) at baseline, respectively.

Table 14.1.23 and Table 14.1.24 display the hypoglycemia by means of Clarke Score and Ryan HYPO Score at baseline, respectively.

Table 14.1.25 displays the glucose variability and hypoglycemia duration derived from the CGMS at baseline. Table 14.1.26 displays the data in percentage.

Table 14.1.27, Table 14.1.28, Table 14.1.29, Table 14.1.30, and Table 14.1.31 display the baseline islet graft function by means of AIR_{glu} and DI, the β-Score (derived from the HbA1c, blood sugar records, and MMTT), and the CPCGR, fasting serum glucose level, and the C-peptide derived from MMTT at baseline, respectively.

Table 14.1.32 displays the FSIGT Insulin Sensitivity (SI) and Glucose Effectiveness (SG) at baseline.

Baseline values for other diabetes control variables are displayed in tables for secondary endpoint (i.e. basal C-peptide, see Table 14.2.4), or efficacy assessments (i.e. glycemic lability index [Table 14.2.91] and number of severe hypoglycemic events [Table 14.2.96]), safety assessments (i.e. clinical ophthalmologic exam [Table 14.3.79 and Table 14.3.80]).

11.2.2 Baseline Quality of Life Variables (QOL)

Baseline QoL variables are displayed in tables for efficacy assessments below (see Section 11.4.1.2).

11.3 Measurements of Treatment Compliance

11.3.1 Compliance with Administration of Investigational Product – LMW-DS

Treatment compliance regarding the investigational LMW-DS product for Protocol CIT-01 was intrinsic to the infusion administration performed by the transplant medical team. Ten (10) subjects received at least one (1) transplant in the Experimental Arm and were therefore exposed to the LMW-DS product. Ten (10) subjects received the IMP in a total of 19 islet transplants, with six (6) subjects receiving one (1) islet transplant, seven (7) receiving two (2) islet transplants, and 1 receiving three (3) LMW-DS transplants.

Please refer to Section 12.1 for details regarding the exposure to IMP.

11.3.2 Compliance with Other Protocol Mandated Concomitant Therapy

Compliance and drug concentration data for use of tacrolimus and cyclosporine for each subject are provided in Appendix 16.2.5.

11.4 Efficacy Results and Tabulations of Individual Subject Data

11.4.1 Analysis of Efficacy

By center display of efficacy results at Baseline, Day 75 and Day 365 are located in CSR Section 14.2.

By subject displays of efficacy results at Baseline, Day 75 and Day 365 are located in CSR Appendix 16.2.6.

11.4.1.1 Primary Endpoint

The primary endpoint for Protocol CIT-01 was the level of stimulated c-peptide at 90-minutes derived from the MMTT at 75+5 days following the first islet infusion.

Three (3) of the 24 subjects who received the first islet infusion had missing primary endpoint: one (1) subject in the LMW-DS treatment arm and two (2) subjects in the control arm.

The null hypothesis was:

H_0: The mean levels of stimulated C-peptide at 90-minutes derived from the MMTT at 75±5 days following the first islet infusion are **equal** for the treatment group receiving immunosuppression and LMW-DS and the control group receiving immunosuppression and heparin.

The alternative hypothesis was:

H_1: The mean levels of stimulated c-peptide at 90-minutes derived from the mixed-meal tolerance test (MMTT) at 75+5 days following the first islet infusion are unequal for the treatment group receiving immunosuppression and LMW-DS and the control group receiving immunosuppression and heparin.

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

The primary analysis was based on an independent-samples two-sided t-test. In order to declare a statistically significant difference it was necessary the overall p-value to be ≤0.05.

The analysis showed that there is no statistically significant evidence to reject the null hypothesis that the subjects who received LMW-DS have the same 90 minute C-peptide response from the MMTT test as the subjects who received heparin (Table 11.4-1). It appears that both treatment groups responded similarly to the MMTT test at 90 minutes on day 75 post initial transplant.

The analyses show that there is no statistically significant evidence to reject the null hypothesis that the variances in the two (2) treatment groups are equal.

Table 11.2 Level of Stimulated C-peptide at 90 Minutes derived from the MMTT at 75+5 Days Post Initial Transplant (Two-sided t-test) – ITT Population

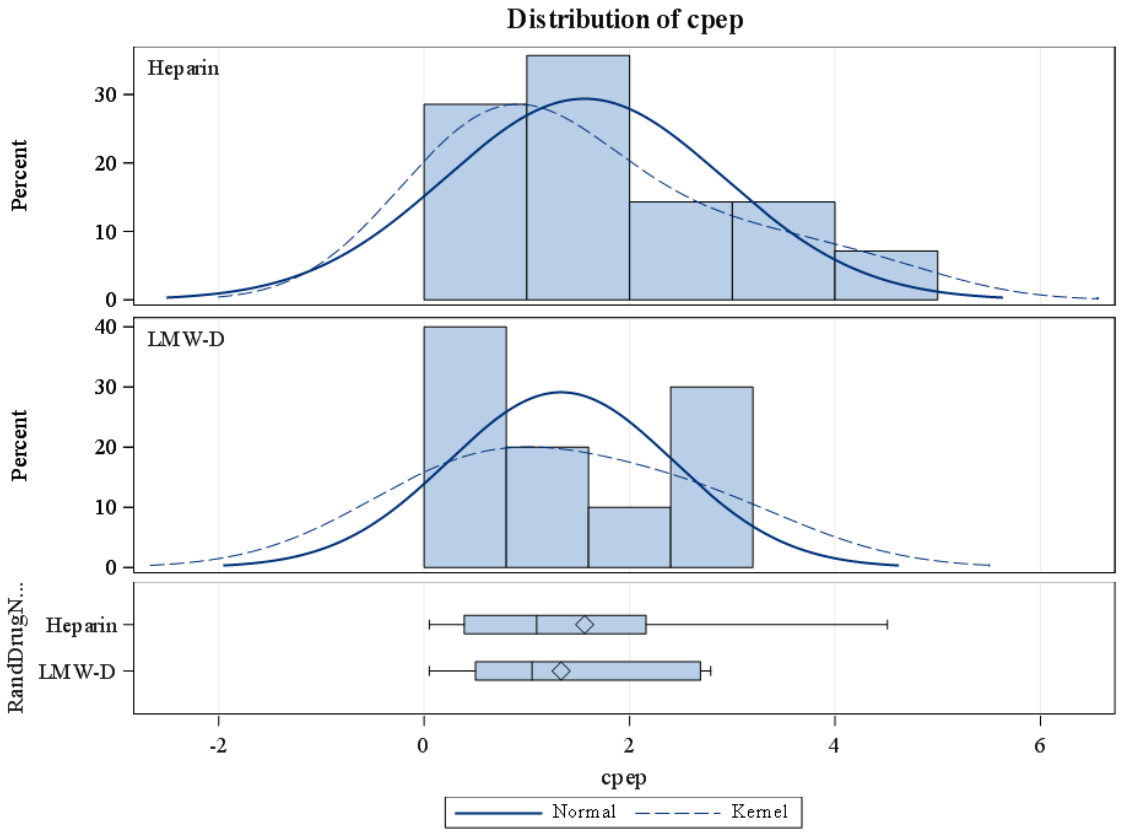
	N	N_{miss}	Mean	SD	Std Err	Min	Max	95% CI Mean	p-value
Heparin	14	2	1.5621	1.3573	0.3628	0.0500	4.5100	(0.7784, 2.3458)	0.6641
LMW-DS	10	1	1.3330	1.0964	0.3467	0.0500	2.7900	(0.5487, 2.1173)	

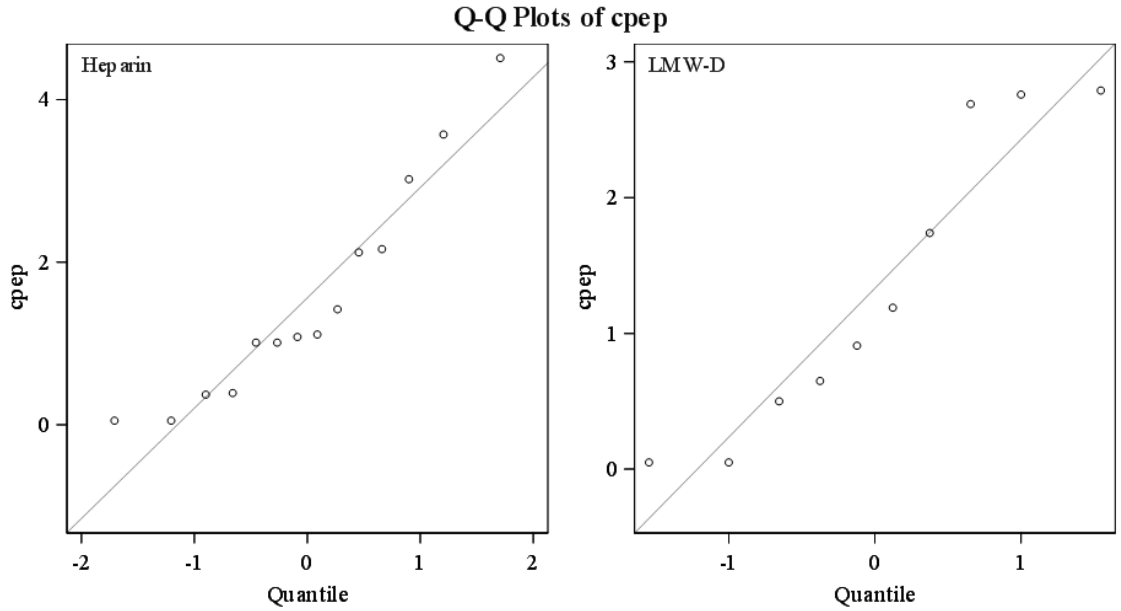
Source: Table 14.2.1.

Note: The lowest observed value, regardless of treatment arm, was 0.05. This value was imputed for all three subjects that had missing primary endpoint values, i.e. Subject 07-003 (LMW-DS), Subject 07-016 (Heparin), and Subject 11-003 (Heparin).

The analyses of the primary endpoint by study center are given in Table 14.2.2. The primary endpoint for each subject who received islet transplant(s) is listed in Table 14.2.3.

The distribution and the QQ-plots of C-peptide support the normality assumption, i.e. no transformation was performed before using the t-test (Figure 11.1). Plots for subjects from each clinical site are available in Figure 14.2.3 through Figure 14.2.8.





Source: Figure 14.2.1 and Figure 14.2.2

Figure 11.1 Distribution and QQ-plots of C-peptide at 90 Minutes derived from the MMTT at 75+5 Days Post Initial Transplant

Sensitivity Analysis: Multiple imputation analyses of C-peptide endpoint at Day 75 post initial transplant

Stimulated C-peptide at day 75 post initial transplant is the primary endpoint for the CIT-01 study. Multiple imputation analysis was performed n SAS with the MI procedure to compare the mean C-peptide between LMW-DS and Heparin treatment groups. Multiple chains with 500 burn-in iterations and a Jefferey's prior distribution were used to generate five imputed data sets. Imputed values had to be 0.05 ng/mL or higher. Each imputed data set was analyzed and the results were combined using the MIANALYZE procedure in SAS.

There were 10 subjects randomized to receive LMW-DS and 14 subjects randomized to receive no LMW-DS. Table 11.3 displays descriptive statistics for C-peptide by treatment group. There is one subject with missing data in the LMW-DS group and two subjects in the No LMW-DS group.

The results from the multiple imputation analysis are shown in Table 11.4.

Based on the multiple imputations, the mean difference in c-peptide between the LMW-DS group and the Heparin group is -0.36, [95% CI (-1.32, 0.60), p = 0.4636]. The confidence interval for the mean difference is (-1.32, 0.60) contains zero which means there is no statistical difference in mean C-peptide levels between the groups.

Table 11.3 Observed C-peptide Data

C-peptide at Day 75	Treatment Group	
	LMW-DS	Heparin
N	10	14
Mean (SD)	1.48 (1.06)	1.81 (1.30)
Min. – Max.	0.05 – 2.79	0.37 – 4.51
Missing	1	2

Table 11.4 Multiple Imputation Results – C-peptide Data

C-peptide at Day 75	Treatment Group	
	LMW-DS	Heparin
N	10	14
Mean (SD)	1.47 (0.33)	1.83 (0.34)
Min. – Max.	0.05 – 2.79	0.37 – 4.51

11.4.1.2 Secondary Endpoints

The Key Secondary Endpoints included:

1) TAT complexes and C-peptide immediately prior to islet infusion, when 125 mL is left in the infusion bag (before rinsing) at 0, 15, 60, 180, 270 and 360 minutes after completion of the islet transplant, and 24 hours after completion of islet transplant;
2) Conduction Velocity and RR interval at screening, and month 12 after first and last islet transplant;
3) Portal pressure before and 15 minutes after completion of islet transplantation;
4) Liver enzymes (ALT, AST), one (1) and seven (7) days after all islet transplantation(s);

5) Quality of life (DTSQs, DTSQc, SF36 Questionnaires), 1 year after the first and final islet infusion, to be compared with the same test done as a part of the screening prior to being put on the waiting list (DTSQs)

11.4.1.2.1 TAT complexes and C-peptide

IBMIR is reflected by e.g. the generation of TAT complexes and release of C-peptide from the islets indicates islet damage. For both factors, median values increased immediately after islet transplantation in both treatment arms following the first and second transplantation. At 24 hours however, levels of both factors were similar or even lower than the pre-transplant levels (Table 14.2.4).

The analyses of both TAT complexes and C-peptide by study center are given in Table 14.2.5. The levels of TAT complexes and C-peptide for each subject who received islet transplant(s) are listed in Table 14.2.6.

11.4.1.2.2 Conduction Velocity

Conduction velocity was assessed by ENeG, temperature threshold, RR variation and SSR, as displayed in Table 14.2.7, Table 14.2.8, Table 14.2.9, and Table 14.2.10, respectively. Overall, the results show that the conduction velocity was similar for all variables regardless of treatment arm and time point.

The data are also displayed by center in Table 14.2.11, Table 14.2.12, Table 14.2.13 and Table 14.2.14.

Data on conduction velocity for each subject who received islet transplant(s) are listed in Table 14.2.15.

11.4.1.2.3 Portal pressure

As presented in Table 14.2.16, intraportal islet transplantation did not alter the portal pressure regardless of treatment arm.

The data are also displayed by center in Table 14.2.17.

Data on portal pressure before and after transplant are listed for each subject who received islet transplant(s) in Table 14.2.18.

11.4.1.2.4 Liver enzymes

The liver enzymes (ALT and AST) increased from Day 1 to Day 7 in both treatment arms following the first and second transplantation. For the two (2) subjects who received a third transplantation, increased levels of ALT and AST were detected in the subject included in the experimental arm, whereas slightly decreased levels were detected in the subject included in the state of the art arm (Table 14.2.19).

The data are also displayed by center in Table 14.2.20, and by subject in Table 14.2.21.

11.4.1.2.5 Quality of Life

Three (3) Quality of Life (QoL) assessments are presented in this section; the DTSQs (status version), the DTSQc (change version) and the SF36 questionnaires.

As demonstrated in Table 14.2.35, the average DTSQs score at Baseline was 18.00 for subjects included in the experimental arm and 14.79 for subjects included in the state of the art arm. One (1) year after first transplantation, the DTSQs score decreased in both treatment arms to 10.00 and 6.13, respectively. Furthermore, one (1) year following the final transplantation, the scores were 7.00 and 7.50, respectively.

The average DTSQc (i.e. difference) score for subjects included in the experimental arm was -2.4 and -10 at one (1) year after the first and final transplantation compared to Baseline, but there was no significant difference. The average DTSQc score for subjects included in the state of the art arm was -8.75 at one (1) year after the first transplantation compared to Baseline and this difference was significant (p=0.023). However, at one (1) year after the final transplantation, the average DTSQc score was -6.75 compared to Baseline and this difference was not significant (Table 14.2.36).

In Table 14.2.37, Table 14.2.38 and Table 14.2.39, data from the DTSQ assessments (DTSQs) are displayed by center. In Table 14.2.40 and Table 14.2.41, the differences in the DTSQ assessments (DTSQc) since Baseline are displayed by center. Table 14.2.42 displays data from the DTSQ assessments by subject.

The average SF36 physical component score at Baseline was 42.14 for subjects included in the experimental arm and 39.18 for subjects included in the state of the art arm. One (1) year after the first transplantation, the physical component score increased in both treatment arms to 49.56 and 40.52, respectively. Furthermore, one (1) year following the final transplantation, the physical component scores were 50.71 and 42.75, respectively (Table 14.2.22).

The average difference for the SF36 physical component score in the experimental arm was 6.35 points at one (1) year after the first transplantation and 3.31 points at one (1) year after the final transplantation compared to Baseline. In the state of the art arm, the average difference for the SF36 physical component score was 2.42 points at one (1) year after the first transplantation and 4 points at one (1) year after the final transplantation compared to Baseline. No significant difference was detected regardless of treatment arm (Table 14.2.23).

The average SF36 mental component score at Baseline was 42.20 for subjects included in the experimental arm and 39.63 for subjects included in the state of the art arm. One (1) year after first transplantation, the mental component score increased in both treatment arms to 52.69 and 43.1, respectively. Furthermore, one (1) year following the final transplantation, the mental component scores were 53.34 and 45.25, respectively (Table 14.2.22).

For subjects included in the experimental arm, the average difference for the SF36 mental component score was 12.27 points at one (1) year following the first transplantation and 6.35 points at one (1) year following the final transplantation compared to Baseline, and both differences were statistically significant (p=0.039 and p=0.031, respectively). The average difference for the SF36 mental component score for subjects included in the state of the art arm was 4.56 points at one (1) year after the first transplantation and 5.25 points at one (1) year after the final transplantation compared to Baseline, but no significant difference was detected (Table 14.2.23).

In Table 14.2.24 through Table 14.2.29, data from the SF36 questionnaires are displayed by center. In Table 14.2.30 through Table 14.2.33, the differences in SF36 components since Baseline are displayed by center. Table 14.2.34 displays data from the SF36 questionnaires by subject.

11.4.1.3 Efficacy Endpoints

The following efficacy assessments were conducted at 75±5 days following the first infusion:

- The percent reduction in insulin requirements
- HbA1c (%), i.e. glycemic control
- Mean amplitude of glycemic excursions (MAGE)
- Glycemic lability index (LI)
- Clarke hypoglycemia awareness score

- Ryan hypoglycemia severity (HYPO) score
- Basal (fasting) glucose and c-peptide and 90-min glucose derived from the mixed-meal tolerance test
- β-score
- C-peptide/(glucose×creatinine) ratio (CPGCR)
- Acute insulin response to glucose (AIR_{glu}), insulin sensitivity, and disposition index derived from the insulin-modified frequently-sampled intravenous glucose tolerance (FSIGT) test
- Glucose variability and hypoglycemia duration derived from the continuous glucose monitoring system® (CGMS)
- The proportion of subjects with full islet graft function.

The following efficacy assessments were conducted at 365±14 days following the first and final islet infusion:

- The proportion of subjects with full islet graft function
- The proportion of subjects with an HbA1c <7.0% and free of severe hypoglycemic events from day 28 through day 365
- The percent reduction in insulin requirements
- HbA1c
- MAGE
- LI
- Clarke score
- HYPO score
- Basal (fasting) and 90-min glucose and C-peptide (MMTT)
- β-score
- C-peptide:glucose×creatinine ratio
- Acute insulin response to glucose (AIR_{glu}), insulin sensitivity, and disposition index derived from the insulin-modified frequently-sampled intravenous glucose tolerance (FSIGT) test
- Glucose variability and hypoglycemia duration derived from the continuous glucose monitoring system® (CGMS)
- The proportion of subjects receiving a second islet infusion
- The proportion of subjects receiving a third islet infusion

11.4.1.3.1 Insulin Requirements

Total daily insulin doses were recorded by self-monitoring diaries and subjects were instructed to administer exogenous insulin to maintain fasting capillary glucose levels at five (5) to nine (9) mmol/L. Table 14.2.43 and Table 14.2.44 display the daily insulin requirements

in units per body weight and in total units adminitered, respectively. The analysis of the daily usage of exogenous insulin shows no statistical differences between the two treatment arms at any time point.

As demonstrated in Table 14.2.45, at Day 75 following the first transplantation, the average reduction in usage of exogenous insulin (total units given) compared to Baseline was 30.71% in the experimental treatment arm and 27.83% in the state of the art arm. At Day 365 following the first transplantation, the mean exogenous insulin usage was reduced by 47.7% and 53.26%, respectively. At Day 365 following the final transplantation, the median insulin usage was reduced by 52.5% and 45.25%.

The insulin requirements and insulin reduction are displayed by center Table 14.2.46, Table 14.2.47 and Table 14.2.48, and by subject in Table 14.2.49.

11.4.1.3.2 Glycemic Control as assessed by HbA1c

Following first islet transplantation, the median HbA1c levels decreased from 7.50% and 7.15% at Baseline to 5.40% and 5.55% at Day 75 for the experimental and the state of art treatment arms, respectively. Furthermore, at Day 365 following the first transplantation, median HbA1c levels levels were 5.80% in both treatment arms and at Day 365 after the final transplantation, the median HbA1c levels were 5.90% and 5.80%, respectively (Table 14.2.50). No difference was detected between the two treatment arms at any time point.

The HbA1c levels are displayed by center and by subject in Table 14.2.51 and Table 14.2.52, respectively.

11.4.1.3.3 The Proportion of Subjects with HbA1c < 7.0% at Day 365 and Free of SHE from Day 28 to Day 365

The SHE data (distribution and number) are displayed by time point in Table 14.2.53 and Table 14.2.54, by center in Table 14.2.55 and Table 14.2.56, and by subject in Table 14.2.57. The analyses of SHE distribution show no statistical difference between treatment arms at any time point.

The proportion of subjects with HbA1c < 7.0% at Day 365 and free of severe hypoglycemic events (SHE) from Day 28 to Day 365 was 20% (initial and final) in the experimental arm and 57% (initial) and 43% (final) in the state of the art arm. There were no significant differences found between the two treatment arms after the initial transplant nor after the final transplant. (Table 11.5). Table 14.2.59 and Table 14.2.60 display the data by center and subject, respectively.

Table 11.5 Proportion of Subjects with HbA1c < 7% and Free of SHE Day 28 to Day 365 after the First and Final Transplants

	Secondary Endpoint	Number of Subjects	Number Missing*	Number of Failures	Number of Successes	Proportion of Successes within Treatment Arm	95% Confidence Interval	p-value
Initial	LMW-D	10	2	6	2	0.20	(3.7, 100)	0.1041
	Heparin	14	1	5	8	0.57	(32.5, 100)	
Final	LMW-D	10	3	5	2	0.20	(3.7, 100)	0.3875
	Heparin	14	1	7	6	0.43	(20.6, 100)	

Source: Table 14.2.58

* Subjects with missing values were imported as failures

11.4.1.3.4 Glycemic Liability as Assessed By MAGE and LI

Glycemic lability was assessed by both the mean amplitude of glycemic excursions (MAGE) and the lability index (LI). A MAGE > 11.1 mmol/L is indicative of marked glycemic lability, whereas a LI ≥ the 90th percentile (433 mmol/L^2/hr*wk^{-1}) of values derived from an unselected group of T1D specifies severe glycemic lability.

The average MAGE decreased from 9.66 mmol/L at Baseline to 4.58 mmol/L at Day 75 following the first transplantation for the experimental treatment arm, and from 8.23 mmol/L to 4.77 mmol/L for the state of art arm. At Day 365 after the first transplantation, the respective values were 4.28 mmol/L and 5.01 mmol/L, and at Day 365 after the final transplantation, the values were 4.19 mmol/L and 4.56 mmol/L. No significant difference was detected between the two treatment arms at any time point (Table 14.2.61).

The MAGE levels are displayed by center and subject in Table 14.2.62 and Table 14.2.63, respectively.

The median LI decreased from 338.07 at Baseline to 102.51 at Day 75 following the first transplantation in the experimental treatment arm and from 404.26 to 175.05 in the state of art arm, respectively. At Day 365 after the first transplantation, the values were 43.09 for the experimental treatment arm and 143.32 for the state of art arm. At Day 365 after the final transplantation, the values were 46.92 and 141.09, respectively. No significant difference was detected between the two treatment arms at any time point (Table 14.2.64).

Table 14.2.65 and Table 14.2.66 display LI data by center and subject, respectively.

11.4.1.3.5 Hypoglycemia as Assessed By Clarke Score and HYPO Score

Hypoglycemia was assessed by the Clarke score and the HYPO score. A Clarke score of ≥ 4 indicates reduced awareness of hypoglycemia and increased risk for severe hypoglycemic events. A HYPO score ≥ the 90th percentile (1047) of values derived from an unselected group of T1D subjects indicates severe problems with hypoglycemia.

The median hypoglycemia assessed by the Clarke score decreased from 6.0 at Baseline to to 4.0 at Day 75 following the first transplantation for the experimental treatment arm and from 6.5 to 4.0 for the state of art arm. Similar results were obtained using the HYPO score, where the median hypoglycemia decreased from 1678 and 610 at Baseline to 32 and 67 at Day 365 following the first transplantation. No significant difference was detected between the two groups (Table 14.2.67 and Table 14.2.70).

As presented in Table 14.2.67, at Day 365 following the final transplantation, the median Clarke Scores were 5.0 for the experimental treatment arm and 1.5 for the state of art arm, and this difference was significant (p = 0.030).The median HYPO Scores at this same time point were 103.5 and 10 for the two treatment arms, respectively, but this difference was not significant (Table 14.2.70).

The Clarke scores are displayed by center and subject in Table 14.2.68 and Table 14.2.69, respectively. The HYPO scores are displayed by center and subject in Table 14.2.71 and Table 14.2.72, respectively.

11.4.1.3.6 Measures derived from the MMTT

Serum glucose and C-peptide levels were measured at before (i.e. 0 minute), 60 and 90 minutes after the MMTT was performed. The median serum glucose levels decreased in both the experimental treatment and state of art arms in response to the mixed meal tolerance test (MMTT) at Day 75 following the first transplantation as well as Day 365 following the first and final transplantation compared to Baseline. Furthermore, this reduction was present at both 60 and 90 minutes, but no significant difference was detected between the treatment arms at any time point (Table 14.2.73).

Table 14.2.74 and Table 14.2.75 display serum glucose levels by center and subject, respectively.

The median serum C-peptide levels increased in both treatment arms in response to MMTT at Day 75 following the first transplantation as well as Day 365 following the first and final transplantation compared to Baseline. This increase was present for all variables, but no difference was detected between the treatment arms at any time point (Table 14.2.76).

Table 14.2.77 and Table 14.2.78 display serum C-peptide levels by center and subject, respectively.

11.4.1.3.7 β–Score

The β–score scale ranges from zero (0) to eight (8), where zero (0) correlates to no graft function and eight (8) correlates to excellent graft function. The median β–scores derived from frequently sampled intravenous glucose tolerance test (FSIGT) were 0.0 in both experimental treatment and state of art arms at Baseline. At Day 75 and at Day 365 following the first transplantation, the median β–scores were 5.0 in both experimental treatment and state of art arms. Furthermore, at Day 365 following the final transplantation, the median β–scores were 5.0 and 4.0 for the experimental treatment and state of art arms, respectively. No difference was detected between the treatment arms at any time point (Table 14.2.82).

Data are presented by center and subject in Table 14.2.83 and Table 14.2.84, respectively.

11.4.1.3.8 C-peptide/(Glucose×Creatinine) Ratio

The CPGCR is used to estimate insulin secretion adjusted for kidney function. As presented in Table 14.2.79, the median CPGCR mesures increased from 0.06 at Baseline to 0.26 at Day 75 following the first transplantation in the experimental treatment arm and from 0.07 to 0.16 in the state of art arm. Furthermore, at Day 365 following the first and final transplantation, the median CPGCR measures were 1.11 and 0.13 as well as 0.80 and 0.36, respectively. No difference was decected beween the two treatment arms at any time point.

CPGCR data are presented by center in Table 14.2.80. Table 14.2.81 displays the CPGCR by subject.

11.4.1.3.9 Acute Insulin Response to Glucose, Disposition Index and Insulin Sensitivity

The FSIGT test was used to determine the acute insulin response to glucose (AIR_{glu}) and disposition index (DI) (Table 14.2.85), as wel as insulin sensitivity (SI) and glucose effectiveness (SG) (Table 14.2.88). As presented in Table 14.2.85, the median AIR_{glu} and DI increased in both treatment arms at Day 75 following the first transplantation and at Day 365 following the first and final transplantation compared to Baseline. Furthermore, a slight increase in SI compared to Baseline was detected in subjects included in the state of the art arm at all time points and in subjects included in the experimental arm at Day 365 following the first and final transplantation (Table 14.2.88). No difference was detected beween the two treatment arms for any variable at any time point.

Data are presented by center in Table 14.2.86 and Table 14.2.89 and by subject in Table 14.2.87 and Table 14.2.90.

11.4.1.3.10 Glucose Variability and Hypoglycemia as Assessed by CGMS

Glucose variability and hypoglycemia were assessed using CGMS. The mean glucose levels at Day 75 following the first transplantation and at Day 365 following the first and final transplantation were lower in both treatment arms compared to Baseline, and no difference was detected between the two treatment arms at any time point. Furthermore, the mean

glucose duration did not fluctuate between the treatment arms regardless of time points (Table 14.2.91).

The time that glucose levels were within the target range (54 to 180 mg/dL) was higher in both treatment arms at Day 75 following the first transplantation and at Day 365 following the first and final transplantation compared to Baseline, but no difference was detected between the groups. Furthermore, the time with glucose levels > 180 mg/dL and the number of hyperglycemic episodes were lower in both treatment arms at Day 75 following the first transplantation and at Day 365 following the first and final transplantation compared to Baseline, but no difference was detected between the treatment arms at any time point. However, at Baseline the number of hyperglycemic episodes was significantly increased in subjects included the experimental treatment arm compared to the state of the art arm. The time with glucose levels < 54 mg/dL and the number of hypoglycemic episodes did not fluctuate between time points or the treatment arms (Table 14.2.94).

Data are presented by center and subject in Table 14.2.92 and Table 14.2.93, respecively. Percent time glycemic control and hypoglycemia are displayed by time point in Table 14.2.94, by center in Table 14.2.95, and by subject in Table 14.2.96.

11.4.1.3.11 The Proportion of Subjects with Full Islet Graft Function

The proportion of subjects with a functioning islet graft at Day 75 following the first transplant was 80.0% in the experimental treatment arm and 85.7% in the state of art arm. Moreover, at Day 75 following the final transplantation, all subjects in the experimental treatment arm (100%, i.e. all 10 subjects) and 85.7% in the state of the state of art arm (i.e. 12 subjects) had a functioning islet graft. At Day 365 following the first and final transplantation, the proportion of subjects were 60.0% (6 subjects) and 71.4% (10 subjects) as well as 50% (5 subjects) and 71.4% (10 subjects), respectively (Table 11.6).

Table 14.2.98 and Table 14.2.99 display the proportion subejcts with a functioning islet graft by center and by subject, respectively.

Table 11.6 Proportion of Subjects with Full Islet Graft Function (C-peptide ≥ 0.3 ng/mL)

		Drug	
Visit	**Transplant**	**LMW-D N = 10 N (%)**	**Heparin N = 14 N (%)**
Day 75	Initial Tx	8 (80)	12 (85.7)
	Final Tx	10 (100)	12 (85.7)
Day 365	Initial Tx	6 (60)	10 (71.4)
	Final Tx	5 (50)	10 (71.4)

Source: Table 14.2.97

11.4.1.3.12 The Proportion of Subjects Receiving a Second Islet infusion

Eight (8) subjects in the experimental arm (80.0%) and eight (8) subjects in the state of the art arm (57.1%) received a second islet infusion (Table 14.2.109).

11.4.1.3.13 The Proportion of Subjects Receiving a Third Islet infusion

One (1) subject in the experimental arm (10.0%) and one (1) subject in the state of the art arm (7.1%) received a third islet infusion (Table 14.2.109).

11.4.2 Statistical/Analytical Issues

11.4.2.1 Adjustment for Covariates

No adjustments for covariates were conducted.

11.4.2.2 Handling of Drop-outs or Missing Data

Three subjects had missing primary endpoint data, which was the 90-minute C-peptide value at Day 75 following the initial transplant. Two subjects were in the Heparin Arm (07-016, 11-003) and one subject (07-003) was in the LMW-D Arm. According to Protocol CIT-01 SAP (Section 10.1), missing primary endpoint data would be handled in the following manner:

- If a value is observed for a subject after the 75 day period but before any subsequent islet infusion then that value will be used in the analysis.
- If no later value is available (e.g. the subject dies or withdraws from the study), then the lowest value observed for all subjects, regardless of treatment group, will be imputed for that subject.

None of the three subjects with missing primary endpoint data had a C-peptide value after Day 75 that was before a subsequent transplant (if a subsequent transplant occurred). The lowest observed value for all subjects was 0.05. This value was imputed for all three subjects.

Missing values were imputed as failures for the following efficacy secondary endpoint:

- The proportion of subjects with an HbA1c < 7.0% and free of severe hypoglycemic events from day 28 through day 365 following the initial (n_{miss} = 3) and final (n_{miss} = 4) transplant.
- Proportion of subjects with graft function (c-peptide ≥ 0.3 ng/mL) at Day 75 (n_{miss} = 3) and Day 365 (n_{miss} = 6) following the initial transplant, and at Day 365 (n_{miss} = 7) following the final transplant.

Missing values were not imputed for any other endpoints.

The results for the multiple imputation analyses of C-peptide endpoint at Day 75 post initial transplant are displayed in Section 11.4.1.1.

11.4.2.3 Interim Analysis and Data Monitoring

The NIDDK DSMB acted in an advisory capacity to the NIDDK and NIAID to monitor subject safety, evaluate the efficacy of the intervention, and evaluate significant changes in protocols. The DSMB meetings were held annually. Section 9.6.2 and Section 9.7.1.3 provide further detail on the DSMB process.

Two interim analyses were performed as planned and an additional analysis was performed as per DSMB request for Protocol CIT-01 (Protocol CIT-01 Section 10.6). Section 9.7.1.3 provides the details on the method chosen for the interim analyses performed. The outcome from the interim analyses performed and the decision-taking leading to the premature stop of the study are described below.

Table 11.7 displays the planned interim and final analyses, the stopping boundaries in the form of both Z values and p-values, and the observed p-values from the actual analyses that were performed.

Table 11.7 Planned and Additional Interim Analyses – Stopping Boundary Values and Observed p-values

Interim Analysis	Number of Subjects Completing Day 75 Follow-up	Boundary Values for Z-test		Associated p-value	Observed p-value
		Lower Boundary	Upper Boundary		
1	12	-3.71	3.71	0.0002	0.6736
Additional					0.4725
2	24	-2.51	2.51	0.0120	0.4300
3*	36	-1.99	1.99	0.0463	N/A

* Interim analysis #3 corresponds to the final analysis if all planned 36 subjects had been enrolled and finished the Day 75 follow-up period. The boundary z-test and p-values described would be used to indicate superiority/inferiority of LMWDS compared to the control group.

Data presented to the DSMB was provided as descriptive statistics for the Experimental and Control Arms. As the DSMB meetings handle several clinical studies included in the same research program, the DSMB meeting minutes are not appended to this Clinical Study Report, but are available upon request.

First Planned Interim Analysis

The first interim analysis was delivered to the DSMB and reviewed on 22-September-2011.

Among the first 16 transplanted subjects at the time of the first interim analysis, 13 had finished the Day 75 follow-up period with usable data. Two analyses were performed for the DSMB meeting. One analysis was conducted as per the interim analyses plan using the first 12 subjects transplanted, and the other analysis was conducted using all 13 subjects with available data.

Out of the first 12 subjects (7 in the LMW-DS group and 5 in the Heparin group), two (2) subjects (both in the Heparin group) had missing data. In accordance with the protocol, the missing data for both subjects were substituted by imputing the lowest observed value. Thus, p-value for the test for difference between C-peptide levels between the two treatment groups was 0.2900, and there was still no evidence for recommending stopping early for efficacy.

Out of the 13 subjects with usable data: seven (7) subjects were enrolled in the Experimental Arm (i.e. LMW-DS), and six (6) subjects in the Control Arm (Heparin). The t-test for a difference between C-peptide levels between the two treatment groups was --0.43 and the p-value was 0.6736, which did not cross the boundary for stopping the study at the first interim look. The stopping rule was still not satisfied.

Additional (Unplanned) Interim Analysis

An additional interim analysis was conducted for CIT-01 as per DSMB request and reviewed on 12-July-2012.

At the time of this unplanned interim analysis, there were 18 transplantde subjects (9 in each group). Of these, 15 subjects had usable data (8 in the Experimental Arm and 7 in the Control Arm). The t-value for the test for difference between c-peptide levels between the two treatment groups was -0.74, and corresponds to a p-value of 0.4725, which did not cross the boundary for stopping the study at that point.

Second Planned Interim Analysis (Final)

The final interim analysis (dated 29-Mar-2013) was delivered to the DSMB as planned and reviewed on 07-May-2013.

At the time of the data freeze (11-Mar-2013), 24 subjects had received their first transplant in the CIT-01 study, with 10 subjects randomized to the Experimental Arm (LMW-DS) and 14 subjects to the Control Arm. Of the 24 subjects, 17 had reached Day 75 and given primary endpoint data. Two (2) subjects had not reached the Day 75 post initial transplant (both subjects were in the Control Arm). Five (5) subjects had not provided primary endpoint data (2 in the LMW-DS Arm and 3 in the Control Arm).

Three (3) sets of analyses were performed to compare the mean C-peptide level between the treatment groups:

- The first analysis set examined observed data only, i.e. subjects with missing endpoint data or who had not reached Day 75 were excluded.
- And two (2) sensitivity analyses were performed:
    - An analysis that assumed a worse-case scenario by including all 22 subjects who had reached Day 75 and imputing the lowest level of detection (i.e. 0.05 ng/mL) for missing values, and
    - Another that used a multiple imputation approach with five imputations and included all 24 subjects. (Please note that this analysis set also included both subjects who had not reached Day 75 yet).

Table 11.8 displays the results of the two sample t-tests that compared mean C-peptide level between treatment groups for each of the analysis sets described above.

Table 11.8 Results of T-tests and Estimated Conditional Power to Detect Differences

Analysis	N	Mean difference between groups (95%)	p-value (2 sample t-test)	Conditional power (%)
1. Observed data	17	-0.50 (-1.83, 0.82)	0.4300	9.9
2. Imputed 0.05 for missing data	22	-0.30 (-1.51, 0.90)	0.6048	2.0
3. Multiple imputation	24	-0.40 (-1.46, 0.66)	0.4587	2.3

The analysis based on observed data for the 17 subjects with endpoint data, showed that the p-value for the test (i.e. 0.4300) did not cross the stopping boundary at the interim look. The mean C-peptide level did not differ statistically between treatment groups in any of the three analyses (i.e. $p > 0.05$ in each analysis). The mean C-peptide level did not differ statistically between the treatment groups in any of the three analyses. This suggests that the IMP (i.e. LMW-DS) is no more effective than the Control (i.e. Heparin) in islet cell transplantation.

The point estimates of the mean difference in each analysis are all less than zero meaning that the C-peptide level in the LMW-DS Arm is on average lower than the Control Arm. The small mean difference between groups suggested that LMW-DS was no more effective than Heparin in islet cell transplantation. The 95% CIs for all three analyses contain zero, this means that there is no statistical difference in mean C-peptide level between the groups, and is consistent with the p-values.

In addition, the conditional power was estimated for each analysis set. Each conditional power calculation was based on the methodology of Lan and DeMets (1988). For each of the three analysis settings, a transformed Z-value, known as the B-value, was calculated. The B-value was then projected out to the end of the study and the chance of rejecting the null hypothesis was calculated, assuming the currently observed trend continues. Based on the worst-case scenario (analysis set 2), the conditional power was 2.0%. Based on the multiple imputation approach (analysis set 3), the conditional power was 2.3%. Both sensitivity analyses resulted in conditional powers that were smaller than the conditional power calculated using the observed data (9.9%). The substantially low conditional power estimate for each analysis indicated that, given the current data, the likelihood of achieving a difference between the groups similar to the planned effect size is essentially zero.

Taken together, these findings suggested that use of LMW-DS did not lead to higher Day 75 C-peptide levels. These results supported a decision to stop CIT-01 study prior to completing enrolment as there was not statistical difference between treatment groups and continuing to enroll subjects would not increase the power of the study to detect the planned effect size.

On 07-May-2013, the DSMB advised NIH to stop enrollment and terminate the study early. Subjects already enrolled in the study continued with their assigned treatment unless the DSMB had any reason to recommend otherwise.

11.4.2.4 Multicenter Studies

Protocol CIT-01 was an open-label, stratified, randomized, multicenter study conducted at two (2) centers in Sweden and one (1) in Norway. The primary analysis was a pooled estimate across centers, but data were also presented and analyzed based on study center (Section 14.2).

11.4.2.5 Multiple Comparison/Multiplicity

Not applicable.

11.4.2.6 Use of an “Efficacy Subset” of Subjects

Not applicable.

11.4.2.7 Active-control Studies Intended to Show Equivalence

Not applicable.

11.4.2.8 Examination of Subgroups

Not applicable.

11.4.3 Tabulation of Individual Response Data

Individual response data and other relevant study information are available in listings in Section 14.2.

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

Subjects included in the Experimental Arm were on average infused with a total dose of 1 029 905 IEQ (14 324 IEQ/kg), whereas subjects included in the Control Arm received an average of 897 303 IEQ (13 807 IEQ/kg). Neither the total IEQ doses nor the IEQ/kg doses were significantly different between the treatment arms (Table 14.2.100).

Table 14.2.102 and Table 14.2.103 summarize the total IEQ infused per purified islet transplant. Table 14.2.104 and Table 14.2.105 summarize the total IEQ/kg infused per purified islet transplant.

11.4.5 Drug-drug and Drug-disease Interactions

Immunosuppression-related SAEs are described in Section 12.3.3.

11.4.6 By-subject Displays

By-subject displays are available in Section 14 as referred to in previous sections.

11.4.7 Efficacy Conclusions

Primary Endpoint

There is no statistically significant evidence to reject the null hypothesis that the subjects who received LMW-DS have the same 90-minute C-peptide response from the MMTT test as the subjects who received Heparin. It appears that both treatment arms responded similarly to the MMTT test at 90 minutes at Day 75 following the first transplantation.

Secondary Endpoints

- The TAT-complexes and C-peptide (median values) increased immediately after islet transplantation in both treatment arms following the first and second transplantation. After 24 hours however, levels of both factors in were similar or even lower than the pre-transplant levels.
- The conduction velocity and RR interval did not vary between the treatment arms or time points.
- Intraportal islet transplantation did not alter the portal pressure regardless of treatment arm.
- One (1) year after first and final transplantation, the DTSQs score decreased in both treatment arms.
- There was no significant DTSQc difference score for subjects included in the experimental arm at one (1) year after the first and final transplantation compared to Baseline. However, the DTSQc difference score for subjects included in the state of the art arm significantly decreased at one (1) year after the first transplantation, but no significant difference was detected at one (1) year after the final transplantation.
- The SF36 mental component score was significantly increased in subjects included in the experimental arm one (1) year after both the first and final transplantation compared to Baseline, whereas no significant difference was detected for subjects included in the state of the art arm.

- No significant difference was detected for the SF36 physical component score regardless of treatment arm or time point.

Efficacy Endpoints

- The percent insulin requirements decreased markedly in both treatment arms at Day 75 following the first transplantation and at Day 365 following the first and final transplantation compared to Baseline.
- No significant difference in the HbA1c levels were detected between the treatment arms at any time point.
- No significant differeces were demonstrated between the two treatment arms regarding the proportion of subjects with HbA1c < 7.0% at Day 365 and free of severe hypoglycemic events (SHE) from Day 28 to Day 365.
- No significant difference in glycemic liability (MAGE and LI) was detected between the treatment arms at any time point.
- No significant difference in hypoglycemia (Clark score and HYPO score) was detected between the treatment arms at Baseline or at Day 365 following the first transplantation. At Day 365 following the final transplantation however, the Clarke score was significantly increased for subjects included in the experimental arm compared to the state of the art arm, whereas no significant difference was reported for the HYPO score.
- No significant difference in serum glucose levels or serum C-peptide levels was detected between the treatment arms in response to the MMTT at any time point.
- There was no significant difference in the β–score between the treatment arms at any time point.
- No significant difference in CPGCR was detected between the treatment arms at any time point.
- No significant difference in AIR_{glu}, SI or DI was detected between the treatment arms at any time point.
- No significant difference in the mean glucose levels was detected between the treatment arms at any time point. Furthermore, the mean glucose duration was comparable at all time points regardless of treatment arm.
- The time that glucose levels were within the target range was higher in both treatment arms at Day 75 following the first transplantation and at Day 365 following the first and final transplantation compared to Baseline, but no difference was detected between the treatment arms.
- The proportion of subjects with a functioning islet graft at Day 75 following the first transplant were 80.0% in the experimental arm and 85.7% in the state of the art arm. Moreover, at Day 75 following the final transplantation, all subjects in the treatment arm (100%) and 85.7% in the state of the art am had a functioning islet graft. At Day 365 following the first and final transplantation, the proportion of subjects were 60.0% and 71.4% in the experimental arm and 50% and 71.4% in the state of the art arm, respectively.
- 70% of the subjects included in the experimental arm and 50% of the subjects included in the state of the art arm received a second islet infusion. Furthermore, 10% of the subjects included in the experimental arm and 7.1% of the subjects included in the state of the art arm received a third islet infusion.

12 SAFETY EVALUATION

12.1 Extent of Exposure

Subjects in the experimental arm (LMW-DS) received an intravenous bolus injection of LMW-DS (1.5 mg/kg) immediately prior to islet transplantation, whereas subjects in the state of the art arm (Heparin) remained untreated. Pancreatic islets, dissolved in LMW-DS (3.0 mg/kg) or Heparin (70 U/kg), were subsequently administered intraportally over a time period of about 32 minutes. After islet transplantation, subjects received LMW-DS or Heparin intraportally for five (5) continuous hours. A second islet transplant was allowed at least 75 days after the first transplantation and a third islet transplant was allowed at least 28 days after the second islet transplant. During the first transplant, subjects received no less than 5,000 IEQ/kg body weight, and at the second and third transplants, subjects received ≥4,000 IEQ/kg body weight. The timing and dose of LMW-DS or Heparin, and islet infusion given to each subject at each are listed in Table 14.2.109.

Table 14.2.106, Table 14.2.107 and Table 14.2.108 sumarize the total dose of Heparin, LMW-DS and LMW-DS-(islet and bolus combined) per purified islet transplant, respectively.

Concomitant medications administrated during the trial are presented by drug code (WHO DDD), ATC and subject in Table 14.1.15, Table 14.1.16 and Table 14.1.17, respectively.

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

There were 18 AEs reported by 12 subjects during the pre-randomization period. Eight (8) subjects reported 12 SAEs and none of the SAEs appeared to have been due to the study interventions (Table 14.3.3).

There were 250 AEs were reported in Study CIT-01 since start of immunosuppression therapy (i.e. randomization) until end of study participation (i.e. Day 365 following the final transplantation).

A total of 36 AEs were reported by ten (10) subjects in the experimental arm (LMW-DS) and 61 AEs were reported by 14 subjects in the state of the art arm (Heparin) from randomization to Day 75 following the first transplantation. Out of these, five (5) SAEs were reported by four (4) subjects receiving LMW-DS and two (2) SAEs were reported by two (2) subjects receiving Heparin (Table 12.1).

Ninety-eight (98) AEs were reported by ten (10) subjects in the experimental arm (LMW-DS) and 126 AEs were reported by 14 subjects in the state of the art arm (Heparin) from randomization to Day 365 following the first transplantation. Out of these, 11 SAEs were reported by six (6) subjects receiving LMW-DS and five (5) SAEs were reported by four (4) subjects receiving Heparin (Table 12.2).

There were 113 AEs reported by ten (10) subjects in the experimental arm (LMW-DS) and 137 AEs were reported by 14 subjects in the state of the art arm (Heparin) from randomization to Day 365 following the final transplantation. Out of these, 12 SAEs were reported by six (6) subjects receiving LMW-DS and seven (7) SAEs were reported by six (6) subjects receiving Heparin (Table 12.3).

Table 14.3.1 and Table 14.3.2 summarize the events reported in the experimental arm (LMW-DS) and the state of the art arm (Heparin), respectively, by body system and grade, and display the calculated incidence rate per 100 person-days as well as the 95% CI derived using the maximum likelihood estimator theory.

The severity of all AEs were graded between one (1) and four (4) on a scale from one (1) to five (5). No death was reported during the study. Importantly, only one (1) SAE, coded neutrophil count decreased, was graded four (4).

AEs have been rated regarding their causality to IMP, islet infusion procedure, immunosuppression and/or infection prophylaxis therapy, and thus categorized as either Unrelated or Related. AEs categorized as “Related” included one of the following descriptors: Definite, Probable, Possible, or Unlikely (see Section 9.5.3.1).

A summary of all AEs from randomization are presented in Table 12.1, Table 12.2 and Table 12.3.

Table 12.1 Summary of Adverse Events from Randomization to Day 75 Following the First Transplantation

	LMW-DS (n=10)	**Heparin** (n=14)
Total number of AEs	36	61
Total number of subjects with at least one AE	10 (100%)	14 (100%)
Total number of SAEs	5	2
Total number of subjects with at least one SAE	4 (40%)	2 (14.3%)

Source: Table 14.3.4

Table 12.2 Summary of Adverse Events from Randomization to Day 365 Following the First Transplantation

	LMW-DS (n=10)	**Heparin** (n=14)
Total number of AEs	98	126
Total number of subjects with at least one AE	10 (100%)	14 (100%)
Total number of SAEs	11	5
Total number of subjects with at least one SAE	6 (60%)	4 (28.6%)

Source: Table 14.3.5

Table 12.3 Summary of Adverse Events from Randomization to Day 365 Following the Final Transplantation

	LMW-DS (n=10)	**Heparin** (n=14)
Total number of AEs	113	137
Total number of subjects with at least one AE	10 (100%)	14 (100%)
Total number of SAEs	12	7
Total number of subjects with at least one SAE	6 (60%)	6 (42.9%)

Source: Table 14.3.1, Table 14.3.2, and Table 14.3.6

The time for AE resolution was calculated and is summarized in Table 12.4.

The analysis shows that the median number of days for resolution of AEs reported from randomization to Day 365 following initial transplantation increases with six (6) days compared with median number of days for resolution of AEs reported during the initial

75 days following the first transplantation (i.e. from randomaization to Day 75 following initial transplantation).

Analyses for the different AE reporting periods are displayed by center in Table 14.3.28, Table 14.3.31, Table 14.3.34, and Table 14.3.37, and by subject in Table 14.3.29, Table 14.3.32, Table 14.3.35, and Table 14.3.38

Table 12.4 Days to Adverse Event Resolution

AE Reporting Period	N	Mean	STD	Median	MIN	MAX
Randomization to Day 75 Initial Transplant	99	77	131	14	0	593
Randomization to Day 75 Final Transplant	102	56	99	14	0	478
Randomization to Day 365 Initial Transplant	232	70	109	20	0	593
Randomization to Day 365 FinalTransplant	250	73	110	21	0	593

Source: Table 14.3.27, Table 14.3.30, Table 14.3.33, and Table 14.3.36

12.2.2 Display of Adverse Event

All AEs reported from randomization to Day 365 following the final transplantation are summarized by system organ class and preferred term in Table 12.5

Table 14.3.7 summarizes the AEs reported from randomization to Day 75 following the first transplantation. Table 14.3.8 summarizes the AEs reported from randomization to Day 365 following the first transplantation.

Table 12.5 Adverse Events Presented by System Organ Class and Preferred Term Day 365 Following the Final Transplantation (1 of 4)

System Organ Class	Preferred Term	LMW-DS (n=10)		Heparin (n=14)	
		Subjects with AE	Number of AEs	Subjects with AE	Number of AEs
Blood and lymphatic system disorders	Anaemia			2 (14.3%)	3
	Febrile neutropenia	1 (10%)	1		
	Granulocytopenia	1 (10%)	1	1 (7.1%)	1
	Haemoglobinaemia			1 (7.1%)	1
	Leukopenia	1 (10%)	2	2 (14.3%)	2
	Lymphadenitis			1 (7.1%)	1
	Neutropenia	2 (20%)	3	3 (21.4%)	5
Cardiac disorders	Atrial fibrillation			1 (7.1%)	1
	Tachycardia			2 (14.3%)	2
Ear and labyrinth disorders	Vertigo			1 (7.1%)	2
Eye disorders	Cataract			1 (7.1%)	1
	Diabetic retinopathy	1	1		
	Macular oedema	1	1		
	Retinopathy	1	1		
	Vision blurred			3 (21.4%)	3
Gastrointestinal disorders	Abdominal pain	2 (20)	3	2 (14.3%)	2
	Abdominal pain upper			2 (14.3%)	2
	Anal pruritus	1 (10%)	1		
	Constipation	1 (10%)	1	2 (14.3%)	2
	Diarrhoea	2 (20%)	2		
	Diabetic gastroparesis	1 (10%)	1		
	Food poisoning	1 (10%)	1		
	Gastritis	2 (20%)	2	3 (21.4%)	3
	Gastrointestinal pain			1 (7.1%)	1
	Gingivitis			1 (7.1%)	1
	Nausea			5 (28.6%)	5
	Oral pain	1 (10%)	1		
	Periodontitis	1 (10%)	1		
	Stomatitis	5 (50%)	7	1 (7.1%)	1
	Vomiting	1 (10%)	2		
General disorders and administration site conditions	Adverse drug reaction	1 (10%)	1	3 (21.4%)	3
	Catheter site pain	2 (20%)	2	3 (21.4%)	3
	Chest pain			1 (7.1%)	1
	Fatigue	3 (30%)	3	3 (21.4%)	3
	Feeling cold	1 (10%)	1	2 (14.3%)	2
	Non-cardiac chest pain			1 (7.1%)	1
	Oedema peripheral	1 (10%)	1	1 (7.1%)	1
	Pain			1 (7.1%)	1
	Pyrexia	2 (20%)	2	2 (14.3%)	2
Hepatobiliary disorders	Cholelithiasis	1 (10%)	1		

Table 12.5 Adverse Events Presented by System Organ Class and Preferred Term Day 365 Following the Final Transplantation (2 of 4)

System Organ Class	Preferred Term	LMW-DS (n=10)		Heparin (n=14)	
		Subjects with AE	Number of AEs	Subjects with AE	Number of AEs
Immune system disorders	Cytokine release syndrome	2 (20%)	2	2 (14.3%)	2
	Transplant rejection	1 (10%)	1		
Infections and infestations	Bronchitis			1 (7.1%)	1
	Catheter related infection	1 (10%)	1		
	Cytomegalovirus infection	1 (10%)	2	2 (14.3%)	2
	Gastroenteritis			1 (7.1%)	1
	Gastroenteritis norovirus			1 (7.1%)	1
	Genital herpes	1 (10%)	1		
	Nasopharyngitis			1 (7.1%)	3
	Tooth infection	1 (10%)	1		
	Upper respiratory tract infection			1 (7.1%)	1
	Urinary tract infection	2 (20%)	5	1 (7.1%)	1
	Urinary tract infection bacterial	2 (20%)	3		
	Viral infection	1 (10%)	1		
Injury, poisoning and procedural complications	Excoriation			1 (7.1%)	1
	Eye operation complication	1 (10%)	1		
	Procedural complication	1 (10%)	1		
	Scratch			1 (7.1%)	1
	Transplant failure	1 (10%)	1		
Investigations	Aspartate aminotransferase increased			1 (7.1%)	1
	Blood calcium decreased	1 (10%)	1		
	Blood creatinine increased	2 (20%)	4	1 (7.1%)	1
	Blood magnesium decreased	1 (10%)	1		
	Glomerular filtration rate decreased	3 (30%)	3	1 (7.1%)	1
	Haemoglobin decreased	3 (30%)	9	1 (7.1%)	2
	Hepatic enzyme increased	3 (30%)	4	3 (21.4%)	4
	Neutrophil count decreased	2 (20%)	3	3 (21.4%)	3

Table 12.5 Adverse Events Presented by System Organ Class and Preferred Term Day 365 Following the Final Transplantation (3 of 4)

System Organ Class	Preferred Term	LMW-DS (n=10)		Heparin (n=14)	
		Subjects with AE	Number of AEs	Subjects with AE	Number of AEs
	Serum ferritin decreased			1 (7.1%)	2
	Weight decreased			2 (14.3%)	2
	White blood cell count decreased	3 (30%)	3	2 (14.3%)	4
	White blood cell count increased	1 (10%)	1		
	White blood cells urine	1 (10%)	1		
Metabolism and nutrition disorders	Decreased appetite			1 (7.1%)	1
	Hypomagnesaemia	1 (10%)	1		
Musculoskeletal and connective tissue disorders	Back pain			1 (7.1%)	1
	Fibromyalgia			1 (7.1%)	1
	Muscle spasms			1 (7.1%)	1
	Myalgia			1 (7.1%)	1
	Pain in extremity			1 (7.1%)	1
	Tendonitis			1 (7.1%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Multiple myeloma			1 (7.1%)	1
	Skin papilloma			1 (7.1%)	1
Nervous system disorders	Balance disorder			1 (7.1%)	1
	Dizziness			1 (7.1%)	1
	Dysgeusia			1 (7.1%)	1
	Formication			1 (7.1%)	1
	Headache	2 (20%)	2	4 (28.6%)	5
	Hypoaesthesia			1 (7.1%)	1
	Migraine	1 (10%)	1		
	Neuropathy peripheral			1 (7.1%)	1
	Syncope	1 (10%)	1		
	Tremor	3 (30%)	3	2 (14.3%)	2
Psychiatric disorders	Depression			1 (7.1%)	2
	Nightmare			1 (7.1%)	2
Renal and urinary disorders	Haematuria	1 (10%)	1		
	Residual urine	1 (10%)	1		
Reproductive system and breast disorders	Menstruation irregular	1 (10%)	1	2 (14.3%)	2
Respiratory, thoracic and mediastinal disorders	Dysphonia			1 (7.1%)	1
	Dyspnoea	1 (10%)	1	1 (7.1%)	2
	Lung infiltration			2 (14.3%)	3
	Oropharyngeal blistering	1 (10%)	1	1 (7.1%)	2
	Rhinorrhoea			1 (7.1%)	1

Table 12.5 Adverse Events Presented by System Organ Class and Preferred Term Day 365 Following the Final Transplantation (4 of 4)

System Organ Class	Preferred Term	LMW-DS (n=10)		Heparin (n=14)	
		Subjects with AE	Number of AEs	Subjects with AE	Number of AEs
Skin and subcutaneous tissue disorders	Acne	3 (30%)	3		
	Alopecia			2 (14.3%)	2
	Hirsutism	1 (10%)	1		
	Nail disorder			1 (7.1%)	1
	Pruritus			1 (7.1%)	2
	Rash	1 (10%)	1	1 (7.1%)	1
	Rash pruritic	1 (10%)	1	1 (7.1%)	2
Surgical and medical procedures	Shoulder operation	1 (10%)	1		
	Tendon operation			1 (7.1%)	1
Vascular disorders	Hypertension			1 (7.1%)	1

Source: Table 14.3.1 and Table 14.3.2

The severity of the AEs was graded on a scale from one (1) to five (5). The AEs were also further categorized based on their relation to islet infusion procedure or immunosuppression.

Table 12.6 summarizes the severity of the AEs related to islet infusion or transplant procedure from randomization to Day 365 following the final transplantation by system organ class and preferred term. Table 12.7 summarizes the severity of the AEs related to immunosuppression from randomization to Day 365 following the final transplantation by system organ class and preferred term.

Table 12.6 Severity of Adverse Events Related to Islet Infusion or Transplant Procedure Day 365 Following the Final Transplantation

System Organ Class	Preferred Term	LMW-DS Number of AEs/Grade				Heparin Number of AEs/Grade			
		1-2	3	4	5	1-2	3	4	5
Injury, poisoning and procedural complications	Procedural complication		1						
Investigations	Aspartate aminotransferase increased					1			
	Hepatic enzyme increased	3	1			2	2		

Source: Table 14.3.23 and Table 14.3.24.

Table 12.7 Severity of Adverse Events Related to Immunosuppression Day 365 Following the Final Transplantation

System Organ Class	Preferred Term	LMW-DS Number of AEs/Grade				Heparin Number of AEs/Grade			
		1-2	3	4	5	1-2	3	4	5
Blood and lymphatic system disorders	Anaemia					2	1		
	Febrile neutropenia		1						
	Granulo-cytopenia		1			1			1
	Leukopenia	2							
	Neutropenia	1	2			5			5
Gastrointestinal disorders	Diarrhoea	2							
	Nausea					4			
	Stomatitis	7				1			
	Vomiting	2							
General disorders and administration site conditions	Adverse drug reaction	1				3			
	Oedema peripheral	1				1			
Hepatobiliary disorders	Cholelithiasis		1						
Immune system disorders	Cytokine release syndrome	2				2			
Infections and infestations	Bronchitis					1			
	Catheter related infection	1							
	Cytomegalo-virus infection	2				2			
	Gastroenteritis	1					1		
	Genital herpes	5							
	Urinary tract infection	2							
	Urinary tract infection bacterial	1							
	Viral infection	1							
Investigations	Glomerular filtration rate decreased	1				1			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Multiple myeloma					1			
	Skin papilloma					1			
Respiratory, thoracic and mediastinal disorders	Lung infiltration					3			
Vascular disorders	Hypertension					1			

Source: Table 14.3.25 and Table 14.3.26.

The severity of the AEs reported from randomization to Day 75 following the first transplantation are summarize in Table 14.3.15 and Table 14.3.16 for events related to islet infusion or transplant procedure, and in Table 14.3.17 and Table 14.3.18 for events related to immunosuppression.

The severity of the AEs reported from randomization to Day 365 following the first transplantation are summarize in Table 14.3.19 and Table 14.3.20 for events related to islet infusion or transplant procedure, and in Table 14.3.21 and Table 14.3.22 for events related to immunosuppression.

12.2.3 Analysis of Adverse Events

AEs During the Pre-randomization Period

Non-serious AEs during the pre-randomization period were only to be reported if they were suspected to be the result of a study (diagnostic) intervention. Consequently, there were six (6) non-serious AEs reported during this period as well as 12 SAEs (Table 14.3.3).

AEs from Randomization to Day 75 Following the First Transplantation

A total of 36 AEs were reported by ten (10) subjects in the experimental arm (LMW-DS) and 61 AEs were reported by 14 subjects in the state of the art arm (Heparin) from randomization to Day 75 following the first transplantation Out of these, five (5) SAEs were reported by four (4) subjects receiving LMW-DS and two (2) SAEs were reported by two (2) subjects receiving Heparin (Table 12.1 and Table 14.3.4).

Calculations of the relative frequency of AEs revealed that urinary tract infection (9.7%) and hepatic enzyme increased (9.7%) were the most frequently occurring AEs in subjects receiving LMW-DS, whereas headache (6.6%) and hepatic enzyme increased (6.6%) were the most frequently reported AEs in subjects receiving Heparin (Table 14.3.9 and Table 14.3.10).

Eight (8) of the AEs were related to the islet infusion or transplant procedure and the most commonly reported AE was hepatic enzyme increased, as reported by three (3) subjects receiving LMW-DS and three (3) subjects receiving Heparin (Table 14.3.7, Table 14.3.15 and Table 14.3.16).

The majority of the AEs however, were related to immunosuppression. A total of 26 AEs were reported (14 in the experimental arm and 12 in the state of the art arm) and the most commonly reported AEs were adverse drug reaction and cytokine release syndrome. Adverse drug reaction was reported by one (1) subject receiving LMW-DS and by three (3) subjects receiving Heparin, whereas cytokine release syndrome was reported by two (2) subjects receiving LMW-DS and by two (2) subjects receiving Heparin (Table 14.3.7, Table 14.3.17 and Table 14.3.18).

AEs from Randomization to Day 365 Following the First Transplantation

A total of 98 AEs were reported by ten (10) subjects in the experimental arm (LMW-DS) and 126 AEs were reported by 14 subjects in the state of the art arm (Heparin) from randomization to Day 365 following the first transplantation. Out of these, 11 SAEs were reported by six (6) subjects receiving LMW-DS and five (5) SAEs were reported by four (4) subjects receiving Heparin (Table 12.2 and Table 14.3.5).

Calculations of the relative frequency of AEs revealed that hemoglobin decreased (8.6%) and stomatitis (7.5%) were the most frequently occurring AEs in subjects receiving LMW-DS, whereas neutropenia (4.1%) and headache (4.1%) were the most frequently reported AEs in subjects receiving Heparin (Table 14.3.11 and Table 14.3.12).

Ten (10) AEs were related to the islet infusion or transplant procedure and the most commonly reported AE was hepatic enzyme increased, as reported by three (3) subjects receiving LMW-DS (4 events) and three (3) subjects receiving Heparin (4 events) (Table 14.3.8, Table 14.3.19 and Table 14.3.20).

There were 69 AEs related to immunosuppression (36 in the experimental arm and 33 in the state of the art arm). Neutropenia and stomatitis constituted the most commonly reported AEs, with eight (8) events each. Neutropenia was reported by two (2) subjects receiving LMW-DS and by five (5) subjects receiving Heparin, whereas stomatitis was reported by five (5) subjects receiving LMW-DS and one (1) subject receiving Heparin (Table 14.3.8, Table 14.3.21 and Table 14.3.22).

AEs from Randomization to Day 365 Following the Final Transplantation

A total of 113 AEs were reported by ten (10) subjects in the experimental arm (LMW-DS) and 137 AEs were reported by 14 subjects in the state of the art arm (Heparin) from randomization to Day 365 following the final transplantation. Out of these, 12 SAEs were reported by six (6) subjects receiving LMW-DS and seven (7) SAEs were reported by six (6) subjects receiving Heparin (Table 12.3, Table 14.3.1, Table 14.3.2, and Table 14.3.6).

Calculations of the relative frequency of AEs revealed that hemoglobin decreased (8.9%) and stomatitis (6.9%) were the most frequently occurring AEs in subjects receiving LMW-DS, whereas headache (3.8%), neutropenia (3.8%) and nausea (3.8%) were the most frequently reported AEs in subjects receiving Heparin (Table 14.3.13 and Table 14.3.14).

No new AEs related to the islet infusion or transplant procedure were reported since Day 365 following the first transplantation (Table 12.6, Table 14.3.23 and Table 14.3.24).

There were 74 AEs related to immunosuppression (only 5 new AEs were reported since Day 365 following the first transplantation). Neutropenia and stomatitis constituted the most commonly reported AEs, with still eight (8) events each. Neutropenia was reported by two (2) subjects receiving LMW-DS and by three (3) subjects receiving Heparin, whereas stomatitis was reported by five (5) subjects receiving LMW-DS and one (1) subject receiving Heparin. Three (3) new AEs were reported in the experimental arm since Day 365 following the first transplantation, all in subjects who had experienced those events previously (1 urinary tract infection and 2 glomerular filtration rate decreased). The two (2) new AEs were reported in the state of the art arm were reported by one (1) nausea and one (1) urinary tract infection, none of the events had been previously reported by the subject (Table 12.7, Table 14.3.25 and Table 14.3.26).

12.2.3.1 Renal Function

The incidence and severity of reduction in GFR related to the immunosuppression treatment administered at 75±5 days and 365±14 days following the first islet infusion is displayed and discussed as appropriate above.

From Baseline to Day 75 after first islet infusion, one (1) subject in each treatment group reported one (1) event of GFR decrease related to immunosuppression. Both events were Grade 1-2 in severity (Table 14.3.7, Table 14.3.17, and Table 14.3.18). At Day 365 after first islet infusion, no new events of GFR decrease related to immunosuppression were reported (Table 14.3.8, Table 14.3.21, and Table 14.3.22).

Table 12.8 displays GFR levels at baseline, and at 75±5 days and 365±14 days following the first islet infusion.

Levels of raw GFR were calculated for none or for only very few of the subjects and show no clear trends.

Analysis of standardised GFR levels shows that average values decreased in the experimental arm (LMW-DS) at Day 75 and again at Day 365 after first islet infusion, while median values did not show any decrease between Baseline and Day 75 after first islet infusion (i.e. 80.5 mL/min/1.73 m^2 at both occasions). For the the state of the art arm (Heparin), both average and median standardised GFR levels decreased at Day 75 after first islet infusion and then increased at Day 365 after first islet infusion to a level higher than that at Baseline.

Table 12.8 GFR Levels at Baseline, Day 75 and Day 365 following the First Islet Infusion

	Baseline		Day 75 Post Transplant		Day 365 Post Transplant	
GFR	**LMW-DS (N=10)**	**Heparin (N=14)**	**LMW-DS (N=10)**	**Heparin (N=14)**	**LMW-DS (N=10)**	**Heparin (N=14)**
Raw, mL/min						
N		5	3	1	4	5
Missing		0	0	0	0	0
Median		91.0	82.0	142.0	89.0	94.0
Mean(S.D.)		94.0 (8.0)	101.3 (37.0)	142.0 (.)	91.5 (7.2)	97.6 (7.7)
Min. - Max.		86.0 - 103.0	78.0 - 144.0	142.0 - 142.0	86.0 - 102.0	92.0 - 110.0
Standardised, mL/min/1.73 m^2						
N	10	9	6	6	8	9
Missing	0	0	1	3	2	0
Median	80.5	74.0	80.5	71.5	74.5	78.0
Mean(S.D.)	82.3 (26.2)	71.7 (20.7)	79.5 (13.2)	71.3 (15.1)	69.9 (19.6)	77.3 (22.7)
Min. - Max.	53.0 - 142.0	36.0 - 97.0	63.0 - 96.0	53.0 - 90.0	38.0 - 95.0	38.0 - 108.0

Source: Table 14.3.85 and Table 14.3.86.

12.2.4 Listing of Adverse Events by Subject

Listings of all AEs are presented in Table 14.3.3, Table 14.3.4, Table 14.3.5, and Table 14.3.6.

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1 Listings of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1.1 Deaths

There was no death reported during the study.

12.3.1.2 Other Serious Adverse Events

SAEs reported from randomization to Day 365 following the final visit are presented in Table 12.9, Table 12.10, Table 12.11 and Table 12.12.

Table 12.9 List of Serious Adverse Events from Randomization to Day 365 Following the Final Transplantation and Attributed to Islet Transplantation, Concomitant therapy or Drug (1 of 2)

System Organ Class	Preferred Term	Drug	Related to product and /or infusion procedure	Related to Concomitant Therapy	Related to Drug	Time from Event to Resolution	Grade
Blood and lymphatic system disorders	Febrile neutropenia	LMW-DS	No	Yes	No	4 days	3
	Granulocytopenia	LMW-DS	No	Yes	No	3 days	3
	Granulocytopenia	Heparin	No	Yes	No	2 days	3
	Neutropenia	Heparin	No	Yes	No	<35 weeks	3
Gastrointestinal disorders	Abdominal pain	LMW-DS	No	No	No	1 day	3
	Constipation	LMW-DS	No	No	No	<1 day	2
General disorders and administration site conditions	Adverse drug reaction	LMW-DS	No	Yes	No	2 days	2
Hepatobiliary disorders	Cholelithiasis	LMW-DS	No	No	No	3 days	3
Immune system disorders	Cytokine release syndrome	LMW-DS	No	Yes	No	11 days	2
Immune system disorders	Transplant rejection	LMW-DS	No	No	No	<7 weeks	2
Infections and infestations	Gastroenteritis	Heparin	No	No	No	1 day	3
	Gastroenteritis norovirus	Heparin	No	No	No	7 days	3
Injury, poisoning and procedural complications	Procedural complication	LMW-DS	Yes	No	No	<1 day	3
	Transplant failure	LMW-DS	No	No	No	2 days	1
Investigations	Neutrophil count decreased	Heparin	No	Yes	No	11 days	4
Metabolism and nutrition disorders	Decreased appetite	Heparin	No	Yes	No	<15 weeks	3

Table 12.9 Summary of Serious Adverse Events from Randomization to Day 365 Following the Final Transplantation and Attributed to Islet Transplantation, Concomitant therapy or Drug (2 of 2)

System Organ Class	Preferred Term	Drug	Related to product and /or infusion procedure	Related to Concomitant Therapy	Related to Drug	Time from Event to Resolution	Grade
Nervous system disorders	Syncope	LMW-DS	No	No	No	2 days	2
Respiratory, thoracic and mediastinal disorders	Lung infiltration	Heparin	No	Yes	No	<9 weeks	2
Surgical and medical procedures	Shoulder operation	LMW-DS	No	No	No	1 day	1

Source: Table 14.3.6 and Table 14.3.39.

Table 12.10 Serious Adverse Events from Randomization to Day 75 Following First Transplantation Attributed to Islet Transplantation, Concomitant therapy or Drug

System Organ Class	Preferred Term	LMW-DS Related to				Heparin Related to			
		Product and/or infusion procedure	Conco-mitant Therapy	Drug	Unrelated to Study Protocol	Product and/or infusion procedure	Concomitant Therapy	Drug	Unrelated to Study Protocol
Blood and lymphatic system disorders	Granulocytopenia		1				1		
Gastrointestinal disorders	Constipation				1				
General disorders and administration site conditions	Adverse drug reaction		1						
Immune system disorders	Cytokine release syndrome		1						
Injury, poisoning and procedural complications	Procedural complication	1							
Investigations	Neutrophil count decreased						1		

Source: Table 14.3.40 and Table 14.3.41.

Table 12.11 Serious Adverse Events from Randomization to Day 365 Following First Transplantation Attributed to Islet Transplantation, Concomitant therapy or Drug (1 of 2)

System Organ Class	Preferred Term	LMW-DS Related to				Heparin Related to			
		Product and/or infusion procedure	Conco-mitant Therapy	Drug	Unrelated to Study Protocol	Product and/or infusion procedure	Concomitant Therapy	Drug	Unrelated to Study Protocol
Blood and lymphatic system disorders	Febrile neutropenia		1						
	Granulocytopenia		1				1		
	Neutropenia						1		
Gastrointestinal disorders	Abdominal pain				1				
	Constipation				1				
General disorders and administration site conditions	Adverse drug reaction		1						
Hepatobiliary disorders	Cholelithiasis				1				
Immune system disorders	Cytokine release syndrome		1						
	Transplant rejection				1				
Infections and infestations	Gastroenteritis								1
Injury, poisoning and procedural complications	Procedural complication	1							
	Transplant failure				1				
Investigations	Neutrophil count decreased						1		

Table 12.11 Serious Adverse Events from Randomization to Day 365 Following First Transplantation Attributed to Islet Transplantation, Concomitant therapy or Drug (2 of 2)

System Organ Class	Preferred Term	LMW-DS Related to				Heparin Related to			
		Product and/or infusion procedure	Conco-mitant Therapy	Drug	Unrelated to Study Protocol	Product and/or infusion procedure	Concomitant Therapy	Drug	Unrelated to Study Protocol
Metabolism and nutrition disorders	Decreased appetite						1		
Nervous system disorders	Syncope				1				
Respiratory, thoracic and mediastinal disorders	Lung infiltration						1		

Source: Table 14.3.42 and Table 14.3.43.

Table 12.12 Serious Adverse Events from Randomization to Day 365 Following Final Transplantation Attributed to Islet Transplantation, Concomitant therapy or Drug (1 of 2)

System Organ Class	Preferred Term	LMW-DS Related to				Heparin Related to			
		Product and/or infusion procedure	Conco-mitant Therapy	Drug	Unrelated to Study Protocol	Product and/or infusion procedure	Concomitant Therapy	Drug	Unrelated to Study Protocol
Blood and lymphatic system disorders	Febrile neutropenia		1						
	Granulocytopenia		1				1		
	Neutropenia						1		
Gastrointestinal disorders	Abdominal pain				1				
	Constipation				1				
General disorders and administration site conditions	Adverse drug reaction		1						
Hepatobiliary disorders	Cholelithiasis				1				
Immune system disorders	Cytokine release syndrome		1						
	Transplant rejection				1				
Infections and infestations	Gastroenteritis								1
	Gastroenteritis norovirus								1
Injury, poisoning and procedural complications	Procedural complication	1							
	Transplant failure				1				

Table 12.12 Serious Adverse Events from Randomization to Day 365 Following Final Transplantation Attributed to Islet Transplantation, Concomitant therapy or Drug (2 of 2)

System Organ Class	Preferred Term	LMW-DS Related to				Heparin Related to			
		Product and/or infusion procedure	Conco-mitant Therapy	Drug	Unrelated to Study Protocol	Product and/or infusion procedure	Concomitant Therapy	Drug	Unrelated to Study Protocol
Investigations	Neutrophil count decreased						1		
Metabolism and nutrition disorders	Decreased appetite						1		
Nervous system disorders	Syncope				1				
Respiratory, thoracic and mediastinal disorders	Lung infiltration						1		
Surgical and medical procedures	Shoulder operation				1				

Source: Table 14.3.44 and Table 14.3.45.

12.3.1.3 Other Significant Adverse Events

Not applicable.

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

Narratives for all SAEs reported in the study are included in Table 14.3.46 and Table 14.3.47.

12.3.3 Analysis and Discussions of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Twelve (12) SAEs were reported by eight (8) subjects prior to randomization. All SAEs required hospitalizations either for the subject's diabetes or for other underlying illnesses and none of the SAEs appeared to have been due to the study interventions (Table 14.3.46).

As presented in Table 12.9, Table 12.10, Table 12.11 and Table 12.12, a total of 19 SAEs were reported for the period following randomization. Out of these, 12 SAEs were reported by six (6) subjects receiving LMW-DS and seven (7) SAEs were reported by six (6) subjects receiving Heparin. Granulocytopenia was the most commonly reported SAE, as reported by one (1) subject in the experimental arm (LMW-DS) and one (1) subject in the state of the art arm (Heparin).

No death was reported during the study and all SAEs were graded between one (1) and four (4) on a scale between one (1) and five (5). Importantly, only one (1) SAE, coded neutrophil count decreased, was graded four (4). All SAEs resolved and the majority of SAEs resolved within a few days. However, the resolution time varied from less than one (1) day to less than 35 weeks and longer resolution time was reported following episodes of neutropenia, transplant rejection, decreased appetite, and lung infiltration (Table 12.9).

One (1) SAE, coded procedural complication, was attributed to the islet infusion procedure and occurred 75 days following the first transplantation. During this episode, the catheter was unintendedly placed in a small branch of the hepatic artery and no islets were transplanted. Importantly, ultrasonography demonstrated that the event did not cause any hematoma or bleeding and the event resolved within less than one (1) day (Table 12.9, Table 12.10 and Table 14.3.47).

There were nine (9) SAEs attributed to concomitant therapy (Table 12.9, Table 12.10, Table 12.11, Table 12.12 and Table 14.3.47):

- One (1) SAE (LMW-DS arm) was coded febrile neutropenia and occurred 365 days following the first transplantation. Treatment with Valganciclovir and Trimethoprim-sulfamethoxazole stopped and the neutrophil count became normal. The event resolved after four (4) days.
- One (1) SAE (Heparin arm) was coded neutropenia and occurred 365 days following the first transplantation. This episode required repeated treatment with the granulocyte colony stimulation factor Filgrastim (Neupogen®) and lasted several months. After switch from Tacrolimus to Cyclosporine, the neutrophil count stabilized and became normal.
- Two (2) SAEs in two (2) subjects (1 in the LMW-DS arm and 1 in the Heparin arm) were coded granulocytopenia and occurred 75 days following the first transplantation. Sirolimus treatment was interrupted in both subjects and in the LMW-DS subject, Valganciclovir and Trimethoprim-sulfamethoxazole treatments stopped. Afterwards, the granulocyte counts were restored and the events resolved after three (3) and two (2) days, respectively.

- One (1) SAE (Heparin arm) was coded neutrophil count decreased and occurred 75 days following the first transplantation. The neutrophil count accidently dropped on one occasion, but after 11 days, the counts were normal again.
- One (1) SAE (LMW-DS arm) was coded adverse drug reaction and occurred 75 days following the first transplantation. This subject experienced nausea and vomiting.Symptoms resolved after withdrawal of mycophenolate mofetil.
- One (1) SAE (LMW-DS arm) was coded cytokine release syndrome and occurred 75 days following the first transplantation. The SAE had onset during the third dose of anti-thymocyte globulin. Symptoms included pleural and peritoneal effusion, malaise, subcutaneous edema, erythema, and dyspnea. The patient's condition had improved already the day after and two (2) additional doses of anti-thymocyte globulin could be given. The event resolved after 11 days.
- One (1) SAE (Heparin arm) coded decreased appetite was suspected to be caused by mycophenolate mofetil. The event occurred 365 days following the first transplantation, and resolved after 15 weeks.
- One (1) SAE (Heparin arm) was coded lung infiltration and occurred 365 days following the first transplantation. This subject experienced prolonged coughing and fever with flu symptoms despite antibiotic treatment and was hospitalized. The event resolved after nine (9) weeks.

None of the SAEs was attributed to LMW-DS or Heparin drug usage. Nine (9) SAEs were considered as unrelated to the study protocol and included abdominal pain, constipation, cholelithiasis, transplant rejection, gastroenteritis, gastroenteritis norovirus, transplant failure, and syncope (Table 12.10, Table 12.11 and Table 12.12).

There was no indication in the SAE narratives that any of the subjects suffered a permanent injury as a consequence of their SAEs.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Measurements by Subject and Each Abnormal Laboratory Value

All laboratory data are listed in Section 14.3.4.

Table 14.3.74 lists all captured hematology and clinical chemistry laboratory values by subject.

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values over Time

Hematology and clinical chemistry

Hematology and clinical chemistry results are summarized in Table 14.3.54, Table 14.3.56, Table 14.3.58, Table 14.3.60, Table 14.3.62, Table 14.3.64, Table 14.3.66, Table 14.3.68, Table 14.3.70, and Table 14.3.72.

Data are summarized by center in Table 14.3.55, Table 14.3.57, Table 14.3.59, Table 14.3.61, Table 14.3.63, Table 14.3.65, Table 14.3.67, Table 14.3.69, Table 14.3.71, and Table 14.3.73.

Development of anti-HLA Antibodies following Initial Transplantation

The incidence of immune sensitization was assessed by measuring anti-HLA antibodies prior to islet transplantation as well as 75 days and 365 days after the initial and final transplant and the presence of anti-HLA antibodies were calculated as panel reactive antibody (PRA). Subjects with PRA values above background, but ≤80% could be included if the specificity of the antibodies could be determined, as specified in the Exclusion Criteria. Two (2) separate central laboratories performed the calculations.

The Pennsylvania Central Laboratory found that three (3) subjects with a Baseline peak PRA value of 0% and one (1) subject with a Baseline peak PRA value of 73% developed anti-HLA antibodies after Baseline with peak PRA values of 3, 24, 86 and 86%, respectively. In three (3) subjects however, equal peak PRA values were detected at Baseline and after Baseline (3, 23 and 75%, respectively). Furthermore, in one (1) subject, the peak PRA value decreased from 27% at Baseline to 0% after Baseline (Table 14.3.48).

The Rudbeck Central Laboratory found that three (3) subjects with a Baseline peak PRA value of 0% developed anti-HLA antibodies after Baseline with peak PRA values of 2, 10 and 24%, respectively, Furthermore, in three (3) subjects, the peak PRA values increased from 1, 22 and 73% at Baseline to 3, 23 and 86% after Baseline. In five (5) subjects however, the peak PRA values decreased from 5, 13, 20, 27 and 76% at Baseline to 0, 0, 3, 3 and 75% after Baseline (Table 14.3.49).

The proportions of subjects with increase in PRA percent from baseline to Day 75 or to Day 365 following initial and final transplant are presented in Table 14.3.52 and Table 14.3.53, respectively.

PRA values are displayed by subject in Table 14.3.50 and Table 14.3.51.

12.4.2.2 Individual Subject Changes

Subject changes were not assessed. For individual data, please refer to Table 14.3.74.

12.4.2.3 Individual Clinically Significant Abnormalities

For individual data, please refer to Table 14.3.74.

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Incidence of a Change in Immunosuppression Regimen

One (1) subject in the experimental arm (LMW-DS) changed immunosuppression regimen at Day 75 following initial transplantation (Table 14.3.75) and one (1) in the state of the art arm (Heparin) at Day 75 following final transplantation (Table 14.3.76), respectively.

As presented in Table 14.3.77, two (2) subjects (20%) in the experimental arm (LMW-DS) and seven (7) subjects (50%) in the state of the art arm (Heparin) changed immunosuppression regimen at two (2) and eight (8) occasions until Day 365 following initial transplantation. The most common cause of change was related to MMF usage, which was reported at two (2) occasions in the LMW-DS arm and at two (2) occasions in the Heparin arm. At Day 365 following the final transplantation, two (2) additional subjects in the Heparin arm changed immunosuppressive regimen, resulting in a total of nine (9) subjects (64%) (Table 14.3.78). The most common causes of a change were related to MMF and Tacrolimus usage.

Incidence of Worsening Retinopathy

The incidence of worsening retinopathy was assessed by change in retinal photography from Baseline to Day 365 following the initial and final transplantation, respectively. The subjects' statuses were defined as normal or non-normal.

Three (3) subjects in the experimental arm displayed normal status at Baseline. At Day 365 following the first transplantation, one (1) subject remained normal, whereas two (2) subjects changed to non-normal status and thus, developed retinopathy. At Day 365 following the final transplantation, one (1) subject still remained normal, one (1) subject displayed non-normal status and for one (1) subject, data are missing (Table 14.3.79 and Table 14.3.80).

Seven (7) subjects in the experimental arm displayed non-normal status at Baseline. Two (2) subjects remained non-normal at Day 365 following the first transplantation, whereas one (1) subject changed to normal status, and data are missing for one (1) subject. At Day 365 following the final transplantation, data are missing for all seven (7) subjects (Table 14.3.79 and Table 14.3.80).

Two (2) subjects in the state of the art arm displayed normal status at Baseline. At Day 365 following the first transplantation, one (1) subject remained normal whereas data are missing for one (1) subject. The same was observed at Day 365 following the final transplantation, i.e. one (1) subject remained normal since Baseline whereas data are missing for one (1) subject (Table 14.3.79 and Table 14.3.80).

Twelve (12) subjects in the state of the art arm displayed non-normal status at Baseline. At Day 365 following the first transplantation, nine (9) subjects remained non-normal, one (1) subject changed to normal status and for two (2) subjects data are missing. At Day 365 following the final transplantation, four (4) subjects remained non-normal, while data are missing for eight (8) subjects (Table 14.3.79 and Table 14.3.80).

Data are presented by center in Table 14.3.81, Table 14.3.82, Table 14.3.83, and Table 14.3.84.

12.6 Safety Conclusions

- Thirty-six (36) AEs were reported by ten (10) subjects in the experimental arm (LMW-DS) and 61 AEs were reported by 14 subjects in the state of the art arm (Heparin) from randomization to day 75 following the initial transplantation. Urinary tract infection and hepatic enzyme increased were the most frequently occurring AEs in subjects receiving LMW-DS, whereas headache and hepatic enzyme increased were the most frequently reported AEs in subjects receiving Heparin.
- There were 98 AEs reported by ten (10) subjects in the experimental arm (LMW-DS) and 126 AEs were reported by 14 subjects in the state of the art arm (Heparin) from randomization to day 365 following the initial transplantation. Stomatitis and hemoglobin decreased were the most frequently occurring AEs in subjects receiving LMW-DS, whereas neutropenia and headache were the most frequently reported AEs in subjects receiving Heparin.
- A total of 113 AEs were reported by ten (10) subjects in the experimental arm (LMW-DS) and 137 AEs were reported by 14 subjects in the state of the art arm (Heparin) from randomization to day 365 following the final transplantation. Stomatitis and hemoglobin decreased were the most frequently occurring AEs in subjects receiving LMW-DS, whereas headache, neutropenia and nausea were the most frequently reported AEs in subjects receiving Heparin.

- All AEs were graded between one (1) and four (4) on a scale from one (1) to five (5) and the majority of the AEs were attributed to immunosuppression.
- There were 31 SAEs reported during the study. No death was reported and all SAEs resolved within 35 weeks. No subject was reported to have experienced any sequelae in association with their SAEs.
- Twelve (12) of the SAEs were reported during the pre-randomization period and none of the SAEs appeared to be due to the study interventions.
- Nineteen (19) of the SAEs were reported during the period following randomization. There were 12 SAEs reported by six (6) subjects in the experimental arm (LMW-DS) and seven (7) SAEs reported by six (6) subjects in the state of the art arm (Heparin).
- The majority of the SAEs were attributed to the concomitant therapy. Granulocytopenia was the most commonly reported SAE, as reported by one (1) subject treated with LMW-DS and one (1) subject treated with Heparin.
- The Pennsylvania Central Laboratory found that three (3) subjects with a Baseline peak PRA value of 0% and one (1) subject with a Baseline peak PRA value of 73% developed anti-HLA antibodies after Baseline with peak PRA values of 3, 24, 86 and 86%, respectively. The Rudbeck Central Laboratory found that three (3) subjects with a Baseline peak PRA value of 0% and three (3) subjects with Baseline peak PRA values of 1, 22 and 73% developed anti-HLA antibodies after Baseline with peak PRA values of 2, 10, 24, 3, 23 and 86%, respectively.
- Two (2) subjects in the experimental arm (LMW-DS) and seven (7) subjects in the control arm (Heparin) changed immunosuppression regimen at two (2) and eight (8) occasions, respectively..
- Two (2) subjects in the experimental arm developed retinopathy.