SUPPLEMENTARY DATA

Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia

Supplementary Materials

SUPPLEMENTARY DATA

Supplementary Appendix S1. The CIT Consortium

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SUPPLEMENTARY DATA

Supplementary Appendix S2. Primary and Secondary Endpoint Definitions

Primary Endpoint: The proportion of patients with an HbA1c <7.0% at Day 365 AND free of severe hypoglycemic events from Day 28 to Day 365 inclusive following the first islet transplant, with the day of transplant designated Day 0.

Severe hypoglycemic event (SHE): An event with one of the following symptoms: memory loss; confusion; uncontrollable behavior; irrational behavior; unusual difficulty in awakening; suspected seizure; seizure; loss of consciousness; or visual symptoms, in which the patient was unable to treat him/herself and which was associated with either a blood glucose level <54 mg/dL (3.0 mmol/L) or prompt recovery after oral carbohydrate, IV glucose, or glucagon administration.

Insulin Independence: Islet transplant recipients will be considered insulin-independent with full islet graft function if they are able to titrate off insulin therapy for at least 1 week and all of the following criteria are met:

- One HbA1c level, one fasting serum glucose level, and a Mixed Meal Tolerance Test are documented within the visit window (e.g. 70-80 days at Day 75) and 7 consecutive days of blood sugar and insulin readings are documented within +/- 7 days of the visit window (e.g. 63 – 87 days at Day 75);
- HbA1c <7.0% or a ≥2.5% decrease from baseline;
- Fasting capillary glucose level should not exceed 140 mg/dL (7.8 mmol/L) more than three times in the 7 consecutive days (fasting is defined as 1st blood sugar reading of the day not noted as post-prandial or bedtime);
- Post-prandial serum glucose ≤ 180 mg/dL (10.0 mmol/L) at 90 minutes during the MMTT;
- Fasting serum glucose level ≤126 mg/dL (7.0 mmol/L): if the fasting serum glucose level is >126 mg/dL (7.0 mmol/L), it must be confirmed in an additional one out of two measurements;
- At least one MMTT fasting or stimulated c-peptide ≥0.5 ng/ml.

SUPPLEMENTARY DATA

Supplementary Appendix S3. Quantitative scores of Clarke score, hypoglycemia severity (HYPO score) and glycemic lability index (LI) and Mean Amplitude of Glycemic Excursions (MAGE)

Measurement	Description	Reference Values
Clarke Score (1)	Patient response to questions on reduced awareness of hypoglycemia and presence or absence of autonomic and neuroglycopenic symptoms associated with low blood glucose in the past year.	Scored 0-8. >4 indicates reduced awareness; <2 indicates awareness of hypoglycemia; derived from a population of 78 T1D patients
HYPO score (2)	Based on 4 week diary of at least 4 times daily Blood Glucose (BG) monitoring with points assigned for symptoms and assistance required with each BG reading <54 mg/dl and recall of severe hypoglycemic episodes (SHE) in the previous 12 months	≥423 and ≥1047 represent the 75^{th} and 90^{th} percentile values derived from a population of 100 patients with T1D
LI (2)	Based on 4 week diary of at least 4 times daily BG monitoring calculated as the sum of all the squared differences in consecutive glucose readings divided by the time between consecutive readings	≥329 and ≥433 $(mmol/l)^2/h \cdot wk^{-1}$ represent the 75^{th} and 90^{th} percentile values derived from a population of 100 patients with T1D
MAGE (2,3)	Based on 2 day diary of at least 7 times daily BG monitoring calculated as the mean of all glycemic excursions (peak minus nadir) >1 S.D. of the mean BG	112-189 mg/dL[1] represents the 25^{th} to 75^{th} interquartile range derived from a population of 100 patients with T1D

[1]To convert to mmol/l, divide by 0.05551.

References for this table:

1. Clarke, WL, Cox, DJ, Gonder-Frederick, LA, Julian, D, Schlundt, D, Polonsky, W. Reduced awareness of hypoglycemia in adults with IDDM. Diabetes Care, 1995. 18(4): 517-522.

2. Ryan E, Shandro T, Green K, Paty B, Senior P, Bigam D, et al. Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. *Diabetes*. 2004 Apr; 53(4):955-62. 2

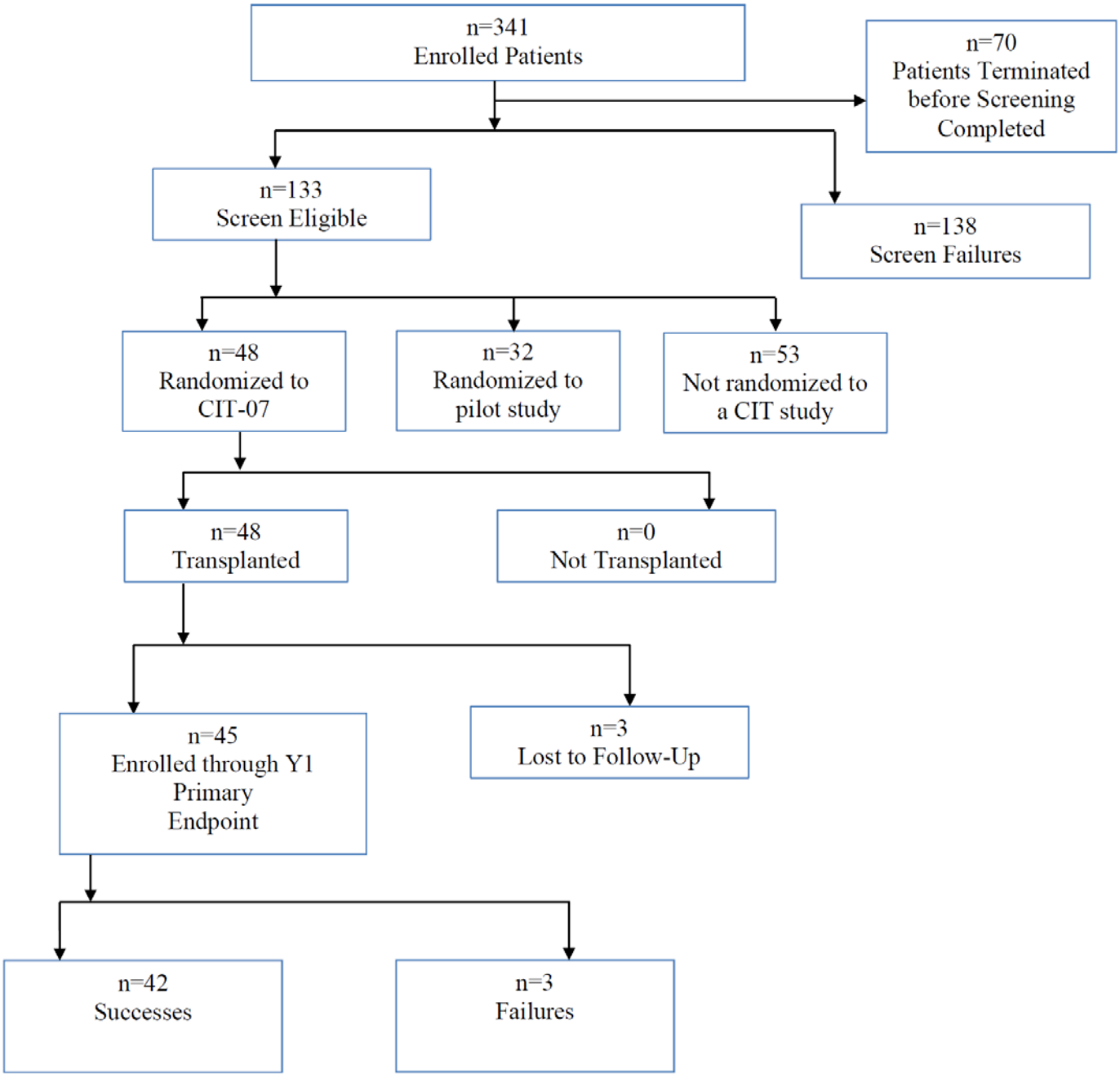
3. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes*. 1970 Sep; 19(9):644-655.

SUPPLEMENTARY DATA

Supplementary Appendix S4. CONSORT Diagram

Three hundred forty-one patients signed written informed consent to participate in a screening/baseline study. Seventy of these patients terminated their participation before completing the screening process. One hundred thirty-eight patients completed screening but were considered screen failures. One hundred thirty-three patients were screening eligible. They were placed on the waitlist to receive a compatible pancreas suitable for islet isolation. When a pancreas became available for a waitlisted patient, that patient was randomized to participate in Protocol CIT-07 or a CIT Phase 2 pilot study. Forty-eight patients were randomized to CIT-07. All 48 patients randomized to Protocol CIT-07 received one or more PHPI transplant(s). Forty-five patients remained enrolled in Protocol CIT-07 through evaluation of the primary end point at one year post-initial transplant; 3 were lost to follow-up. Forty-two of the 45 remaining patients achieved success on the primary end point.

SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

Supplementary Appendix S5. Definition of Reduced Awareness of Hypoglycemia, Lability and Qualification for the Study Based on the Elements of the Definition

Criteria for Study Entry	Number (%) of Patients Qualifying Based on Criterion
A Clarke score of 4 or more OR a HYPO score greater than or equal to the 90th percentile (1047) during the screening period and within the last 6 months prior to transplant	Clarke score: 47 (97.9%) HYPO score: 30 (62.5%)
Marked glycemic lability characterized by wide swings in blood glucose despite optimal diabetes therapy and defined by an LI score greater than or equal to the 90th percentile (433 mmol/L^2/h·wk) during the screening period and within the last 6 months prior to transplant	40 (83.3%)
A composite of a Clarke score of 4 or more and a HYPO score greater than or equal to the 75th percentile (423) and a LI greater than or equal to the 75th percentile (329) during the screening period and within the last 6 months prior to transplant	28 (58.5%)

SUPPLEMENTARY DATA

Supplementary Appendix S6. CIT Questionnaire Documenting Severe Hypoglycemia (completed by each patient's treating physician)

1.) Did your patient have onset of Type I diabetes prior to age 40 years?

Yes _____ No _____

2.) Has your patient been insulin-dependent for more than 5 years?

Yes _____ No _____

3.) Has your patient been under the management of an endocrinologist, diabetologist, or other diabetes specialist for at least one year, with at least three clinical evaluations over this past year?

Yes _____ No _____

4.) Has your patient followed for at least one year a program of intensive diabetes management, including:
a. Self monitoring of blood glucose at least three times daily on average, AND
b. Administration of three or more injections of insulin daily on average or use of an insulin pump

Yes _____ No _____

5.) Has your patient been UNABLE to achieve glycemic control without hypoglycemic episodes (HbA1c >7%, or HbA1c <7% but with reduced awareness of hypoglycemia)?

Yes _____ No _____

6.) Has your patient had over the past six months either:

a. Reduced hypoglycemic awareness (Clarke score ≥4 or HYPO score ≥1047, OR
b. Marked glycemic lability (Lability Index ≥433) with wide swings in blood glucose despite optimized diabetes therapy, OR
c. The combination of a Clarke score ≥4 AND a HYPO score ≥423 AND a Lability Index ≥329 (see attached letter)?

Yes _____ No _____

7.) Has your patient had in the past year at least one severe hypoglycemic event (requiring assistance of another person, and with measured blood glucose <54 mg/dL [3.0 mmol/L] and/or prompt recovery after administration of carbohydrate or glucagon)?

Yes _____ No _____

Signed _____ Date _____

Supplementary Appendix S7. Standardized Lot Release Criteria Interim Certificate of Analysis Fields

Test	Requirement
Identity	
Recipient Identity	Recipient Study ID # and Recipient Medical Record Number on this CoA and on each infusion bag label are identical to that in the Production Batch Record, Section 12.3
Islets Identity	Islets are present in each product bag
Volumes in Bags	
Suspension Volume	200 mL per product bag ≤600 mL total in three product bags
Settled Tissue Volume	≤7.5 mL per product bag ≤15.0 mL total in three product bags
Potency	
High Purity Islets GSIR Index (Pre-culture Sample)	For Information Only
Islets Quantity	First Infusion: ≥ 5.0 x 10^3 IEQ/kg of Recipient's Body Weight (Total IEQ/infusion) Subsequent Infusions: ≥4.0 x 10^3 IEQ/kg of Recipient's Body Weight (Total IEQ/infusion)
Viability	≥70% in each product bag
Purity	
Islets Concentration	≥20,000 Total IEQ/mL Total Settled Tissue Volume
Safety	
Appearance	Light yellow to amber liquid with visible aggregates in each product bag
Endotoxins	≤5.0 EU/kg of Recipient's Body Weight (Total EU/infusion)
Gram Stain (Islets Purity Levels Pre-combination Samples)	No Organisms Seen

SUPPLEMENTARY DATA

Final Certificate of Analysis Fields

Test	Requirement
Identity	
Recipient Identity	Recipient Study ID # and Recipient Medical Record Number on this CoA and on each infusion bag label are identical to that in the Production Batch Record, Section 12.3
Islets Identity	Islets are present in each product bag
Volumes in Bags	
Suspension Volume	200 mL per product bag ≤600 mL total in three product bags
Settled Tissue Volume	≤7.5 mL per product bag ≤15.0 mL total in three product bags
Potency	
High Purity Islets GSIR Index (Pre-culture Sample)	For Information Only
High Purity Islets GSIR Index (Post-culture Sample	Glucose Stimulated Insulin Release Index > 1
Islets Quantity	First Infusion: ≥5.0 x 10^3 IEQ/kg of Recipient's Body Weight (Total IEQ/infusion) Subsequent Infusions: ≥4.0 x 10^3 IEQ/kg of Recipient's Body Weight (Total IEQ/infusion)
Viability	≥ 70% in each product bag
Purity	
Islets Concentration	≥20,000 Total IEQ/mL Total Settled Tissue Volume
Safety	
Appearance	Light yellow to amber liquid with visible aggregates in each product bag
Endotoxins	≤5.0 EU/kg of Recipient's Body Weight (Total EU/infusion)
Gram Stain (Islets Purity Levels Pre-combination Samples)	No Organisms Seen
Sterility (21CFR610.12 or validated alternate)	No Growth in each product bag

Supplementary Appendix S8. Study Treatment Regimen

Drug	Manufacturer	Indication	Dosing	Target Trough Level
ATG (Thymoglobulin®)	Sanofi/Genzyme Corporation	Induction regimen for 1st transplant	0.5 mg/kg on day -2 1.0 mg/kg on day -1 1.5 mg/kg on days 0, +1, and +2	N/A
Sirolimus (Rapamune®)	Pfizer	Maintenance immunosuppression	0.05-0.2mg/kg on day -2 0.05-0.1mg/kg QD	10-15 ng/mL through month 3 8-12 ng/mL thereafter
Tacrolimus (Prograf®)	Astellas	Maintenance immunosuppression	0.015 mg/kg BID on day +1	3-6 ng/mL
Cyclosporine (Neoral®)	Novartis Pharmaceuticals	Maintenance immunosuppression: substitute for tacrolimus due to intolerance	6 mg/kg/d in 2 divided doses	150-200 ng/mL
Mycophenolate mofetil (MMF, Cellcept®)	Roche Palo	Maintenance immunosuppression: substitute for tacrolimus or sirolimus due to intolerance	500-1500 mg BID	N/A
Mycophenolate Sodium (Myfortic®)	Novartis Pharmaceuticals	Maintenance immunosuppression: alternate substitute for tacrolimus, sirolimus, or MMF	360 to 720 mg BID	N/A
Basliximab (Simulect®)	Novartis Pharmaceuticals	Induction regimen for 2nd or 3rd transplants	20 mg on day 0 and day +4	N/A
Etanercept (Enbrel®)	Immunex/Amgen	Immunosuppressive/anti-imflammatory therapy for each transplant	50 mg IV on day 0 25 mg SC on days +3, +7 and +10	N/A
Trimethoprim / sulfamethoxaxole (Septra SS® / Bactrim®)	Mutual Pharmaceutical Company	Pneumocystis prophylaxis for each transplant	80 mg/400 mg QD for 6 months	N/A
Clotrimazole (Mycelex Troche®)	Bayer	Antifungal prophylaxis for each transplant	1 troche QID for 3 months	N/A
Valganciclovir (Valcyte®)	Hoffmann - La Roche Inc	Anti-CMV prophylaxis for each transplant. Adjusted or eliminated when donor and recipient are CMV negative.	450 mg PO QD increasing to 900 mg QD by day 12 through week 14	N/A
Heparin	At investigator's discretion	Anticoagulation prophylaxis for each transplant	70 U/kg body weight divided equally in islet bags followed by 3U/kg/hr IV for next 4 hours. From 5-48 hours post-transplant, heparin titrated to achieve and	N/A

SUPPLEMENTARY DATA

Drug	Manufacturer	Indication	Dosing	Target Trough Level
			maintain PTT= 50-60 seconds.	
Enoxaparin (Lovenox®)	Sanofi Aventis US	Anticoagulation prophylaxis for each transplant	30 mg SC BID starting 48 hours after transplant (when heparin discontinued) through day 7. Dose can be modified or extended at discretion of investigator.	N/A
aspirin	At investigator's discretion	Anticoagulation prophylaxis for each transplant	81 mg start PM 24 hours post-transplant and continued as medically indicated	N/A
pentoxifylline	At investigator's discretion	Anti-inflammatory for each transplant	400 mg slow release TID starting day -2 and continuing to day +7	N/A
acetaminophen	At investigator's discretion	Premedication for each ATG infusion	650 mg PO/PR ½ hr before and midway through ATG infusion	N/A
diphenhydramine	At investigator's discretion	Premedication for each ATG infusion	50 mg PO ½ hr before and midway through ATG infusion	N/A
methylprednisolone	At investigator's discretion	Premedication for initial ATG infusion	1 mg/kg IV one hour prior to and as needed during infusion	N/A

SUPPLEMENTARY DATA

Supplementary Appendix S9. Patient Listings for Primary Endpoint and Secondary Endpoint Components in Y1

Patient*	Primary Endpoint	HbA1c Level at Day 365	Number of SHE Day 28-Day 365	Number of TX	Total IEQ/kg	Insulin Independence at Day 75	Insulin Independence at Day 365
01	Success	5.7	0	1	9781	Failure	Failure
02	Success	6.4	0	2	12,188	Failure	Failure
03	Success	6.3	0	2	12,109	Failure	Failure
04	Success	5.1	0	1	7445	Success	Success
05	Success	6.1	0	3	18,200	Failure	Failure
06	Success	6.9	0	1	5775	Failure	Failure
07	Success	5.2	0	1	11,493	Failure	Success
08	Success	5.5	0	1	12,221	Failure	Success
09	Success	6.4	0	1	8163	Failure	Failure
10	Success	5.3	0	2	14,706	Failure	Failure
11	Success	5.7	0	2	13,769	Failure	Insufficient data
12	Success	5.4	0	2	13,335	Failure	Success
13	Success	5.4	0	1	9080	Success	Success
14	Success	6.6	0	2	16,953	Insufficient data	Failure
15	Success	5.8	0	2	19,470	Failure	Failure
16	Success	5.6	0	2	15,354	Failure	Success
17	Success	6.2	0	2	10,865	Insufficient data	Insufficient data
18	Success	5.5	0	1	12,073	Success	Success
19	Success	5.4	0	1	9450	Success	Success
20	Success	5.4	0	1	11,069	Failure	Success
21	Success	5.2	0	2	12,444	Failure	Success
22	Success	5.5	0	1	7853	Success	Success
23	Success	5.3	0	1	9218	Success	Success
24	Success	5.6	0	2	12,509	Failure	Success
25	Success	5.3	0	2	9480	Failure	Success
26	Success	6.0	0	2	12,679	Failure	Success
27	Success	5.2	0	1	6294	Success	Success
28	Success	5.5	0	1	5924	Success	Success
29	Success	5.4	0	2	12,152	Failure	Success

SUPPLEMENTARY DATA

Patient*	Primary Endpoint	HbA1c Level at Day 365	Number of SHE Day 28-Day 365	Number of TX	Total IEQ/kg	Insulin Independence at Day 75	Insulin Independence at Day 365
30	Success	5.7	0	2	15,478	Failure	Success
31	Success	5.7	0	2	10,595	Failure	Insufficient data
32	Success	4.8	0	2	12,988	Failure	Success
33	Success	5.6	0	1	6325	Success	Success
34	Success	5.6	0	1	5233	Failure	Insufficient data
35	Success	6.0	0	2	14,205	Failure	Insufficient data
36	Success	6.3	0	2	11,898	Insufficient data	Failure
37	Success	5.4	0	2	15,860	Insufficient data	Success
38	Success	6.6	0	1	7521	Success	Success
39	Success	5.2	0	2	25,553	Insufficient data	Success
40	Success	5.8	0	2	16,507	Failure	Failure
41	Success	5.2	0	2	12,550	Failure	Success
42	Success	6.8	0	2	12,080	Insufficient data	Failure
43	Failure	7.0	1	1	8644	Insufficient data	Failure
44	Failure	.	.	1	8127	Insufficient data	Insufficient data
45	Failure	7.3	0	1	7898	Success	Failure
46	Failure	.	.	2	12,754	Failure	Failure(termination)
47	Failure	7.6	3	1	9325	Failure	Insufficient data
48	Failure	.	.	1	5277	Failure	Failure(termination)

*Patient numbers in this table are not in temporal order.

SUPPLEMENTARY DATA

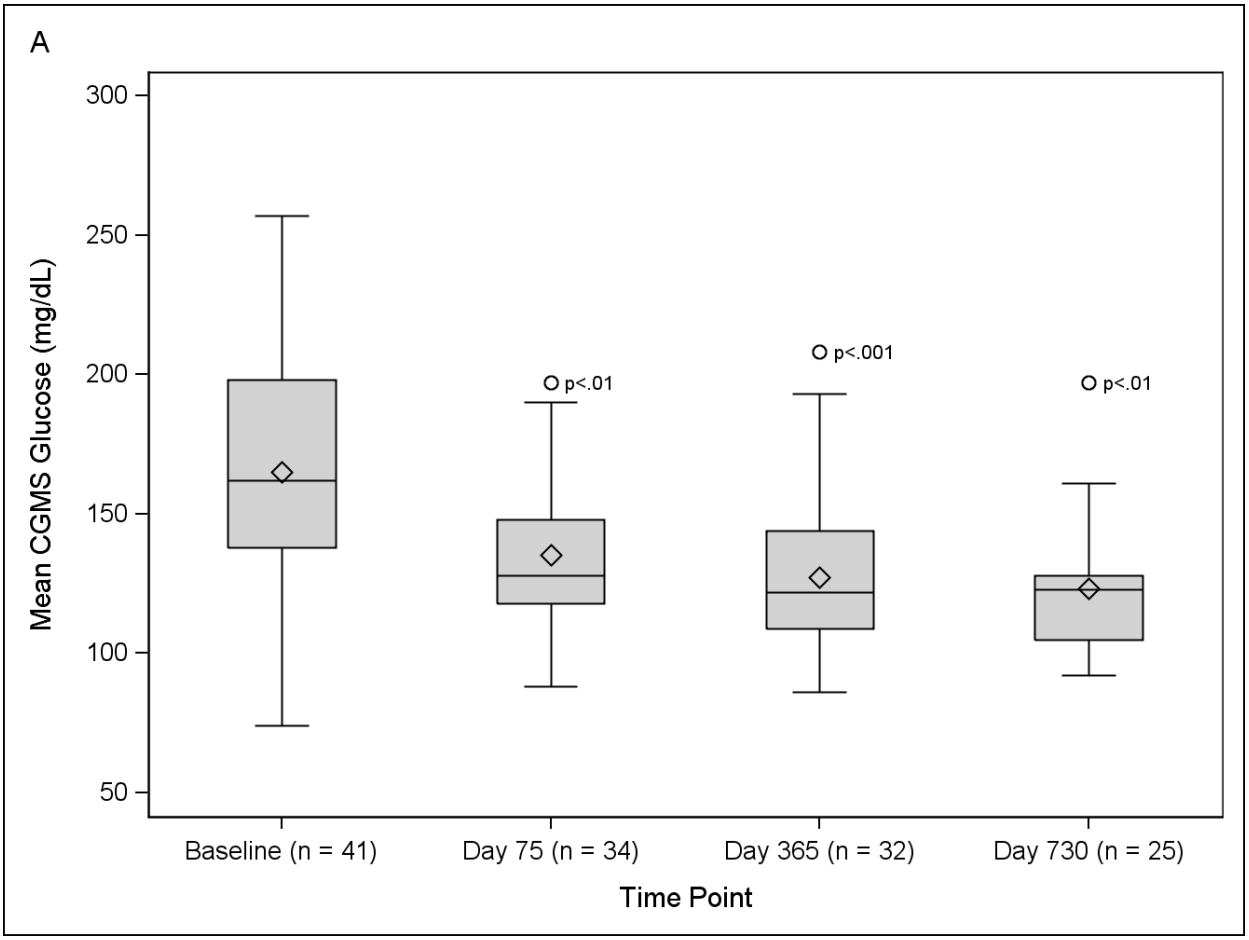
Supplementary Appendix S10. Reasons for Failure to Meet Primary Endpoint (HbA1C<7%, and no SHE* between days 28 and 365 following first transplant).

Patient**	Failed/Insufficient data	Comments
43	Failed	HbA1c at Day 365 post-initial transplant was 7.0% (53 mmol/mol). Patient also had SHE between Day 28 and Day 365.
44	Insufficient data	Lost to follow up.
45	Failed	HbA1c at Day 365 post-initial transplant was 7.3% (56 mmol/mol).
46	Insufficient data	Lost to follow-up.
47	Failed	HbA1c at Day 365 post-initial transplant was 7.6%(60 mmol/mol). Patient also had SHE between Day 28 and Day 365.
48	Insufficient data	Withdrew from study 5 months following initial transplant.

* Severe hypoglycemic episodes
**Patient numbers in this table are not in temporal order.

SUPPLEMENTARY DATA

Supplementary Appendix S11. Supplementary Figure 1 Containing CGMS Data



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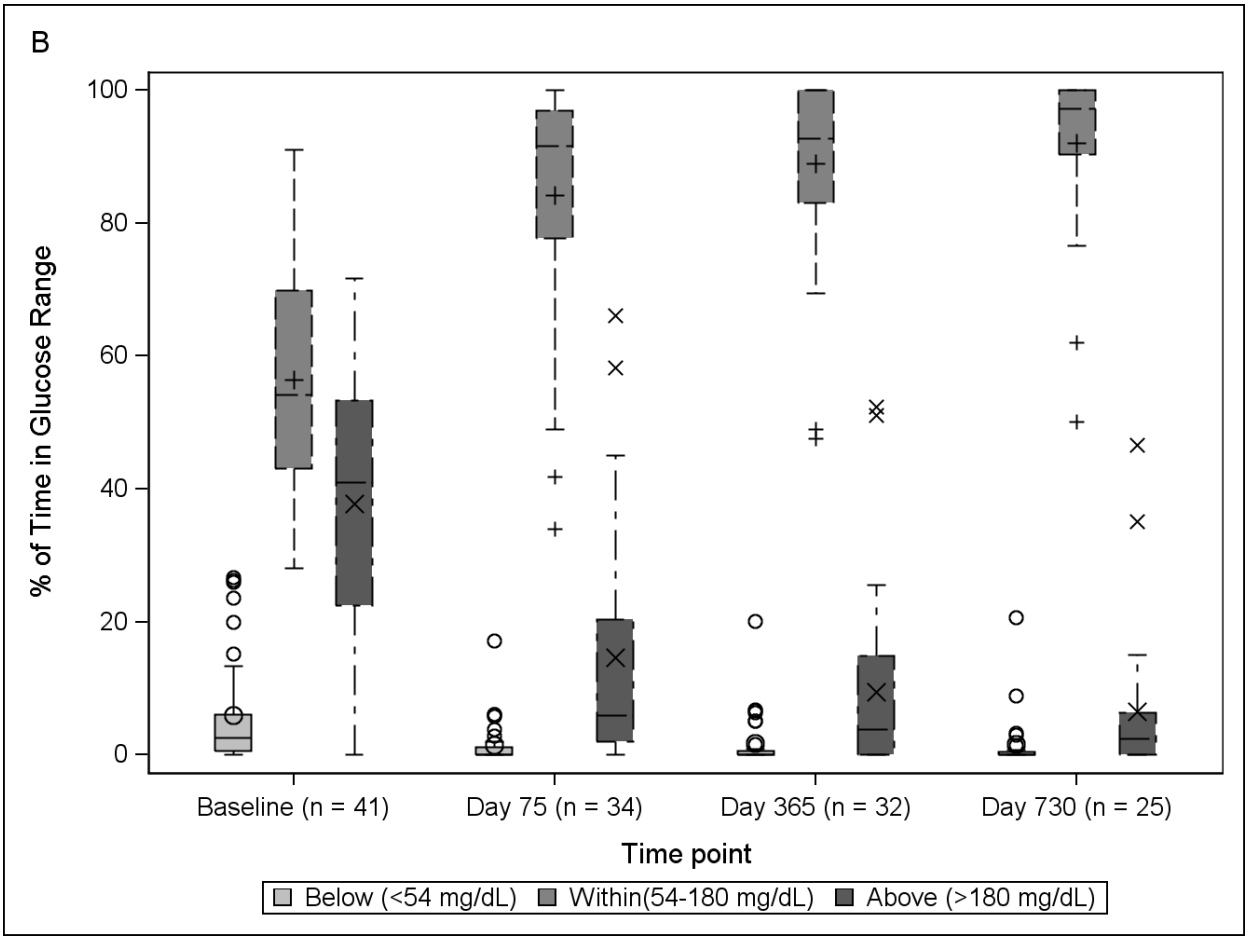

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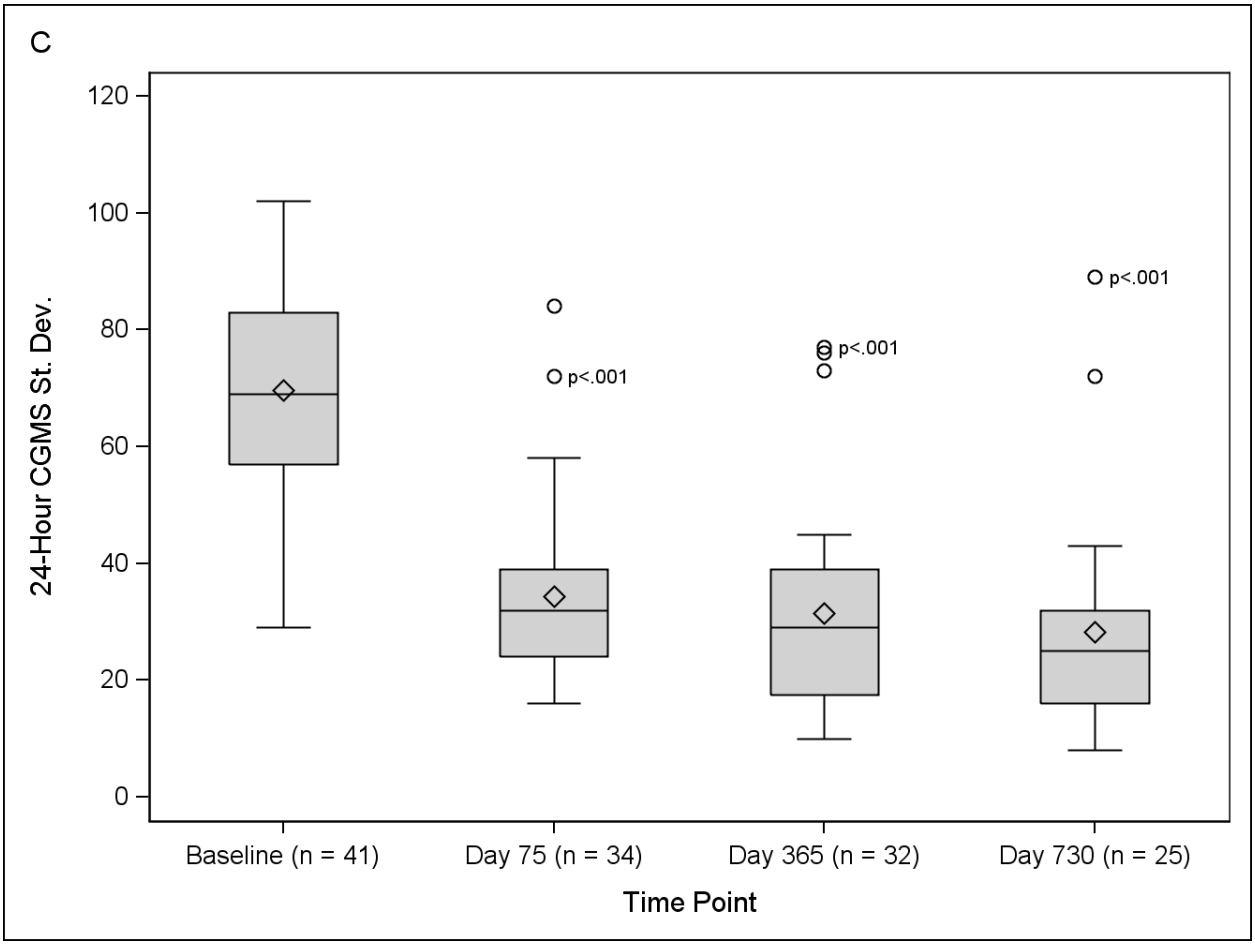

SUPPLEMENTARY DATA

Panel A:
Box plots of CGMS mean glucose at baseline, at Day 75, Day 365 and Day 730 following the first islet infusion. Median CGMS wear time was 72 hours at baseline and Y1 and 71 hours at Y2.

The Wilcoxon Signed Rank Test for paired outcomes was used to compare the median CGMS glucose between baseline (N = 41) and Day 75 (N = 34) between baseline and Day 365 (N = 32), and between baseline and Day 730 (N = 23).

The Bonferroni method was used to adjust the level of significance for these three comparisons in order to preserve the overall Type 1 error rate of 0.05.

The adjusted p-value for the comparison between baseline and Day 75 is 0.0053.

The adjusted p-value for the comparison between baseline and Day 365 is 0.0010.

The adjusted p-value for the comparison between baseline and Day 730 is 0.0010.

Panel B:
Box plots of CGMS glucose below 54, within target of 54 and 180, and above 180 mg/dL at baseline, Day 75, Day 365 and Day 730 following the first islet infusion.

The Wilcoxon Signed Rank Test was used to compare the percent of time in each range among the time periods

For each blood glucose range (<54 mg/dL, 54–180 mg/dL, and >180 mg/dL) the Bonferroni method was used to adjust the level of significance for the two comparisons made between baseline (N = 41) and Day 75 (N = 34), between baseline and Day 365 (N = 32), and between baseline and Day 730 (N = 23).

The adjusted p-value for the comparison of the percent of time blood glucose was below 54 mg/dL between baseline and Day 75 is 0.0016.

The adjusted p-value for the comparison of the percent time blood glucose was below 54 mg/dL between baseline and Day 365 is 0.0178.

The adjusted p-value for the comparison of the percent of time blood glucose was below 54 mg/dL between baseline and Day 730 is 0.0010.

All other adjusted p-values are less than 0.0003.

Panel C:
Box plots of CGMS glucose standard deviation at baseline, Day 75, Day 365 and Day 730 following the first islet infusion.

The Wilcoxon Signed Rank test was used to compare the median CGMS glucose standard deviation between baseline (N = 41) and Day 75 (N = 34) between baseline and Day 365 (N = 32), and between baseline and Day 730 (N = 23).

The Bonferroni method was used to adjust the level of significance for these three comparisons in order to preserve the overall Type 1 error rate of 0.05.

The adjusted p-values for these three tests are less than 0.0003.

Supplementary Appendix S12. Patient Disposition Table Through Y2

			Outcomes at Year 1 Post-initial Transplant				Outcomes at Year 2 Post-initial Transplant				
Patient*	**Initial Transplant Date**	**Termination Date**	**Primary endpoint**	**HbA1c (%)**	**SHE**	**Insulin Independence**	**Composite HbA1c and SHE (Secondary) Endpoint**	**HbA1c**	**SHE ****	**Insulin Independence**	**Termination Reason/Comments**
1	17JUL2009	23JUL2010	Success	5.7	0	Failure	Terminated	.	0	Terminated	Patient consented under V3 of the protocol, which called for only 1 year of follow-up. Last HbA1c 7/20/10 = 5.7% (39 mmol/mol).
2	04MAR2011	06AUG2013	Success	6.4	0	Failure	Failure	7.2	0	Failure	
3	11JAN2011	23NOV2012	Success	6.3	0	Failure	Failure	.	0	Failure	This patient terminated before Y2 but within the 3-month window for that visit, so s/he is considered a failure rather than a termination. Last HbA1c 9/18/12 = 6.6%.
4	01AUG2011	20AUG2013	Success	5.1	0	Success	Success	6.2	0	Failure	
5	05AUG2011	18SEP2012	Success	6.1	0	Failure	Terminated	.	0	Terminated	Patient withdrew consent. Last HbA1c 9/18/12 = 6.2% (44 mmol/mol).
6	24OCT2010	19MAY2012	Success	6.9	0	Failure	Terminated	.	0	Terminated	Second transplant in non-CIT protocol. Last HbA1c 4/12/12 = 6.9% (52 mmol/mol).
7	12JUL2010	16JUL2012	Success	5.2	0	Success	Success	5.8	0	Failure	
8	23MAY2011	03JUN2013	Success	5.5	0	Success	Success	5.3	0	Failure	
9	28APR2010	29APR2012	Success	6.4	0	Failure	Success	6.2	0	Failure	
10	04APR2010	13DEC2012	Success	5.3	0	Failure	Success	5.6	0	Failure	
11	10JAN2010	30MAY2012	Success	5.7	0	Failure	Success	6.1	0	Failure	

SUPPLEMENTARY DATA

			Outcomes at Year 1 Post-initial Transplant				Outcomes at Year 2 Post-initial Transplant				
Patient*	Initial Transplant Date	Termination Date	Primary endpoint	HbA1c (%)	SHE	Insulin Independence	Composite HbA1c and SHE (Secondary) Endpoint	HbA1c	SHE **	Insulin Independence	Termination Reason/Comments
12	19JUL2011	16JAN2014	Success	5.4	0	Success	Success	5.5	0	Success	
13	24JAN2010	26JAN2012	Success	5.4	0	Success	Success	5.6	0	Success	
14	26AUG2011	02JAN2014	Success	6.6	0	Failure	Success	6.1	0	Failure	
15	16JUL2010	09MAR2013	Success	5.8	0	Failure	Failure	9.2	2	Failure	
16	21FEB2011	05JUL2013	Success	5.6	0	Success	Success	4.8	0	Failure	
17	22SEP2011	28MAY2014	Success	6.2	0	Failure	Success	6.6	0	Failure	
18	12OCT2008	18OCT2012	Success	5.5	0	Success	Success	5.3	0	Failure	
19	12MAY2010	09MAY2012	Success	5.4	0	Success	Success	5.5	0	Failure	
20	10MAR2010	13MAR2012	Success	5.4	0	Success	Success	5.6	0	Success	
21	07MAR2011	24JUL2013	Success	5.2	0	Success	Success	5.4	0	Success	
22	04NOV2008	09NOV2010	Success	5.5	0	Success	Success	5.5	0	Success	
23	07JUN2010	06JUN2012	Success	5.3	0	Success	Success	5.6	0	Failure	
24	03SEP2010	08JAN2013	Success	5.6	0	Success	Success	5.6	0	Failure	
25	12JUN2011	01OCT2013	Success	5.3	0	Success	Success	5.5	0	Success	
26	07JUL2011	28APR2014	Success	6	0	Success	Success	5.9	0	Failure	
27	31MAR2011	01APR2013	Success	5.2	0	Success	Success	5.3	0	Success	
28	26FEB2009	02MAR2011	Success	5.5	0	Success	Success	5.6	0	Success	
29	10SEP2011	04DEC2013	Success	5.4	0	Success	Success	5.4	0	Success	
30	17SEP2011	22JAN2014	Success	5.7	0	Success	Success	6.1	0	Success	
31	30MAY2010	01NOV2012	Success	5.7	0	Failure	Success	6.2	0	Failure	
32	09JUN2009	05DEC2011	Success	4.8	0	Success	Success	5.4	0	Failure	

SUPPLEMENTARY DATA

			Outcomes at Year 1 Post-initial Transplant				Outcomes at Year 2 Post-initial Transplant				
Patient*	**Initial Transplant Date**	**Termination Date**	**Primary endpoint**	**HbA1c (%)**	**SHE**	**Insulin Independence**	**Composite HbA1c and SHE (Secondary) Endpoint**	**HbA1c**	**SHE ** **	**Insulin Independence**	**Termination Reason/Comments**
33	24MAY2009	24JUN2011	Success	5.6	0	Success	Success	5.6	0	Success	
34	06MAY2009	09MAY2011	Success	5.6	0	Failure	Success	5.6	0	Failure	
35	01SEP2011	12FEB2014	Success	6	0	Failure	Failure	7.7	0	Failure	
36	18SEP2011	03APR2014	Success	6.3	0	Failure	Success	6	0	Failure	
37	10SEP2011	13JAN2014	Success	5.4	0	Success	Success	5.3	0	Failure	
38	29MAR2010	06APR2012	Success	6.6	0	Success	Success	6.1	0	Failure	
39	06JUN2010	02SEP2012	Success	5.2	0	Success	Success	4.9	0	Failure	
40	11JAN2011	14JUN2013	Success	5.8	0	Failure	Success	6.1	0	Success	
41	17FEB2010	12DEC2011	Success	5.2	0	Success	Failure	.	0	Failure	This patient terminated before Y2 but within the 3-month window for that visit, so s/he is considered a failure rather than a termination. She began taking Januvia without discussing in advance with study staff—because she wanted to reduce her insulin needs—and was therefore terminated. Last HbA1c 9/19/11 = 5.6% (38 mmol/mol).
42	21JUL2011	03APR2014	Success	6.8	0	Failure	Failure	7.6	0	Failure	
43	03MAR2009	11APR2011	Failure	7	1	Failure	Failure	7	2	Failure	
44	07MAR2009	26JUL2010	Failure	.	.	Failure	Terminated	.	.	Terminated	Lost to follow-up. Last HbA1c 11/25/2008 = 8.4% (68 mmol/mol).

SUPPLEMENTARY DATA

			Outcomes at Year 1 Post-initial Transplant				Outcomes at Year 2 Post-initial Transplant				
Patient*	**Initial Transplant Date**	**Termination Date**	**Primary endpoint**	**HbA1c (%)**	**SHE**	**Insulin Independence**	**Composite HbA1c and SHE (Secondary) Endpoint**	**HbA1c**	**SHE ****	**Insulin Independence**	**Termination Reason/Comments**
45	07MAY2010	07MAY2012	Failure	7.3	0	Failure	Success	5.9	0	Success	This patient had parvovirus that may have affected Y1 HbA1c.
46	28JAN2011	02OCT2011	Terminated	.	0	Terminated	Terminated	.	0	Terminated	Lost to follow-up. Last HbA1c 4/15/11 = 5.5% (37 mmol/mol).
47	24SEP2011	11OCT2013	Failure	7.6	3	Failure	Failure	7.8	6	Failure	
48	23AUG2011	03MAY2012	Terminated	.	0	Terminated	Terminated	.	0	Terminated	Patient withdrew consent. Last HbA1c 2/20/12 = 4.6% (27 mmol/mol).

*Patient numbers in this table are not in temporal order.
**SHE cumulative at Y2.

SUPPLEMENTARY DATA

Supplementary Appendix S13. Reasons for Failure to Complete 2 Years of Follow-Up in CIT-07

Patient*	Comments
1	Consented under an early version of the CIT-07 protocol that called for only one year of follow-up.
3	Withdrew consent due to frequency of study visits.
5	Withdrew consent due to frequency of study visits.
6	Received an islet transplant in a study outside of CIT.
41	Started taking Januvia, a study prohibited medication; withdrawn from study.

*Patient numbers in this table are not in temporal order

SUPPLEMENTARY DATA

Supplementary Appendix S14. Serious Adverse Event Listing

		Year					
		1		2		Cumulative Total	
System Organ Class	Preferred Term	# of Events	# of patients with event	# of Events	# of patients with event	# of Events	# of patients with event
Blood and lymphatic system disorders	Febrile neutropenia	3	2	0	0	3	2
	Neutropenia	3	2	0	0	3	2
	Pancytopenia	1	1	0	0	1	1
Cardiac disorders	Atrial flutter	1	1	0	0	1	1
Gastrointestinal disorders	Abdominal pain upper	1	1	0	0	1	1
	Vomiting	2	2	0	0	2	2
General disorders and administration site conditions	Adverse drug reaction	1	1	0	0	1	1
	Chest discomfort	0	0	1	1	1	1
	Infusion site haemorrhage[1]	1	1	0	0	1	1
	Non-cardiac chest pain	2	2	0	0	2	2
Immune system disorders	Cytokine release syndrome	1	1	0	0	1	1
	Food allergy	0	0	1	1	1	1
	Serum sickness	1	1	0	0	1	1
Infections and infestations	Appendicitis	0	0	1	1	1	1
	Gastroenteritis	2	2	0	0	2	2
	Pneumocystis jiroveci pneumonia	0	0	1	1	1	1
	Pyelonephritis	0	0	1	1	1	1
Injury, poisoning and procedural complications	Drug toxicity	1	1	0	0	1	1
	Hepatic haematoma[2]	1	1	0	0	1	1
	Hip fracture	0	0	1	1	1	1
	Medication error	1	1	0	0	1	1
	Post procedural complication[1]	2	2	0	0	2	2
	Post procedural haemorrhage[1]	2	2	0	0	2	2
Investigations	Immunosuppressant drug level increased	1	1	0	0	1	1
Metabolism and nutrition disorders	Hypoglycaemic unconsciousness	1	1	1	1	2	1
Nervous system disorders	Dementia	0	0	1	1	1	1

SUPPLEMENTARY DATA

		Year					
		1		2		Cumulative Total	
System Organ Class	Preferred Term	# of Events	# of patients with event	# of Events	# of patients with event	# of Events	# of patients with event
Psychiatric disorders	Conversion disorder	1	1	0	0	1	1
Renal and urinary disorders	Renal failure acute	1	1	0	0	1	1

[1] Procedure-related bleeding events.

[2] Secondary to motor vehicle accident.

SUPPLEMENTARY DATA

Supplementary Appendix S15. Serious Adverse Event Descriptions

System Organ Class	Preferred Term	Patient	Description
Blood and lymphatic system disorders	Febrile neutropenia	9	The patient had neutropenia and fever 3 days after islet transplantation, attributed to conditioning regime and/or immunosuppression. The event resolved without sequelae on the following day.
Blood and lymphatic system disorders	Febrile neutropenia	28	The patient had neutropenia with fever 26 days after the initial islet transplant, attributed to the conditioning regimen and/or ongoing immunosuppression and/or infection prophylaxis (valganciclovir and TMP/SMX). The valganciclovir and TMP/SMX doses were reduced. The neutropenia resolved after a single dose of G-CSF and dose reduction of valganciclovir and switch from TMP/SMX to inhaled pentamidine. The event resolved without sequelae at approximately 5 months after onset.
Blood and lymphatic system disorders	Febrile neutropenia	28	The patient was readmitted 3 days after a febrile neutropenia event, 34 days after the initial islet transplant, for continued fatigue. The patient had slow resolution with supportive care. The event was attributed to immunosuppression and/or the conditioning regimen. The event resolved without sequelae in just over 3 weeks.
Blood and lymphatic system disorders	Neutropenia	33	Starting 18 days after initial islet transplantation, the patient was diagnosed with asymptomatic neutropenia, and was treated with daily doses of G-CSF for three days, with valganciclovir and TMP/SMX held until WBC>3.0. The event resolved without sequelae in three days.
Blood and lymphatic system disorders	Neutropenia	47	The patient was diagnosed with asymptomatic neutropenia, 2 days after initial islet transplantation. The thymoglobulin and TMP/SMX doses were reduced and the patient was treated with a single dose of G-CSF. The event was attributed to immunosuppression and/or the conditioning regimen. The event resolved without sequelae on the following day.
Blood and lymphatic system disorders	Neutropenia	47	The patient was diagnosed with recurrent asymptomatic neutropenia starting 74 days after initial islet transplantation, attributed to the conditioning regimen and/or immunosuppression. The patient was treated with three doses of G-CSF and the sirolimus dose was reduced by 20%. The event resolved without sequelae after one month.
Blood and lymphatic system disorders	Pancytopenia	3	The patient was noted to have leukopenia, mild anemia and thrombocytopenia 2 days after initial islet transplant. The event was attributed to the immunosuppression and/or conditioning regimen. A single dose of G-CSF was given with a brisk response. The event resolved without sequelae on the following day.

SUPPLEMENTARY DATA

System Organ Class	Preferred Term	Patient	Description
Cardiac disorders	Atrial flutter	38	The patient experienced asymptomatic, irregular tachycardia (HR=108) and subsequently was diagnosed with atrial flutter on the 2nd day after initial islet transplant. The event was evaluated as being possibly related to the islet infusion procedure or possibly related to the immunosuppressive and conditioning regimen. The patient was treated with cardioversion and four weeks of coumadin anticoagulation. The event did not recur and resolved without sequelae on the following day.
Gastrointestinal disorders	Abdominal pain upper	40	The patient reported epigastric pain 8 days after initial islet transplantation. A multisystem workup was negative except for a markedly elevated sirolimus level (25), with pain resolving with resolution of elevated sirolimus levels. The event was attributed to elevated sirolimus levels and/or late onset pain associated with the islet infusion procedure. The event resolved without sequelae on the following day.
Gastrointestinal disorders	Vomiting	18	The patient experienced vomiting and headache on day 5 after the initial islet transplant. The event was attributed to the islet infusion procedure and/or immunosuppression, and/or the patient's established history of migraine. The event resolved without sequelae on the following day.
Gastrointestinal disorders	Vomiting	28	The patient reported worsening nausea and vomiting on 3 days after initial islet transplantation. The patient was admitted for supportive care; immunosuppressant doses were reduced, with subsequent resolution of symptoms. The event was attributed to immunosuppression. The event resolved without sequelae two days later.
General disorders and administration site conditions	Adverse drug reaction	45	During pre-transplant conditioning, the patient developed urticaria on the face, abdomen and back. The event was attributed to thymoglobulin. The patient received a 7 day course of prednisone, and the planned islet transplant was cancelled; the patient subsequently received a transplant approximately 6 months later. The event resolved without sequelae approximately six weeks after onset.
General disorders and administration site conditions	Chest discomfort	16	Approximately 12 and 17 months after islet transplantation procedures, the patient reported chest pressure radiating across the upper chest with dyspnea and palpitation. During the subsequent hospitalization, the workup was negative for acute MI or cardiac ischemia. Orthostatic hypotension was newly diagnosed. The event was not attributed to the islet product or infusion and not attributed to the IS regimen or infectious prophylaxis. The event resolved one day later.
General disorders and administration site conditions	Infusion site haemorrhage	27	The patient complained of nausea and upper abdominal pain one day after the islet transplant, performed via percutaneous access to the portal vein. The workup led to laprascopic evacuation of intra-abdominal blood. The event was attributed to the islet infusion procedure. The event resolved without sequelae.

SUPPLEMENTARY DATA

System Organ Class	Preferred Term	Patient	Description
General disorders and administration site conditions	Non-cardiac chest pain	11	Approximately 2 months and 6 months after islet transplantation procedures, and one day after a follow-up visit, the patient was hospitalized with complaints of chest pain and palpitations. Clinical evaluation directed at possible cardiac ischemia or PE etiologies was negative. Metoprolol was started to treat a pre-existing history of episodic palpitations. No specific etiology was uncovered. The event was not attributed to the islet product or infusion and not attributed to the IS regimen or infectious prophylaxis. The event resolved without sequelae after one day.
General disorders and administration site conditions	Non-cardiac chest pain	29	Approximately 4 months and 6 months after islet transplantation procedures, the patient experienced sudden left subscapular pain, radiating to the anterior chest, exacerbated by breathing, and was admitted with concern for cardiac ischemic or PE etiologies, but the workup was negative. No specific etiology was found. The event was not attributed to the transplant or the immunosuppressive or infectious prophylaxis. The event resolved without sequelae after 2 weeks.
Immune system disorders	Cytokine release syndrome	31	Prior to this event, the patient experienced multiple symptoms during pre-transplant ATG, including diaphoresis, flushing, headache, emesis. Post-transplant ATG doses were reduced and these were tolerated. Heparin therapy was also discontinued due to thromocytopenia. On day 5 after transplant, several hours prior to a scheduled ATG infusion, the patient had the onset of headache nausea, diaphoresis, photosensitivity and difficulty speaking while at home. The scheduled ATG dose was not given, investigations/consultations including head CT and MRA were negative, and symptoms resolved with supportive care. The event was attributed to the immunosuppressive conditioning regimen. The event resolved one day later.
Immune system disorders	Food allergy	29	Approximately 11 months and 14 months after islet transplantations, the patient reported acute difficulty breathing after eating shrimp. The patient was seen in a local ER and was administered two doses of epinephrine. Subsequent outpatient allergy consultation diagnosed an allergy to shrimp tropomyosin. The patient was advised to avoid crab and lobster also. The event was not attributed as related to the islets or the procedure, nor to the immunosuppression or infection prophylaxis. The event was reported as resolved approximately three weeks later without sequelae.

SUPPLEMENTARY DATA

System Organ Class	Preferred Term	Patient	Description
Immune system disorders	Serum sickness	45	Subsequent to pre-transplantation conditioning, the patient experienced a persistent rash, recurring after the completion of a 7 day course of prednisone for an allergic reaction attributed to thymoglobulin. Low levels of complement C3 and C4 were interpreted as consistent with serum sickness. A longer tapering course of prednisone was given. The event was attributed to the immunosuppressive conditioning regimen; the scheduled islet infusion had already been cancelled. The event was reported as resolved without sequelae approximately 6 weeks after onset.
Infections and infestations	Appendicitis	29	17 months after initial islet transplant and 15 months after 2nd islet transplant, the patient presented with nausea, RUQ pain with rebound. After abdominal ultrasound, the patient had an uncomplicated laproscopic appendectomy. The event was not attributed to the transplanted islets or the procedure; the event was not attributed to the immunosuppressive regimen or anti-infective prophylaxis. The event was reported as resolved without sequelae approximately 3 weeks after onset.
Infections and infestations	Gastroenteritis	18	The patient presented with headache, nausea and vomiting, 70 days after initial islet transplant. The event was not attributed to the islets or procedure, and not attributed to the immunosuppression or infection prophylaxis. The event was attributed to the patient's pre-existing history of migraine. The event was reported as resolved without sequelae 2 days later.
Infections and infestations	Gastroenteritis	30	Approximately 4 months and 7 months after islet transplantation procedures, the patient developed acute nausea vomiting and diarrhea shortly after a salmon lunch. The symptoms resolved with hospitalization, hydration, and supportive care. The event was considered to be non-infectious, and not attributed to the islets or the procedure, nor associated with the immunosuppression or anti-infection prophylaxis. The event was reported as resolved without sequelae one day after onset.

SUPPLEMENTARY DATA

System Organ Class	Preferred Term	Patient	Description
Infections and infestations	Pneumocystis jiroveci pneumonia	20	Approximately 620 days after the patient's only islet transplantation, the patient was transferred to the transplant hospital after 3 days local hospitalization marked by progressive dyspnea, hypoxia, fever, and pulmonary infiltrates not responding to antibacterial therapy. BAL cytology revealed pneumocystis. The patient was not on Bactrim due to rash, and started treatment with clindamycin + primaquin + prednisone which was modified to bactrim + prednisone after desensitization. The patient had a supplemental O2 requirement (peak 10L NC) that slowly improved over ~10 days. Due to concerns about hyperkalemia, the patient was subsequently placed on atovaquone treatment almost two weeks into the 21 day treatment course. The patient was on insulin but was able to discontinue supplemental insulin at the completion of the prednisone course. The patient remained on atovoqone prophylaxis with uncomplicated recovery after completing pneumocystis therapy. The event was attributed to the immunosuppressive regimen. The event resolved without sequelae 1 month after onset.
Infections and infestations	Pyelonephritis	27	Approximately 540 days after the patient's only islet transplantation, the patient presented with acute dysuria and fever and was diagnosed with a urinary tract infection. Levofloxacin was given. After initial symptomatic improvement, the patient developed chills and flank pain and was admitted to the hospital. New cultures and imaging were negative. The antibiotic regimen was changed to cefepime and subsequently oral cefpodoxime for a 14 day course. The event was attributed to immunosuppressive therapy. The event resolved without sequelae.
Injury, poisoning and procedural complications	Drug toxicity	41	The patient presented with vomiting and elevated transaminases 6 days after transplant. The symptoms were attributed to sirolimus, due to an elevated (non-trough) sirolimus level. Dosing was adjusted during a three day hospitalization. The event was not attributed to the procedure or the islet product, but was attributed to the immunosuppressive regimen. The event resolved without sequelae three days after onset.
Injury, poisoning and procedural complications	Hepatic haematoma	11	Slightly less than 2 months after a second islet transplant and 5 months after initial islet transplant, the patient was in a motor vehicle accident: the car the patient was driving was hit by another car on the driver's side. The patient did not have any loss of consciousness or hypoglycemia; the patient needed to be extracted from the car. Emergency department evaluation led to a radiographic diagnosis of subcapsular liver hematoma. The patient was hospitalized for observation for 2 days, was clinically stable, and was discharged without additional intervention. The event was not attributed to either the procedure/islet infusion and not attributed to immunosuppression/infection prophylaxis. The event resolved without sequelae three days after onset.

SUPPLEMENTARY DATA

System Organ Class	Preferred Term	Patient	Description
Injury, poisoning and procedural complications	Hip fracture	28	The patient tripped on a sticky floor and fell. X-rays disclosed hip fracture. The patient underwent surgical treatment with no postoperative complications. The event was not attributed to the procedure/islet infusion and not attributed to the immunosuppression/infection prophylaxis. The resolved without sequelae three days after onset.
Injury, poisoning and procedural complications	Medication error	42	A medication error led to administration of an incorrect, very high insulin dose via intravenous drip infusion (250 units per hour for approx 35 minutes) during hospitalization prior to transplant. The blood glucose dropped as low as 31. The patient received multiple ampules of D50; the episode was fully resolved more than 4 hours prior to transplant procedure. The event was not attributed to the procedure/islet infusion and not attributed to the immunosuppression. The event resolved without sequelae on the day of onset.
Injury, poisoning and procedural complications	Post procedural complication	26	The patient received a second transplant which was performed percutaneously with ultrasound and fluoroscopic guidance, with gelfoam used to seal the catheter tract. The patient's hemoglobinwas stable (11g/dL) until 9 days after the procedure, at which time the patient reported acute onset of severe pain and nausea and vomiting. A local emergency department provider prescribed outpatient antiemetics and narcotic analgesic after noting a hemoglobin of 9 and perihepatic fluid. Patient returned to the emergency department after another acute episode of pain. At that point, the abdomen was distended and tender, with hemoglobin now down to 5. Two units of packed red cells were given and a workup revealed a large pseudoaneurysm in the left hepatic artery distribution that was successfully treated with coil embolization. The patient's anemia and subcapsular hematoma slowly resolved. The event was attributed to the islet infusion procedure, and not attributed to the immunosuppression/infectious prophylaxis. The event resolved without sequelae.
Injury, poisoning and procedural complications	Post procedural complication	37	The patient received an initial transplant via percutaneous approach and complained of right upper quadrant pain 4 hours after the procedure. Heparin was discontinued and 2 units of packed red cells were transfused. Ultrasound imaging was interpreted as consistent with a hepatic hematoma. No other treatment was required. The hemoglobin returned to normal within 15 days of transplant. The event was attributed to the islet infusion procedure, and not attributed to the immunosuppression/infection prophylaxis. The event resolved without sequelae.

SUPPLEMENTARY DATA

System Organ Class	Preferred Term	Patient	Description
Injury, poisoning and procedural complications	Post procedural haemorrhage	46	On the day after receiving an initial transplant via percutaneous approach, the patient complained of severe upper abdominal pain. Ultrasound disclosed periportal and pelvic fluid collections, accompanied by a serial decrease in hemoglobin. On the next day, laparoscopy was performed with evacuation of clot and a collection of bloody fluid, and hemostasis of the liver surface was achieved. Two units of packed red cells were transfused. The event was attributed to the islet infusion procedure, and not attributed to the immunosuppression/infection prophylaxis. The event resolved without sequelae.
Injury, poisoning and procedural complications	Post procedural haemorrhage	30	This event occurred during a second islet transplant approximately 4 months after initial islet transplant. Transplant access was performed in interventional radiology with hemorrhage noted upon withdrawal of the intraportal catheter, despite use of the gelfoam pledget. The transplant surgeons performed emergent exploratory laparatomy with coagulation of the puncture site and evacuation of 1000 ml of hemoperitoneum. Protocol-scheduled heparin was not started; 3 units of packed red cells and 1 unit of fresh frozen plasma were administered. The event was attributed to the islet infusion procedure, and not attributed to the immunosuppression/infection prophylaxis. The event resolved without sequelae.
Investigations	Immunosuppressant drug level increased	4	The patient had elevated tacrolimus and sirolimus levels 4 days after transplant, without symptoms. Both drugs were held and doses subsequently adjusted. The event was not attributed to the islet infusion procedure, but was attributed to the immunosuppression treatment. The event resolved without sequelae.
Metabolism and nutrition disorders	Hypoglycaemic unconsciousness	43	Approximately 11 months after the patient's only islet transplantation, this patient remained on insulin pump therapy. The patient awoke with no clearly recalled symptoms, but checked a BG, which was 49. The patient ate cookies and then has no clear recollection of events until she awakened on the kitchen floor. The patient called a friend who arrived to assist several minutes later. The patient was advised to adjust/lower the insulin boluses. The event was not attributed to the islet infusion procedure, and not attributed to immunosuppression. The event resolved without sequelae.

SUPPLEMENTARY DATA

System Organ Class	Preferred Term	Patient	Description
Metabolism and nutrition disorders	Hypoglycaemic unconsciousness	43	Approximately 16 months after the patient's only islet transplant, the patient experienced a hypoglycemic episode while driving into work. Emergency medical personnel tested the Blood sugar with a result of 10 g/Dl. They administered glucagon and IV dextrose. Glucose transiently improved, and then hypoglycemia recurred (BG=22) so the patient received glucagon and IV glucose, and was transported to the hospital. The patient was advised to adjust/lower insulin therapy. The event was not attributed to the islet infusion procedure, and not attributed to immunosuppression. The event resolved without sequelae.
Nervous system disorders	Dementia	24	This event occurred approximately 19 months and 23 months after the patient's islet transplant procedures. The patient had a pre-transplant history of mild cognitive deficits that slowly progressed, with the patient being transferred to an assisted living facility due to inability to perform activities of daily living. Frontotemporal dementia was diagnosed. The event was not attributed to the islet infusion procedure, and not attributed to the immunosuppression/infection prophylaxis. The event was closed as resolved with continuing, progressive symptoms.
Psychiatric disorders	Conversion disorder	27	The patient was admitted to hospital approximately 9 months after the islet transplant procedure, following a suspected seizure at the workplace; tacrolimus was held due to suspicion of PRES. Workup including continuous EEG monitoring was considered to be suggestive of pseudoseizures, especially in light of multiple recent social stressors. The patient was subsequently discharged with no subsequent seizure/pseudoseizure episodes on outpatient follow-up. The event was not attributed to the islet infusion procedure, and not attributed to the immunosuppression/infection prophylaxis. The event was closed as resolved without sequelae 10 days after onset.
Renal and urinary disorders	Renal failure acute	40	Three months after the patient's initial islet transplantation, there was a progressive increase in the patient's serum creatinine over a three week period, to peak of 3.0 mg/dL, 3 times the pre-transplant value. The patient received outpatient IV hydration, with progressive improvement in creatinine, which stabilized at 1.4-1.5 mg/dL. The event was not attributed to the islet infusion procedure, but was attributed to immunosuppression. The event resolved without sequelae 10 weeks after the onset.