



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

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OBJECTIVE

Impaired awareness of hypoglycemia (IAH) and severe hypoglycemic events (SHEs) cause substantial morbidity and mortality in patients with type 1 diabetes (T1D). Current therapies are effective in preventing SHEs in 50–80% of patients with IAH and SHEs, leaving a substantial number of patients at risk. We evaluated the effectiveness and safety of a standardized human pancreatic islet product in subjects in whom IAH and SHEs persisted despite medical treatment.

RESEARCH DESIGN AND METHODS

This multicenter, single-arm, phase 3 study of the investigational product purified human pancreatic islets (PHPI) was conducted at eight centers in North America. Forty-eight adults with T1D for >5 years, absent stimulated C-peptide, and documented IAH and SHEs despite expert care were enrolled. Each received immunosuppression and one or more transplants of PHPI, manufactured on-site under good manufacturing practice conditions using a common batch record and standardized lot release criteria and test methods. The primary end point was the achievement of HbA_{1c} <7.0% (53 mmol/mol) at day 365 and freedom from SHEs from day 28 to day 365 after the first transplant.

RESULTS

The primary end point was successfully met by 87.5% of subjects at 1 year and by 71% at 2 years. The median HbA_{1c} level was 5.6% (38 mmol/mol) at both 1 and 2 years. Hypoglycemia awareness was restored, with highly significant improvements in Clarke and HYPO scores ($P > 0.0001$). No study-related deaths or disabilities occurred. Five of the enrollees (10.4%) experienced bleeds requiring transfusions (corresponding to 5 of 75 procedures), and two enrollees (4.1%) had infections attributed to immunosuppression. Glomerular filtration rate decreased significantly on immunosuppression, and donor-specific antibodies developed in two patients.

CONCLUSIONS

Transplanted PHPI provided glycemic control, restoration of hypoglycemia awareness, and protection from SHEs in subjects with intractable IAH and SHEs. Safety events occurred related to the infusion procedure and immunosuppression, including bleeding and decreased renal function. Islet transplantation should be considered for patients with T1D and IAH in whom other, less invasive current treatments have been ineffective in preventing SHEs.

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Hypoglycemia remains a critical limiting factor in the glycemic management of patients with type 1 diabetes (T1D) (1). Recurrent hypoglycemic episodes impair counterregulatory responses and hypoglycemia awareness, creating a cycle of more frequent, severe, and sometimes fatal hypoglycemia (1,2). Impaired awareness of hypoglycemia (IAH), which is present in 30–40% of patients with T1D (3,4), confers a threefold to sixfold increased risk of severe hypoglycemic events (SHEs) (3,4). One of three Americans with T1D experiences at least one SHE each year (5). Recurrent severe hypoglycemia interferes with adherence to strict glycemic control (1) and contributes to substantial morbidity (6).

Structured education, insulin analogs, and technological interventions, such as continuous subcutaneous insulin infusion (CSII), real-time continuous glucose monitoring systems (CGMSs), and sensor-augmented insulin pumps with low-glucose suspend features, can reduce the frequency, severity, and duration of hypoglycemia, and are the first-line therapies for patients with IAH and SHEs (7,8). However, despite acceptance of an elevated HbA_{1c} target of <8.0% (64 mmol/mol) (9), these interventions are not successful in all patients (4,10–13). In a recently reported cohort at a specialist hypoglycemia service (10), 50% of patients with T1D and recurrent SHEs experienced resolution of SHEs, and 30% subsequently underwent pancreas or islet transplantation for persistent severe hypoglycemia. Thus, SHEs persist in some patients despite having access to all medical interventions and accepting an elevated HbA_{1c} level of <8.0% (64 mmol/mol) (as recommended by the American Diabetes Association [ADA] in 2012) (9). Even higher glycemic targets are less effective in preventing SHEs (11).

The National Institutes of Health established the Clinical Islet Transplantation (CIT) Consortium to evaluate more rigorously the risks and benefits associated with islet transplantation in T1D (12–14). Previous trials of islet transplantation

(15), while providing preliminary evidence of benefit, were not considered adequate for licensure of an islet product. The CIT-07 trial was designed to be a license-enabling multicenter phase 3 clinical trial of a standardized, well-defined islet product, using a stringently defined, clinically relevant primary end point. Study participants had T1D of >5 years duration, and had persistent IAH and SHEs despite expert management by a diabetologist or endocrinologist for at least 1 year prior to study enrollment. In consultation with the U.S. Food and Drug Administration (FDA) (16), this trial was designed as an uncontrolled, nonrandomized study to avoid randomization of participants with a life-threatening condition to a treatment that had previously been ineffective in preventing SHEs. Here we report the primary outcome of the CIT-07 trial. The full details of the clinical protocol and the common islet manufacturing process used at all sites can be found at www.isletstudy.org.

RESEARCH DESIGN AND METHODS

Study Oversight

This independently monitored study was performed in accordance with U.S. FDA regulations and Good Clinical Practice Guidelines under a U.S. Investigational New Drug application for purified human pancreatic islets (PHPI). Clinical and manufacturing protocols, end points, and the statistical analysis plan were developed by the CIT Consortium with guidance from the FDA, to serve as a license-enabling study. The study was approved by local institutional review boards and was overseen by an independent National Institute of Diabetes and Digestive and Kidney Diseases–sponsored Data Safety Monitoring Board. Serious adverse events (SAEs) were reviewed by site physicians, the Data Coordinating Center at the University of Iowa, and the National Institute of Allergy and Infectious Diseases medical monitors, who made the final determination of seriousness and attribution. All authors vouch for the completeness and accuracy of the data and fidelity to the study protocol.

Study Design and Outcome Measures

This phase 3, prospective, open-label, single-arm study was conducted at eight centers in North America. The decision to design a single-arm trial derived from ethical concerns about randomizing patients who had already failed expert management to continued medical therapy, during which time they would be prevented from seeking an islet or pancreas transplant elsewhere or availing themselves of any new therapies that might become available during the course of the trial; the extremely low likelihood that individuals meeting the study entry criteria could spontaneously achieve the primary end point (defined below); and the FDA guidance that a single-arm trial would be acceptable as a license-enabling study (16). The primary end point was the achievement of an HbA_{1c} level of <7.0% (53 mmol/mol), the glycemic goal then recommended by the ADA (17), at day 365 and freedom from SHEs from day 28 to day 365 after the first islet transplant. This end point was chosen to reflect the effectiveness of this therapy specifically for the treatment of intractable IAH and associated SHEs. Key secondary end points included the achievement of an HbA_{1c} level of $\leq 6.5\%$ (48 mmol/mol), the target recommended by the American Association of Clinical Endocrinologists (18), at 1 year and freedom from SHEs from day 28 to day 365, individual components of the composite end points, and insulin independence (confirmed by meeting the following criteria during a 7-day period without exogenous insulin: HbA_{1c} <7.0% [53 mmol/mol], fasting capillary glucose levels >140 mg/dL [7.8 mmol] three or fewer times, fasting serum glucose <126 mg/dL [7.0 mmol], a mixed meal tolerance test [MMTT] showing serum glucose <180 mg/dL [10 mmol] at 90 min, and at least one serum C-peptide level [fasting or stimulated] ≥ 0.5 ng/mL). Other efficacy outcomes included glycemic lability index (LI) (19), hypoglycemia score (19), and 72-h glucose profiles by use of a CGMS (Medtronic

Clinical trial reg. no. NCT00434811, clinicaltrials.gov.

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See accompanying article, p. 1072.

Table 1—Recipient, donor, and graft characteristics

Recipient characteristics	Observations (n)	Median (minimum–maximum) or N (%)
Gender (% male)	48	19 (39.6)
Age (years)	48	48.4 (26.2–65.5)
Weight (kg)	48	68.8 (48.0–111.1)
BMI (kg/m ²)	48	25.1 (18.9–29.8)
Duration of diabetes (years)	48	28.5 (11–57)
HbA _{1c} (%)	48	7.2 (5.7–9.2)
HbA _{1c} (mmol/mol)	48	55 (39–77)
Insulin requirement*	48	
Units/day		32.6 (11.4–62.1)
Units/kg/day		0.5 (0.2–0.8)
Autoantibodies	45†	
Anti-insulin (% positive)		44 (97.8)
Anti-GAD65 (% positive)		29 (64.4)
Anti-ICA512 (% positive)		20 (44.4)
Clarke score‡	48	6 (3–7)
HYPO score‡	48	1,253.5 (58–8,467)
SHE 1 year pretx (N)	48	6.5 (0–336)
Glycemic LI‡	48	622 (100–1,500)
GFR (mL/min/1.73 m ²)	48	102 (80–130)
Diab Microvasc Complic	48	
Nonproliferative retinopathy (%)		16 (33.3)
Proliferative retinopathy (%)		6 (16.7)
Microalbuminuria (%)		5 (10.4)
Donor/pancreas characteristics		
Donor age (years)	75	42.8 (18.6–60.7)
Donor BMI (kg/m ²)	75	33.4 (20.9–50.3)
Donor sex (% male)	75	53 (70.7)
Pancreas cold ischemia time (h/per isolation)	75	7.7 (3.7–13.0)
PHPI lot characteristics§		
Total IEQ transplanted (per lot)	75	480,500 (282,156–1,005,822)
Tissue volume (mL/lot)	75	4.0 (0.8–11.5)
Total dose/subject		
Total IEQ transplanted (per subject)	48	820,286 (286,565–1,562,425)
Total IEQ/kg transplanted (per subject)	48	11,972 (5,227–25,553)

Diab. Microvasc. Complic, diabetic microvascular complications; pretx, pretransplant. *Subject's report of 7 days of insulin usage data nearest to the date of transplant. †Baseline autoantibody samples were not collected from three subjects. ‡See full definitions in Appendix 3 in the Supplementary Data. §One donor pancreas produced one lot of PHPI, which was one dose administered.

Minimed). Safety outcomes included the incidence of SAEs related to the islet transplant procedure or immunosuppression and the incidence of de novo anti-HLA antibodies. All aspects of the study design are consistent with the FDA guidance document *Considerations for Allogeneic Pancreatic Islet Cell Products* (16).

The first subject consented on 10 October 2008. All subjects reached the primary end point by 24 September 2012 and the secondary end points by 13 May 2014. We report the primary and secondary end points, assessed at

day 365, and the results at 2 years after the initial transplant.

Recipient Selection

Inclusion criteria included the following: age 18–65 years, T1D for ≥5 years, absent stimulated C-peptide, IAH and/or marked glycemic lability (19,20), and a history of SHEs in the prior 12 months despite medical care provided by an endocrinologist or diabetologist, who asserted that the candidate had been adherent with respect to office visits (three or more in the preceding 12 months), self-monitoring of blood

glucose levels (three or more times daily), and the use of an insulin pump or administration of three or more injections of insulin daily as prescribed. Among those subjects deemed eligible, 37 had used CSII, and 21 had used CGMS. Each patient's diabetes specialist confirmed that the patient was unable to achieve glycemic control without hypoglycemic episodes, even when the HbA_{1c} level was allowed to rise above 7% (53 mmol/mol), and that, in the year preceding enrollment, each had experienced one or more SHEs, defined as events with memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure, seizure, loss of consciousness, or visual symptoms, during which the subject was unable to treat himself/herself and which were associated with either a blood glucose level of <54 mg/dL (3.0 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration (2). Exclusion criteria included the following: BMI >30 kg/m², weight ≤50 kg, insulin requirement >1.0 units/kg/day or <15 units/day, HbA_{1c} level >10% (86 mmol/mol), measured glomerular filtration rate (GFR) <80 mL/min/1.73 m², history of panel-reactive anti-HLA antibodies by flow cytometry, and significant comorbid conditions.

Donor Selection, Islet Manufacture, and Islet Transplantation

PHPI were manufactured at the transplant site. The CIT-defined good manufacturing practice process included standardized lot release criteria and test methods (21). Pancreata from deceased donors 15–65 years of age were processed within 12 h of procurement. Donor exclusion criteria included history of diabetes, HbA_{1c} level >6% (42 mmol/mol), and donation after cardiac death status.

Each PHPI lot (dose), containing >5,000 islet equivalents (IEQ)/kg for the first dose and ≥4,000 IEQ/kg for subsequent doses (if any), was prepared from a single pancreas (14) and was transplanted by portal vein infusion. Access to the portal vein was achieved percutaneously or by minilaparotomy. Subjects who were not insulin independent at 75 days after the first dose, or 30 days after a second dose, were eligible for a subsequent infusion until

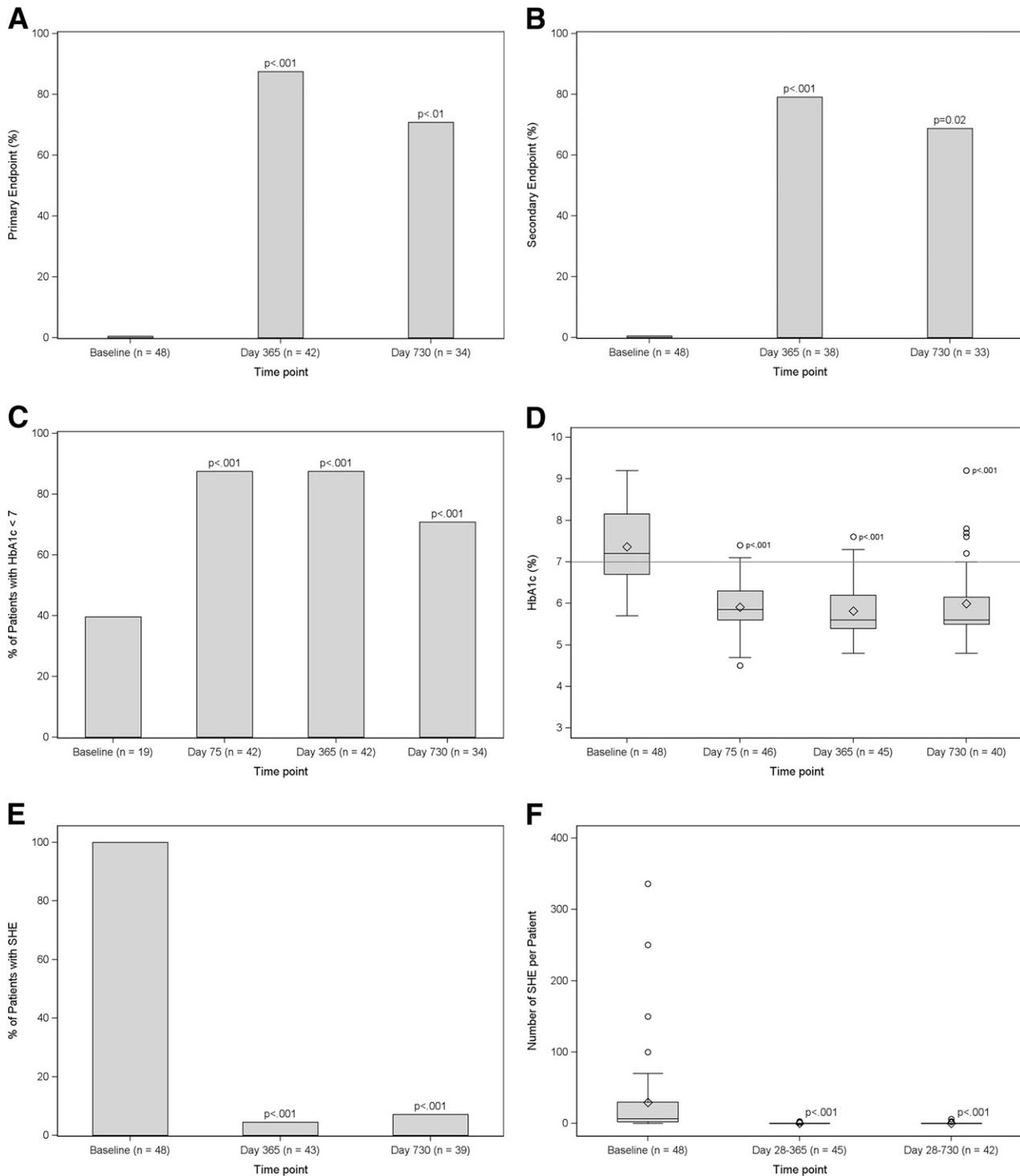


Figure 1—Primary composite end point and components. *A*: Proportion of subjects meeting the primary end point (with HbA_{1c} <7.0% [53 mmol/mol]) at baseline, day 365, and day 730 after the first islet transplant (ADA criterion). *N* = 48. An exact one-sided test for proportion ≤0.5 vs. >0.5 was performed at days 365 and 730. The Bonferroni method was used to adjust the level of significance for these two comparisons in order to preserve the overall type I error rate. *B*: Proportion of subjects meeting the key secondary end point (with HbA_{1c} ≤6.5% [48 mmol/mol]) at screening, day 365, and day 730 after the first islet transplant. *N* = 48. An exact one-sided test for proportion ≤0.5 vs. >0.5 was performed at days 365 and 730. The Bonferroni method was used to adjust the level of significance for these two comparisons in order to preserve the overall type I error rate. *C*: Percentage of subjects with HbA_{1c} <7.0% (53 mmol/mol) at baseline (*N* = 48) and at days 75 (*N* = 46), 365 (*N* = 45), and 730 (*N* = 40) after the first islet transplant. A McNemar test for paired binomial outcomes was used to compare the proportion of subjects with HbA_{1c} <7% (53 mmol/mol) between baseline and day 75, between baseline and day 365, and between baseline and day 730. The Bonferroni method was used to adjust the level of significance for these three comparisons in order to preserve the overall type I error rate of 0.05. *D*: Box plots of HbA_{1c} levels at baseline (*N* = 48), at day 75 (*N* = 46), at day 365 (*N* = 45), and at day 730 (*N* = 40) after the first islet transplant. The Wilcoxon signed rank test for paired outcomes was used to compare the median HbA_{1c} levels between baseline and day 75, between baseline and day 365, and between baseline and day 730. The Bonferroni method was used to adjust the level of significance for these three comparisons in order to preserve the overall type I error rate of 0.05. *E*: Percentage of subjects with at least one SHE during the year before the first islet

8 months after the initial transplant. This left a 4-month interval for stabilization prior to assessment of the primary end point.

Other Study Treatments

Induction immunosuppression consisted of rabbit anti-thymocyte globulin and etanercept (13) for the first transplant, with basiliximab replacing rabbit anti-thymocyte globulin at subsequent transplants. Sirolimus and low-dose tacrolimus were used for maintenance immunosuppression (12).

Statistical Analysis

Analysis of the primary end point was based on estimating the true rate of success, which was defined as the proportion of subjects in the intention-to-treat population achieving the primary end point successfully. An exact one-sided 95% lower confidence bound was computed. The prespecified criterion for efficacy requires that the lower bound exceed 50%. With 48 transplanted subjects, and if the true rate is at least 70%, then the power to declare islet transplantation effective is at least 84%. Outcomes for the intention-to-treat analysis included three imputed failures for subjects who withdrew prior to being evaluated for the primary end point. Results for the primary and secondary end points and 2-year follow-up are presented in graphical form. Separate pairwise comparisons are presented for days 75, 365, and 730 versus baseline. Signed rank tests are used for continuous outcomes and McNemar tests for binary outcomes. Two-sided *P* values are adjusted for multiple comparisons using the Bonferroni method. Details of study definitions, subject outcomes, study treatment regimen, PHPI product, and adverse events can be found in appendices in the Supplementary Data. Study data sets are available at <https://www.itntrialshare.org>, a public website managed by the Immune Tolerance Network.

RESULTS

Characteristics of the subjects, donors, donor pancreata, and PHPI doses are presented in Table 1. The 48 subjects received 75 PHPI infusions, as follows: 22 subjects (45.8%) received one infusion, 25 (52.1%) received two infusions, and 1 subject (2.0%) received three infusions. The median total dose was 820,286 IEQ/subject (range 286,565–1,562,425), with a median of 11,972 IEQ/kg recipient body weight (range 5,227–25,553).

Efficacy

Primary and key secondary end point results are presented in Fig. 1. Forty-two of 48 subjects (87.5% [lower confidence interval boundary 76.8%]) achieved a successful primary end point (eradication of SHEs with excellent glycemic control; HbA_{1c} level \leq 7% [53 mmol/mol]) (Fig. 1A). Based on the a priori minimum threshold of 50%, this supports the conclusion that islet transplantation is effective. Similar results were observed for the key secondary end point, which required an HbA_{1c} level of \leq 6.5% (48 mmol/mol) (Fig. 1B).

The proportion of subjects with an HbA_{1c} level $<$ 7.0% (53 mmol/mol) (Fig. 1C) increased from 40% at baseline to 87.5% at 75 days (*P* $<$ 0.0003) and to 87.5% at 365 days after the first islet transplant (*P* $<$ 0.0003). Median HbA_{1c} levels decreased from 7.2% (55 mmol/mol) at baseline to 5.9% (41 mmol/mol) and 5.6% (38 mmol/mol) at days 75 and 365, respectively (Fig. 1D) (*P* $<$ 0.0003). All subjects had experienced at least one SHE in the year prior to enrollment; only 2 of 45 evaluable subjects reported SHEs in the year after islet transplantation (Fig. 1E and F) (*P* $<$ 0.0003). These two subjects had a total of four SHEs. At the time of the events, both subjects had evidence of graft function and were receiving exogenous insulin. In both cases, hypoglycemia awareness had been restored, as evidenced by a drop in Clarke score from 7 at baseline to 1

at day 365. Both subjects, however, were documented to be medically nonadherent. This suggests that these episodes of hypoglycemia were due to excessive doses of exogenous insulin and were not related to IAH.

Insulin independence was achieved by 23% of subjects at day 75 and by 52.1% at day 365 (Fig. 2A). Among 25 subjects who were insulin independent at 1 year, 13 received one islet infusion, and 12 received two islet infusions. As of day 730, the median interval without exogenous insulin among the 25 subjects was 684 consecutive days (range 210–720); 20 of the 48 enrolled subjects (42%) remained insulin independent at day 730.

The median insulin use dropped from 0.49 units/kg at baseline to 0.13 units/kg at day 75 and 0.00 units/kg at day 365 (range 0.00–0.43) (Fig. 2B) (*P* $<$ 0.0003). C-peptide levels increased and glucose levels decreased in response to a MMTT (Fig. 2C and D) (*P* $<$ 0.0003). The proportions of subjects with a functioning islet graft, defined as a basal or stimulated serum C-peptide level $>$ 0.3 ng/mL, were 95% and 94% at days 75 and 365, respectively. Measures of hypoglycemia awareness, hypoglycemic events, and glycemic lability and variability, specifically using the Clarke score (Fig. 3A), HYPO score (Fig. 3B), LI (Fig. 3C), and mean amplitude of glycemic excursions (MAGEs) (Fig. 3D), all improved significantly (*P* $<$ 0.0002). The CGMS demonstrated significant improvements in mean glucose level, time within glucose target range of 54–180 mg/dL (3.1–10 mmol/L), time with glucose $<$ 54 mg/dL (3.1 mmol/L), and other measures of glycemic control (Fig. 3E and Supplementary Fig. 1).

At 2 years, 34 of 48 subjects (71%) successfully achieved the criteria set for the 1-year primary end point, including one subject who failed at year 1 because of an HbA_{1c} level of 7.3% (56 mmol/mol). Among the nine subjects who were successful at year 1 but not

transplant and from day 28 to day 365 and day 730 inclusive, after the first islet transplant. Based on diabetologist's medical report, a McNemar test for paired binomial outcomes was used to compare the proportion of subjects with at least one severe episode of hypoglycemia at baseline (*N* = 48) to the proportion at day 365 (*N* = 45) and to the proportion at day 730 (*N* = 42). The Bonferroni method was used to adjust the level of significance for both comparisons in order to preserve the overall type I error rate of 0.05. The adjusted *P* values for both tests are $<$ 0.0002. *F*: Box plots of the number of episodes of severe hypoglycemia experienced per subject during the year before the first islet transplant and from day 28 to day 365 and day 730 inclusive, after the first islet transplant. Based on subject recall over the year prior to enrollment. The Wilcoxon signed rank test for paired outcomes was used to compare the median number of severe episodes of hypoglycemia between baseline (*N* = 48) and day 365 (*N* = 45) and between baseline and day 730 (*N* = 42). The Bonferroni method was used to adjust the level of significance for both comparisons in order to preserve the overall type I error rate of 0.05. The adjusted *P* values for both tests are $<$ 0.0002.

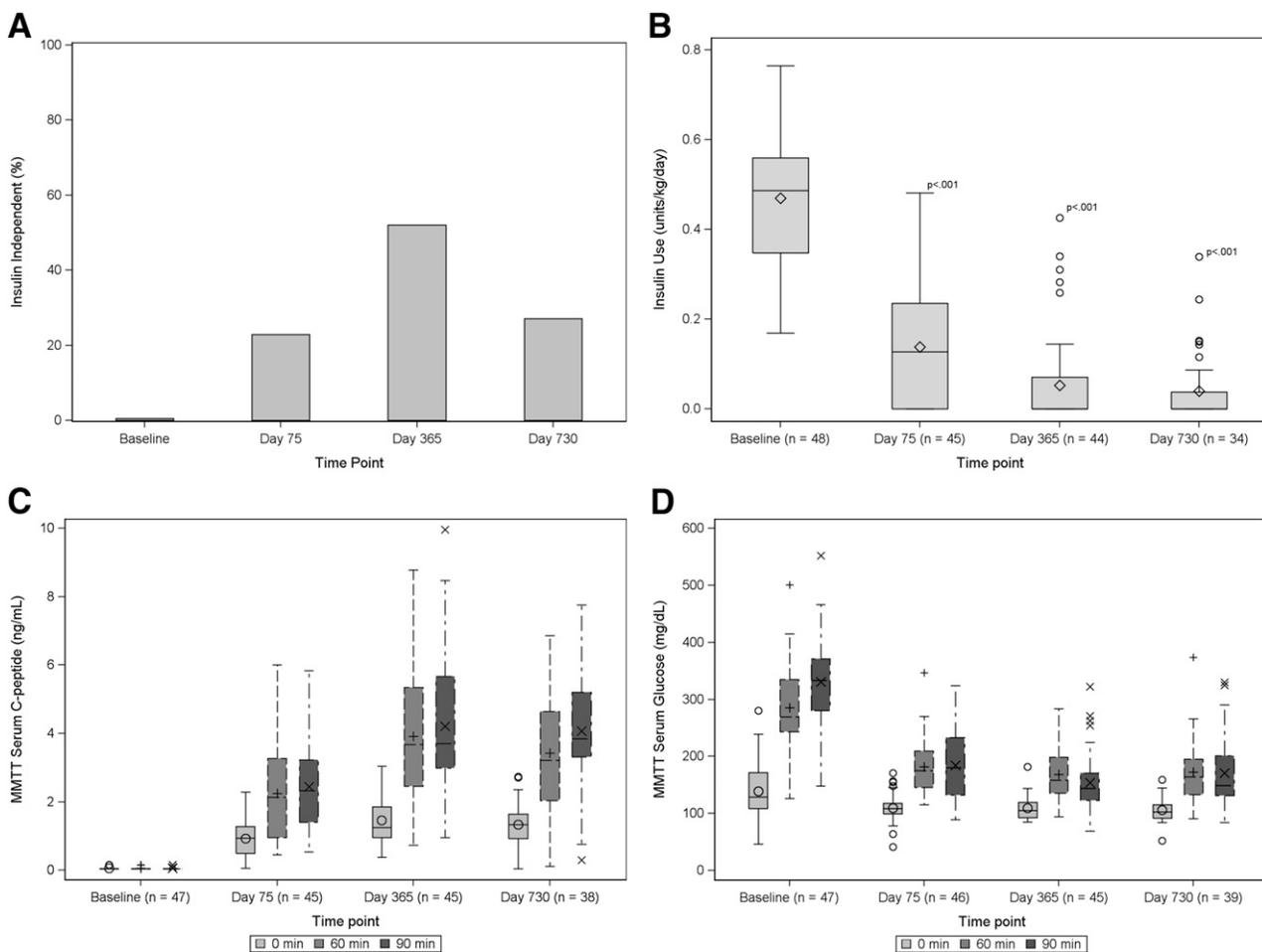


Figure 2—Key secondary end points. **A:** Proportion of insulin-independent subjects at day 75, day 365, and day 730 after the first islet infusion ($N = 48$). At day 75, insulin independence could not be evaluated for 11 subjects because of insufficient data; these subjects were imputed as failures. At day 365, insulin independence could not be evaluated for 10 subjects, 8 of whom provided insufficient data and 2 of whom were no longer enrolled in the study; all of these were imputed as failures. At day 730, insulin independence could not be evaluated for 28 subjects, 22 of whom provided insufficient data, and 6 of whom were no longer enrolled in the study; all of these were imputed as failures. **B:** Box plots of daily insulin usage (units/kilogram/day) at baseline, day 75, day 365, and day 730. The Wilcoxon signed rank test for paired outcomes was used to compare the median insulin use (measured in units per kilogram of body weight) between baseline ($N = 48$) and day 75 ($N = 45$), between baseline and day 365 ($N = 44$), and between baseline and day 730 ($N = 34$). The Bonferroni method was used to adjust the level of significance for these three comparisons in order to preserve the overall type I error rate of 0.05. The adjusted P values for these three tests are <0.0003 . **C:** Box plots of serum C-peptide levels before (zero minutes) and 60 and 90 min after MMTT was performed at baseline, day 75, day 365, and day 730 after the first islet infusion. The Wilcoxon signed rank test was used to compare the zero minute C-peptide level between baseline ($N = 47$) and day 75 ($N = 46$), between baseline and day 365 ($N = 45$), and between baseline and day 730 ($N = 39$). Comparisons between baseline and day 75 and between baseline and day 365 were performed in a similar manner for the 60-min C-peptide levels as well as the 90-min C-peptide levels. Within each set of three readings, the Bonferroni method was used to adjust the level of significance for the three comparisons made between baseline and day 75, between baseline and day 365, and between baseline and day 730. The three adjusted P values for each set of readings are <0.0003 . **D:** Box plots of serum glucose levels before (zero minutes) and 60 and 90 min after MMTTs performed at baseline, day 75, day 365, and day 730 after the first islet infusion. The Wilcoxon signed rank test was used to compare the zero minute serum glucose level between baseline ($N = 47$) and day 75 ($N = 46$), between baseline and day 365 ($N = 45$), and between baseline and day 730 ($N = 39$). Comparisons between baseline and day 75 and between baseline and day 365 were performed in a similar manner for the 60-min serum glucose levels as well as the 90-min serum glucose levels. Within each set of three readings, the Bonferroni method was used to adjust the level of significance for the three comparisons made between baseline and day 75, between baseline and day 365, and between baseline and day 730. The adjusted P value for the zero minute comparison between baseline and day 75 is 0.002. The adjusted P value for the zero minute comparison between baseline and day 365 is 0.0005. The adjusted P value for the zero minute comparison between baseline and day 730 is 0.0034. All other adjusted P values are <0.0003 .

at year 2, five withdrew consent and were therefore imputed failures; the remaining four subjects had HbA_{1c} values of $\geq 7.0\%$ (53 mmol/mol) (7.2%, 7.6%, 7.7%, and 9.2%, or 55, 60, 61, and 77 mmol/mol). One of the nine subjects experienced an SHE in year 2. The

estimated probability of SHE-free survival among evaluable subjects at 2 years after the initial islet transplant was 93% (Fig. 3F).

Three subjects (6%) were nonevaluable for the primary end point (year 1), and an additional five subjects were

nonevaluable at 2 years (17% of original cohort). All were imputed failures in the study analysis. Two subjects were lost to follow-up despite repeated attempts at contact; the loss of one was due to the failure of the site to renew consent after 1 year; three subjects withdrew consent,

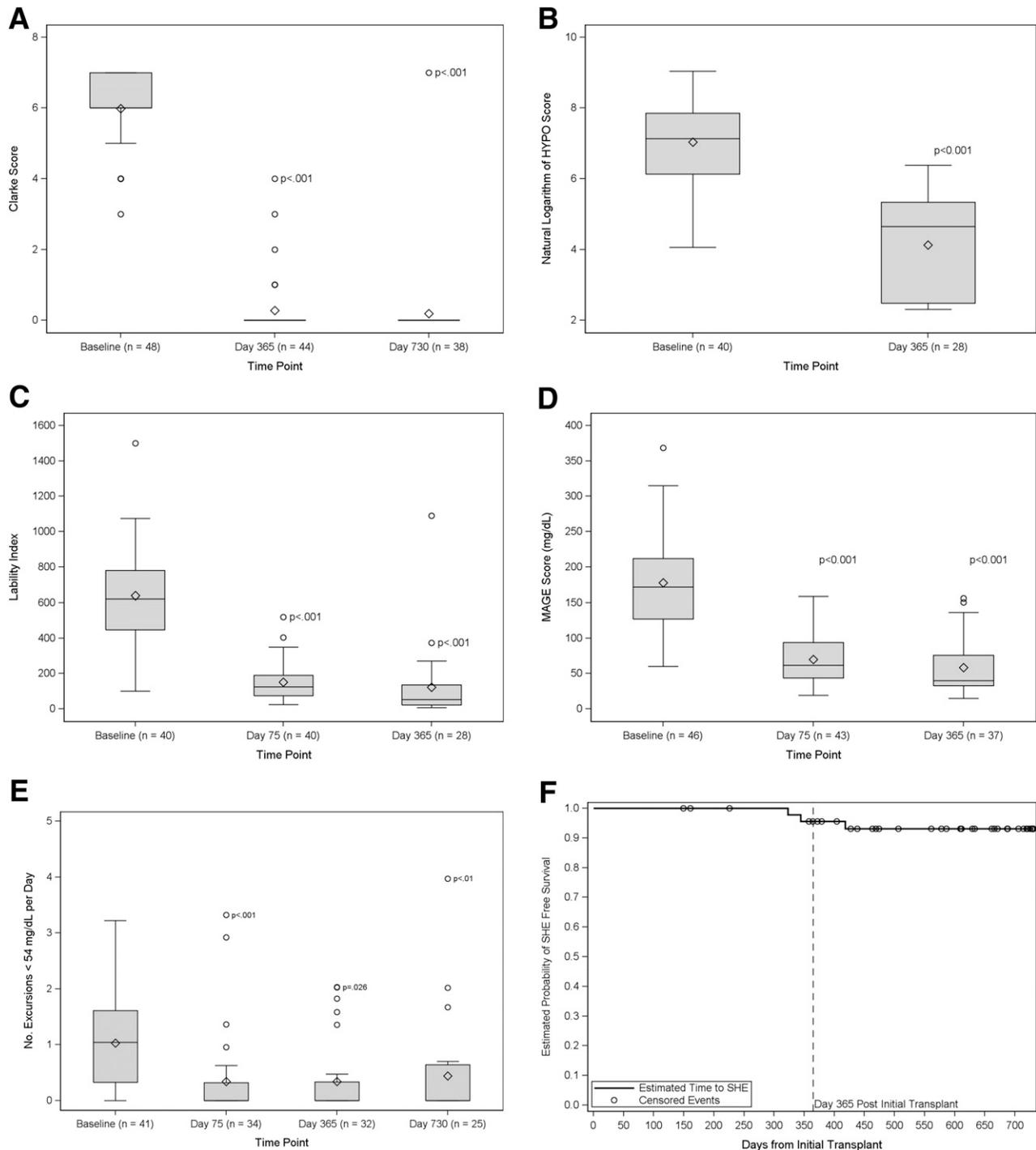


Figure 3—Other efficacy end points. **A:** Clarke score at baseline, day 365, and day 730 after the first islet infusion. The Wilcoxon signed rank test for paired outcomes was used to compare the median Clarke score between baseline ($N = 48$) and day 365 ($N = 44$). The P value for this test is <0.0001 . **B:** Natural logarithm of the HYPO score at baseline and day 365 after the first islet infusion. HYPO score was not collected at day 730. The Wilcoxon signed rank test for paired outcomes was used to compare the median HYPO score between baseline ($N = 40$) and day 365 ($N = 28$). The P value for this test is <0.0001 . **C:** Glycemic LI at baseline, at day 75, and at day 365 after the first islet infusion. Glycemic LI was not collected at day 730. The Wilcoxon signed rank test for paired outcomes was used to compare the median glycemic LI between baseline ($N = 40$) and day 75 ($N = 40$) and between baseline and day 365 ($N = 28$). The Bonferroni method was used to adjust the level of significance for these two comparisons in order to preserve the overall type I error rate of 0.05. The adjusted P values for these two tests are both <0.0002 . **D:** MAGEs at baseline, day 75, and day 365 after the first islet infusion. MAGE was not collected at day 730. The Wilcoxon signed rank test for paired outcomes was used to compare the median MAGE between baseline ($N = 46$) and day 75 ($N = 43$) and between baseline and day 365 ($N = 37$). The Bonferroni method was used to adjust the level of significance for these two comparisons in order to preserve the overall type I error rate of 0.05. The adjusted P values for these two tests are both <0.0002 . **E:** Box plots of the number of CGMS-determined hypoglycemic excursions (<54 mg/dL) per day (24 h) at baseline, day 75, day 365, and day 730 after the first islet infusion. The Wilcoxon signed rank test was used to compare the median number of hypoglycemic excursions between baseline ($N = 41$) and day 75 ($N = 34$), between baseline and day 365 ($N = 32$), and between baseline and day 730 ($N = 25$). The

two because of the frequency of study visits, and one without a reason given; one subject chose to have an additional islet transplant outside of the CIT protocol; and one subject wished to take a study-prohibited medication.

Adverse Events

SAEs are reported from initiation of induction immunosuppression to day 365, and from day 366 to day 730. A complete description of all SAEs is included in appendices in the Supplementary Data. There were 30 SAEs in 21 subjects in year 1, with 22 attributed to the transplant procedure and/or immunosuppression, and 8 to nonstudy causes. Procedure-related bleeding events occurred in 5 of 56 percutaneous cannulations of a portal vein, requiring transfusion and/or surgical intervention. There were no SAEs related to access by minilaparotomy (19 procedures). Immunosuppression-related events included cytopenias, abdominal pain with or without vomiting, toxic drug levels, adverse drug reactions (urticaria, serum sickness, cytokine release), infection, and renal dysfunction. Eight SAEs occurred in year 2, of which two were infections attributed to immunosuppression, while the remaining six were not study related. No SAE resulted in death or disability, and none required expedited reporting to the FDA.

The median GFR decreased from 102 mL/min/1.73 m² (range 80–130) at baseline to 98 mL/min/1.73 m² at day 75 ($P = 0.09$, range 42–140), and to 90 mL/min/1.73 m² at day 365 ($P = 0.0008$ vs. baseline, range 59–129). The median GFR for the last available observation (>2 years, $n = 35$) was 82 mL/min/1.73 m² ($P < 0.0001$ vs. baseline, range 54–123).

At the 2-year follow up, six subjects had positive calculated panel reactive antibody levels of 2%, 14%, 29%, 64%, 74%, and 98%, respectively; the last two subjects had donor-specific antibodies (DSAs).

CONCLUSIONS

Despite medical management provided by a diabetes specialist, none of the participating subjects with long-standing T1D and IAH had maintained HbA_{1c} levels $<7.0\%$ (53 mmol/mol) with the absence of SHEs in the year prior to study enrollment. In contrast, 87.5% of study subjects had an HbA_{1c} level of $<7.0\%$ (53 mmol/mol) at day 365 and were free of SHEs from day 28 to day 365 after their first islet transplant, thus meeting the composite primary end point of the study (Fig. 1A). The median HbA_{1c} level decreased from 7.2% (55 mmol/mol) pretransplant to 5.6% (38 mmol/mol) at 1 year post-transplant (Fig. 1B). In addition, recipients of PHPI showed highly significant improvements in all other measures of glycemic control (e.g., glycemic LI, MAGEs, time within glucose target range) and also experienced the restoration of hypoglycemia awareness, as demonstrated by markedly reduced Clarke and HYPO scores (Fig. 3A and B). Insulin independence, measured stringently across multiple parameters, was achieved in 52% of subjects and with fewer transplants per subject and smaller doses of islets than in previous multicenter trials (14,22,23); it persisted at 2 years in at least 80% of those who achieved it by year 1. Subjects experienced 22 study-related SAEs in year 1 and 2 study-related SAEs in year 2. An episode of acute kidney injury of unclear etiology resolved with a substantial decrease in the subject's GFR; no other study-related SAE resulted in death or permanent injury. Postprocedural bleeding occurred in 8.9% of transplants performed by percutaneous access of the portal vein but in none of the transplants performed by minilaparotomy. Immunosuppression-related events accounted for 43% of all study SAEs. There was a significant drop in median iohexol-measured GFR from study entry to day 75 after the first islet transplant, followed by

further decreases at days 365 and 730. DSAs developed in few subjects (2 of 48 subjects [4%]) compared with other islet and organ transplant studies (24,25).

These findings demonstrate that transplantation of human islets was effective in treating IAH and SHEs in patients with T1D in whom SHEs had persisted while under the care of a diabetes specialist, using then available modalities and treatment guidelines according to their best judgment. This trial also shows, in contrast to prior studies (1), that protection from SHEs can be achieved without accepting an elevated HbA_{1c} target. Vascularized pancreas transplantation, which is generally reserved for patients needing a simultaneous kidney transplant (26), is the only other intervention capable of achieving similar results (27,28), but is uncommonly used in nonuremic T1D patients (26).

Severe hypoglycemia is a debilitating, life-threatening complication of T1D (1,2,6,29) that, in some patients, is refractory to medical treatment (7,8,10). CSII, real-time CGMSs, and sensor-augmented insulin pumps with automated low-glucose insulin suspension can reduce the incidence of major hypoglycemic events (30–32) but do not restore hypoglycemia awareness or normal hormonal counterregulation of hypoglycemia or eliminate SHEs (7,8). Meticulous prevention of hypoglycemia (33–35) and structured education and/or behavioral therapies aimed at hypoglycemia awareness restoration (4,36,37) improve the awareness of hypoglycemia, hormonal counterregulation to hypoglycemia, and protection from SHEs, but 20–30% of patients so treated have persistent SHEs and IAH, as evidenced by elevated Clarke or Gold scores (4,10,36,37). In addition, their HbA_{1c} levels remain elevated at 7.8% (62 mmol/mol) to 8.4% (68 mmol/mol) (4,10,36,37). Thus, this trial is the first phase 3 trial to show effectiveness of

Bonferroni method was used to adjust the level of significance for these three comparisons in order to preserve the overall type I error rate of 0.05. The adjusted P value for the comparison between baseline and day 75 is 0.0003. The adjusted P value for the comparison between baseline and day 365 is 0.0258. The adjusted P value for the comparison between baseline and day 730 is 0.0015. F : Time to first severe hypoglycemic episode. The Kaplan-Meier estimate of the survival function for the time to first severe hypoglycemic episode is shown. Three subjects experienced SHEs. The first two subjects experienced events beginning prior to day 365 after the initial transplant, and a third subject had two SHEs between days 365 and 730 after the initial transplant. The time to censoring for subjects who did not experience a SHE was the number of days between the initial transplant and the date of the last blood sugar diary reading. The median SHE-free survival time is >730 days after the initial transplant.

any therapy in restoring both sustained normoglycemia and protection from SHEs in patients with long-standing T1D complicated by IAH and recent SHEs. Emerging diabetes technologies such as next-generation insulin pumps with predictive low-glucose management technology (38) and closed-loop pumps with glucose-responsive insulin or insulin and glucagon delivery (39) have not yet been tested in patients with T1D and problematic hypoglycemia; further testing is needed to determine how these interventions compare with islet transplantation (40).

The clear benefits of islet transplantation must be evaluated in the context of the associated risks. Serious procedural bleeding occurred in 5 of the 48 subjects (5 of the 75 islet infusions) performed in this study. The islet product stimulated the development of DSAs in two subjects; this rate of DSA is low, but these antibodies will present a barrier to subsequent transplants in those affected. All of the other study-related SAEs were related to, and expected from, the use of immunosuppression. Of those, the most concerning is the decrement in renal function, which is attributable to the use of calcineurin-inhibiting drugs (36). The drop in GFR over 2 years was both clinically and statistically significant. Evaluation of renal function and of a patient's ability to tolerate a decrease in renal function will be critical in the evaluation of candidates for islet transplantation. The immunosuppression-related adverse events in this trial highlight the need for more specific or tolerogenic immunomodulatory regimens for transplant recipients. Until such regimens are developed, islet transplantation will not be a suitable treatment for the majority of individuals with T1D. Those who have IAH and intractable SHEs need to be informed of these risks and, with their physician, decide whether they wish to accept them in order to achieve eradication of SHEs with stable and near-normal glycaemic control.

Despite the rigor of many aspects of this study, it has limitations. The standards and modalities for treating patients with IAH and SHEs have evolved since this study was designed. The ADA Standards of Medical Care in Diabetes specified for the first time in 2012 that less stringent glycaemic goals, such as $HbA_{1c} < 8\%$ (64 mmol/mol), may be

appropriate for patients with a history of SHEs (17). Structured diabetes education on flexible insulin therapy and diabetes technologies have improved. Currently, the majority of patients presenting with problematic hypoglycemia are expected to experience resolution of severe hypoglycemia with optimal medical therapy that includes access to these interventions in a stepped-care approach (7,8,10). Accordingly, some of the 48 subjects who were considered treatment failures at the time of enrollment in this trial, including the 11 who had not used CSII and the 27 who had not used a CGMS prior to enrollment, might well have responded to the medical and technological interventions now available. Only patients who continue to experience SHEs after having completed a stepped-care approach to prevention of SHEs, as is currently recommended (7,8), preferably under the supervision of a specialist hypoglycemia service or as part of a clinical trial, should be deemed unresponsive to medical therapy and thus be considered for evaluation for islet transplantation. On the other hand, as discussed above, even with the best available nontransplant interventions of the current era, 20–50% of patients with SHEs fail to achieve the eradication of SHEs (7,10); thus, islet transplantation is a relevant option for these patients. We report outcomes at 1 and 2 years; longer follow-up of transplanted patients will be needed to determine whether the benefits associated with restoration of near-normoglycemia and protection from SHEs will outweigh the risks associated with chronic immunosuppression. To this end, all study subjects were offered participation in a long-term follow-up study.

Some readers may find a single-arm trial unconvincing. In our view, all available medical approaches should be exhausted in treating patients with IAH and SHEs before resorting to islet transplantation; a patient who continues to have SHEs despite having the benefit of those therapies should not be randomized to them for the sake of research. Finally, while the number of unevaluable subjects (three [6%] at year 1, and a total of eight [17%] at year 2) did not limit our ability to evaluate the effectiveness of islet transplantation using prespecified criteria, it may have led to an underestimation of the effectiveness of PHPI and/or underreporting of adverse events.

This is the first license-enabling trial of a cellular product for treatment of T1D demonstrating multisite compliance with common manufacturing processes and release criteria. The manufacturing and clinical data generated in this study may be cross-referenced for the purpose of filing a Biologics License Application with the FDA for PHPI. Product licensure is important for many reasons, as follows: first, and most important, it will ensure the purity, potency, identity, consistency, and safety of the islet product; second, licensure will provide patient access (with third-party coverage) to islet transplantation; and third, continued research in this area will be accelerated if third-party coverage is available to defray the clinical costs. The standardized procedures established in this trial will likely also inform the development of stem cell-derived and xenogeneic islet cell therapeutics in the future (40).

In conclusion, this trial demonstrates that transplantation of human islets is an effective treatment for T1D complicated by IAH and SHEs, resulting in the restoration of hypoglycemia awareness, elimination of SHEs, and normal or near-normal glycaemic control in 87.5% of participants. Islet transplantation should be considered for patients with T1D and IAH in whom a stepped-care approach, including current educational, pharmacological, and technological interventions, has failed to prevent life-threatening SHEs.

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sion of the manuscript. B.J.H., W.R.C., N.D.B., and T.L.E. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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