

Clinical Pharmacology BLA Review

Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT),

Office of Tissues and Advanced Therapy (OTAT)

Submission Number: 125734/00

Product Name: DONISLECEL (Purified Allogenic Islets of Langerhans for Transplant)

Proposed Indication: Treatment of Brittle Type I Diabetes Mellitus

Applicant: CellTrans Inc.

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RPM: Edward Thompson

Reviewer: Million Tegenge, PhD

Clinical Pharmacology Reviewer, General Medicine Branch 2, DCEPT, OTAT

Through: Ilan Irony, MD

Deputy Director, DCEPT, OTAT

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1. Executive Summary

Allogeneic islet transplantation involves isolation of islets from a deceased donor pancreas and infusion into portal vein for delivery to the liver of a patient with Type 1 diabetes mellitus (T1DM). Currently, islet transplantation is considered an experimental procedure and there are no approved islet cell products for transplantation in the US. In this BLA submission, the Applicant propose DONISLECEL, for the “treatment of brittle type 1 diabetes mellitus (labile diabetes) in adults whose symptoms are not well controlled despite intensive insulin therapy.” After review of the BLA, FDA recommended a change in the proposed indication as “ allogeneic pancreatic islet cellular therapy, for the treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.”

The data supporting clinical pharmacology of DONISLECEL were based on two clinical studies:

- The #UIH-001 study was a Phase 1/2, open-label, single-center study of allogeneic islet transplantation in patients with brittle T1DM. Ten adult patients received up to 3 islet transplantations to assess safety, pharmacodynamics, and initial efficacy data.
- The #UIH-002 study was a Phase 3, nonrandomized, single-center study in which 20 adult patients with brittle T1DM were enrolled for 1 to 3 allogeneic pancreatic islet transplants.

In both #UIH-001 & #UIH-002 studies a target islet dose of 10,000 IE/kg was proposed based on the findings of previous experience with Edmonton Protocol for allogeneic islet transplantation. From a total of 30 subjects, 11 (37%), 12 (40%) and 7 (23%) were treated with single, two and three dose of islet transplantation, respectively. For subject who received multiple infusions, the mean inter-dose interval between the first and the second infusion was 279 days (range 25 to 1029 days), and between the second and third infusions was 984 days (range 62-2815 days). The mean administered dose per infusion was 7207 IE/kg (range 4186-13624). The mean total administered dose per subject was 13,453 IE/kg (range 4208-29,404).

Based on the combined data (#UIH-001 & 002) a dose-response relationship was not established for both HbA1c and C-peptide levels. The mean fasting and stimulated glucose and c-peptide levels were substantially reduced from the baseline values one-year after last treatment with DONISLECEL. There were no age-related or sex-related differences in fasting and stimulated glucose and C-peptide levels following treatment with DONISLECEL. Overall, the clinical pharmacology results support the primary efficacy analysis and the pharmacodynamics (PD) of

allogenic islet cells is most clearly demonstrated without much confounding in subjects who are free from the requirement of exogenous insulin. Specifically, the fasting glucose level was 106 ± 17 mg/dL and the stimulated glucose level (90-min) was 142 ± 40 mg/dL for subjects who are free from the exogenous insulin at time of 1-year PD assessments. The mean fasting and stimulated C-peptide levels were higher than the proposed target level of 0.5 ng/mL for over 95% of the subjects who are free from the exogenous insulin at time of 1-year PD assessments.

2. Recommendations

The clinical pharmacology information in this BLA is acceptable, provided that satisfactory agreement is reached between the Applicant and FDA regarding the labeling. Please refer to section 5 for Clinical Pharmacology Labeling Recommendations.

3. Background

The beta (β) cells of the islets of the pancreas secrete insulin which is responsible to move blood glucose into cells where it will be stored and later used for energy. Type 1 diabetes mellitus (T1DM) is considered an autoimmune disease in which the patient's immune system attacks and destroys the islets resulting in little or no insulin production. Intensive insulin therapy is life-saving and can reduce complications associated with T1DM for most patients. Despite insulin therapy, some patients with T1DM still have blood glucose levels above normal range. Those who can keep their blood glucose levels near normal often have trouble with low blood glucose resulting in hypoglycemia-associated complications.

Allogenic islet transplantation involves isolation of islets from a deceased donor pancreas and infusion into the portal vein for delivery to the liver of a patient with T1DM. The recipient of islet transplant must take immunosuppressive drugs to keep the body from rejecting the islets which may put the person at risk for infections and certain cancers. The potential advantage of islet transplantation is that the transplanted islets would maintain normal blood glucose and would not produce excess insulin resulting in hypoglycemia. In 2000, Dr. James Shapiro and his colleagues (Edmonton, Canada), published a report describing seven consecutive subjects who didn't need insulin injections for at least 4 months following one, two, or three islet transplantations. The transplants were done with a protocol using steroid-free immunosuppression and large numbers

of donor islets¹. Currently, islet transplantation is considered an experimental procedure and there are no approved islet cell products for transplantation.

In this BLA submission, the Applicant propose DONISLECEL, for the “treatment of brittle type 1 diabetes mellitus (labile diabetes) in adults whose symptoms are not well controlled despite intensive insulin therapy.” Based on review of BLA data and the recommendations of the advisory committee, FDA recommended that the Applicant modify the indication to “DONISLECEL, allogeneic pancreatic islet cellular therapy, for the treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.” DONISLECEL is a cellular therapy derived from deceased donor’s pancreas. Islets contain several types of hormone secreting endocrine cells, including β -, α -, δ -, and ϵ -cells. The mechanism of action is primarily believed to be the secretion of insulin by beta (β) cells of the allogenic islets of the DONISLECEL. DONISLECEL was delivered to the portal vein via either transvenous or percutaneous transhepatic access under fluoroscopic and ultrasound guidance in the two main clinical studies supporting this BLA submission (#UIH-001 and UIH-002).

4. Summary of Clinical Pharmacology Findings

The data supporting clinical pharmacology of DONISLECEL were based on two clinical studies:

- The #UIH-001 study was a Phase 1/2, open-label, single-center study of allogeneic islet transplantation in patients with brittle T1DM. Ten patients received up to 3 islet transplantations to assess safety, pharmacodynamics, and initial efficacy data.
- The #UIH-002 study was a Phase 3, nonrandomized, single-center study in which 20 patients with brittle T1DM were enrolled for 1 to 3 allogeneic pancreatic islet transplants.

The major clinical pharmacology findings from these two clinical studies are summarized in the following sections.

¹ <https://www.citisetstudy.org/islet.html>

Dose-Response Analysis

- In both #UIH-001 & #UIH-002 studies a target islet dose of 10,000 IE/kg was proposed based on the findings of previous experience with Edmonton Protocol for allogeneic islet transplantation.
- From a total of 30 subjects, 11 (37%), 12 (40%) and 7 (23%) were treated with single, two and three dose of islet transplantation, respectively.
- For subject who received multiple infusions, the mean inter-dose interval between the first and the second infusion was 279 days (range 25 to 1029 days), and between the second and third infusions was 984days (range 62-2815 days).
- The mean administered dose per infusion was 7207 IE/kg (range 4186-13624). The mean total administered dose per subject was 13,453 IE/kg (range 4208-29,404).
- Based on the combined data (#UIH-001 & 002) no dose-response relationship was established for both HbA1c and C-peptide levels.
- Five out of twenty nine subjects (17%) who received lower total dose (<10000 IE/kg) did not achieve the target HbA1c level ($\leq 6.5\%$) at 1 year following islet infusion. Also, 2 out of 28 (7%) subjects who received lower dose (<10000 IE/kg) did not achieve the target C-peptide level (≥ 0.5 ng/mL) at 1 year following islet infusion.
- Overall, based on the combined data (#UIH-001 & 002) a dose-response relationship was not established for both HbA1c and C-peptide levels; however, a clear effect of islet transplantation was observed on the glucose levels in subjects who are free from requirement of exogenous insulin (see below).

Pharmacodynamic (PD) Assessments

- The baseline fasting glucose level was 165 ± 70.5 mg/dL and decreased to 108 ± 22 mg/dL one-year after last treatment with DONISLECEL.

- The mean fasting blood glucose levels declined within the first 2 weeks after treatment with DONISLECEL and remained below the baseline values at 52 weeks after the first treatment, but there was high inter-individual variability.
- The baseline stimulated (90-min) glucose level was 353 ± 81.9 mg/dL and decreased to 157 ± 57.6 mg/dL one-year after last treatment with DONISLECEL.
- The baseline fasting C-peptide level was 0.01 ± 0.024 ng/mL and increased to 1.31 ± 0.61 ng/mL one-year after last treatment with DONISLECEL.
- The baseline stimulated (90-min) C-peptide level was 0.02 ± 0.055 ng/mL and increased to 3.74 ± 0.61 ng/mL one-year after last treatment with DONISLECEL.
- The mean fasting and stimulated C-peptide levels were higher than the proposed target level of 0.5 ng/mL for over 90% of the subjects.
- There were no age-related or sex-related differences in fasting and stimulated glucose and C-peptide levels following treatment with DONISLECEL.
- In general, the PD results support the primary efficacy analysis and the PD profile of allogenic islet cells is most clearly demonstrated without much confounding in subjects who are free from the requirement of exogenous insulin. Specifically, the fasting glucose level was 106 ± 17 mg/dL and the stimulated glucose level (90-min) was 142 ± 40 mg/dL for subjects who are free from the exogenous insulin at time of 1-year PD assessments. The mean fasting and stimulated C-peptide levels were higher than the proposed target level of 0.5 ng/mL for over 95% of the subjects who are free from the exogenous insulin at time of 1-year PD assessments.

Immunogenicity Risk Assessments

- For the combined UIH-001 & 002, 6 out of 28 (21%) patients transitioned from panel-reactive antibodies (PRA Class I, Class II, or both) <20% at baseline to ≥ 20 % following islet transplant.
- A trend for increased risk for PRA (either Class I or II) with multiple vs single infusion was observed. For example, about 11%, 25% and 29% of subjects transitioned to ≥ 20 % PRA when infused with one, two or three islet transplantation, respectively. Also, two out of the

3 (67%) patients who transitioned from Class II PRA <20% at baseline to ≥20% posttransplant did so only after receiving more than one transplant (second infusion in both cases).

- Under the proposed immunosuppressive regimen, the development of post-transplant PRA ≥20% did not appear to impact islet graft function, as 5/6 (83%) patients who transitioned from PRA <20% at baseline to ≥20% posttransplant achieved HbA1c ≤6.5% at 1 year post-last transplant.
- Antibodies against islet cells, glutamic acid decarboxylase 65 (GAD65), islet antigen 2 (IA2) and insulin did not increase at 48 weeks after last transplant as compared to the baseline levels.

5. Clinical Pharmacology Labeling Comments

At the time of finalization of this review memorandum, negotiations on the labeling are ongoing between FDA and the Applicant. As they currently stand, the following are clinical pharmacology labeling comments that will be communicated with the Applicant:

Section 6: Adverse Reactions

6.2. Immunogenicity

- Requested to include the results of panel reactive antibodies

Section 12: CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

- Recommended revision to provide more specific information based on mechanistic data derived from DONISLECEL.

12.2. Pharmacodynamics

- Recommended to revise pharmacodynamic data focusing on the basal and stimulated glucose levels.
- Removed Hb1Ac and c-peptide levels due to confounding factors, baseline values, etc.
- Revised basal and stimulated glucose level to reflect the values for subjects who are free from the requirement of exogenous insulin to minimize the impact of confounding factors.

6. Comprehensive Clinical Pharmacology Review

6.1. General Pharmacology and Pharmacokinetics

DONISLECEL is a cellular therapy derived from deceased donor's pancreas. Islets contain several types of hormone secreting endocrine cells, including β -, α -, δ -, and ϵ -cells. The mechanism of action is primarily believed to be the secretion of insulin by beta (β) cells of the allogenic islets of the DONISLECEL. The therapeutic effect of islet allotransplantation has been shown to depend on the mass of islet β -cells that survives engraftment. Islet cells transplantation at > 9000 islet equivalents (IE)/kg resulted in about 25% of β -cells secretory capacity of normal².

No formal clinical dose finding, or dose regimen exploration studies have been performed during the development of DONISLECEL for treatment of T1DM. Published studies based on Edmonton protocol recommend a total islet dose of ≥ 8000 to 9000 islet equivalents (IE)/kg administered over 1 to 3 infusion to achieve a desirable clinical benefit. In both #UIH-001 & #UIH-002 studies a target islet dose of 10,000 IE/kg was proposed based on the findings of previous experience with Edmonton Protocol for allogeneic islet transplantation.

In both #UIH-001 & #UIH-002 studies a target islet dose of 10,000 IE/kg was proposed based on the findings of previous experience with Edmonton Protocol for allogeneic islet transplantation. From a total of 30 subjects, 11 (37%), 12 (40%) and 7 (23%) were treated with single, two and three dose of islet transplantation, respectively. For subject who received multiple infusions, the mean inter-dose interval between the first and the second infusion was 279 days (range 25 to 1029 days), and between the second and third infusions was 984 days (range 62-2815 days). The mean administered dose per infusion was 7207 IE/kg (range 4186-13624). The mean total administered dose per subject was 13,453 IE/kg (range 4208-29,404).

² Rickels MR and Robertson RP. Pancreatic Islet Transplantation in Humans: Recent Progress and Future Directions Endocrine Reviews 40: 631 – 668, 2019.

Based on the combined data no dose-response relationship was established for both HbA1c and C-peptide level (Figure 1). Five out of twenty nine subjects (17%) who received lower total dose (<10000 IE/kg) did not achieve the target HbA1c level at 1 year following islet infusion. Also, 2 out of 28 (7%) subjects who received lower dose (<10000 IE/kg) did not achieve the target C-peptide level at 1 year following islet infusion. All five subjects with HbA1c > 6.5% received fewer than 700,000 total islets. Among patients with 1-year data available and C-peptide <0.5%, both received fewer than 500,000 total islets.

Pharmacokinetic (PK) studies of DONISLECEL have not been performed in humans. Because of the cellular nature of DONISLECEL, conventional methods cannot be applied for PK monitoring. The following preliminary PK findings regarding islet cells distribution and clearance are summarized based on published human studies:

- Potential for extrahepatic distribution of islet cells were demonstrated by RT-PCR detection in the blood for up to 10 weeks after islet transplantation³.
- Visualization by positron-emission tomography (PET) showed heterogenous distribution of labeled transplanted islet cells within the liver and potential for loss of about 25-50% of the cells^{4,5}.
- PET monitoring of hepatic uptake of [11C]5-hydroxytryptophan ([11C]5-HTP) indicated a correlation with metabolic functions of islet cells following intraportal islet graft in 10 subjects⁶.

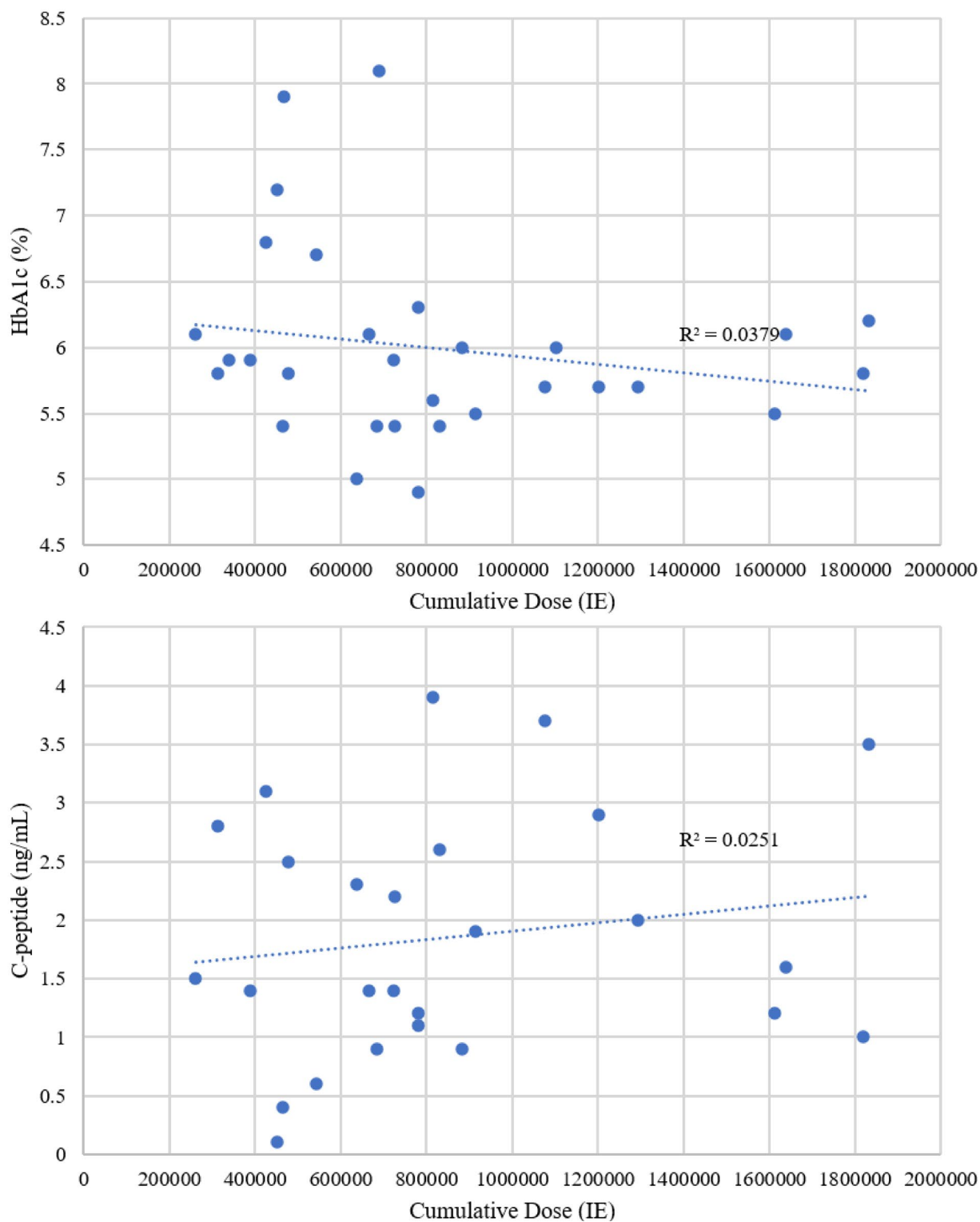
³ Ritz-Laser et al. *Molecular detection of circulating beta-cells after islet transplantation*. Diabetes, 2002. **51**: 557-61.

⁴ Eich et al. *Visualization of early engraftment in clinical islet transplantation by positron-emission tomography*. N Engl J Med, 2007. **356**: 2754-5.

⁵ Eriksson et al., *Positron emission tomography in clinical islet transplantation*. Am J Transplant, 2009. **9**: 2816-24.

⁶ Eriksson et al. *Positron Emission Tomography to Assess the Outcome of Intraportal Islet Transplantation*. Diabetes, 2016. **65**: 2482-89.

Figure 1. HbA1c (%) and C-Peptide Level at 1 Year after Last Transplant, by Dose (UIH-001&002– Main Group)



Source: UIH-001 Listings [16.2.6a](#) and [16.2.6d](#), UIH-002 Listings [16.2.6a](#) and [16.2.6d](#)

Reviewer Comments: The available dose-response data don't indicate a clear relationship presumably due to the nature of the product and the associated inherent variabilities. Some potential sources of variabilities include product manufacturing attributes, immunosuppressive regimens and other concomitant drugs, donor and recipient subjects related characteristics. In response to clinical information request, the Applicant stated that the criteria for a second or third infusion in UIH-001 and UIH-002 were based on:

- Daily blood glucose measurements outside the normal range
- Absence of insulin independence (i.e., absence of exogenous insulin use while achieving $\text{HbA1c} \leq 6.5\%$ at the time of evaluation), or HbA1c levels $>6.5\%$
- In several cases, subjects also received an additional transplant due to loss of islet function, which was defined as C-peptide levels <0.3 ng/mL for 2 consecutive follow-up visits after the last transplant
- Contraindications for additional infusions included noncompliance and safety concerns with immunosuppression (such as severe infections or malignancies).

Overall, there was high inter-patient variability in the administered dosing regimen and no clear dose-response relationship was established.

6.2. Pharmacodynamic Assessments

The pharmacodynamic effects of DONISLECEL are a result of hormones, especially insulin, that are secreted by the transplanted islets in response to fluctuations in blood glucose levels. For combined PD analysis of UIH-001 and UIH-002 the following parameters were analyzed at baseline vs 1 year following a patient's last transplant during Studies.

- HbA1c levels,
- Basal and stimulated blood glucose, and
- Basal and stimulated C-peptide

The combined results from UIH-001 and UIH-002 studies are summarized in Table 5. At 1 year after last transplant, the mean HbA1c levels were reduced to 6.01 % from the baseline value of 7.38% (~18.6% reduction). The fasting and stimulated glucose were reduced by 34% and 55%,

respectively. The fasting and stimulated C-peptide were higher than the proposed target level of 0.5 ng/mL (Table 1).

Table 1. HbA1c, Blood Glucose, and C-peptide Levels at Baseline and 1 Year After Final Transplant

| Parameter | | Baseline | 1 Year after Last Transplant |
|---------------------------|--------------|------------------|------------------------------|
| HbA1c % | | | |
| | Mean (SD); n | 7.38 (0.936); 29 | 6.01 (0.738); 29 |
| MMTT | | | |
| Glucose mg/dL (fasting) | Mean (SD); n | 165 (70.5); 28 | 108 (22.0); 25 |
| Glucose mg/dL (90-min) | Mean (SD); n | 353 (81.9); 28 | 157 (57.6); 25 |
| C-peptide ng/mL (fasting) | Mean (SD); n | 0.01 (0.024); 28 | 1.31 (0.610); 25 |
| C-peptide ng/mL (90-min) | Mean (SD); n | 0.02 (0.055); 28 | 3.74 (1.739); 25 |

mbined UIH-001 & UIH-002)

Source: ISE Table 14.2.2b

A plot of mean fasting blood glucose levels (measured during planned study visits) over time between initial transplant and 1 year after initial transplant is provided in Figure 2. Fasting blood glucose levels decline within the first 2 weeks after transplant. This effect was stable over subsequent weeks and remain below the baseline values at 52 weeks after the first transplant (Figure 2).

Reviewer Comments: In general, the PD results support the primary efficacy analysis and the PD profile of allogenic islet cells is most clearly demonstrated without much confounding in subjects who are free from the requirement of exogenous insulin. Specifically, the fasting glucose level was 106 ± 17 mg/dL and the stimulated glucose level (90-min) was 142 ± 40 mg/dL for subjects who are free from the exogenous insulin at time of 1-year PD assessments. The mean fasting and stimulated C-peptide levels were higher than the proposed target level of 0.5 ng/mL for over 95% of the subjects who are free from the exogenous insulin at time of 1-year PD assessments. We further evaluated the relationship between number of islet transplant versus baseline glucose and stimulated glucose level. The following is summary of the analysis:

- The basal (fasting) glucose level (mg/dL) at 1-year PD assessments following one transplant was 115 ± 24 (n=7). The corresponding values for subjects who received two and three transplants were 104 ± 45 (n=11) and 105 ± 28 (n=7), respectively. The % reduction in basal glucose levels at 1-year PD assessment as compared to the pretreatment values was 29%, 37%, 38%.
-
- The stimulated (90-min) glucose level (mg/dL) at 1-year PD assessments following one transplant was 205 ± 60 (n=7). The corresponding values for subjects who received two and three transplants were 138 ± 45 (n=11) and

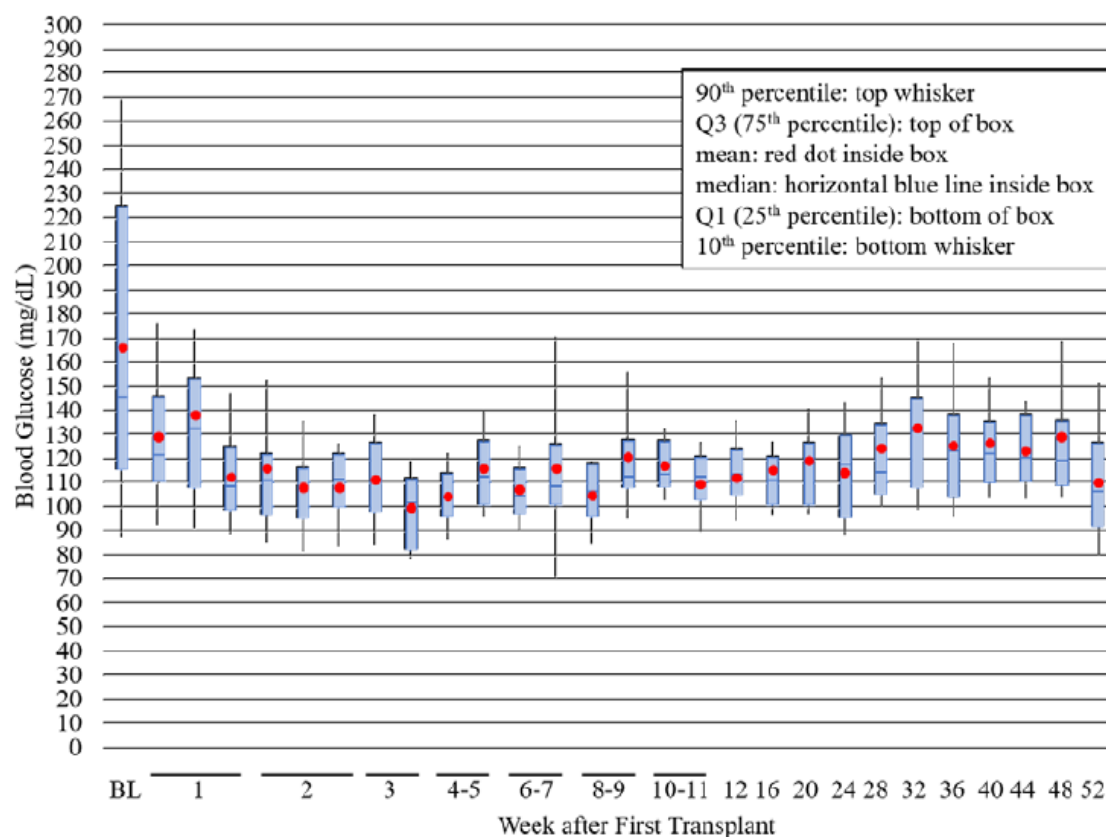
128 ± 30 (n=7), respectively. The % reduction in stimulated glucose levels at 1-year PD assessment as compared to the pretreatment values was 45%, 61%, 60%.

- These results of the PD analysis provide supportive evidence on the benefit of the second or third islet transplantation in reducing the blood sugar level.

Effect of Intrinsic/Extrinsic Factors on Pharmacodynamic Analysis:

Most patients in the UIH 001&002 studies were white (30/30 [100%] identified as Caucasian and 1/30 [3%] co-identified as Native American) and only one subject identified as Hispanic. Thus, subgroup analysis by race or ethnicity is not informative. For analysis by age, 47 years was used as the boundary between the older and younger groups, as this was the mean and median age for UIH 001&002 studies. There were no age-related or sex-related differences in HbA1c, fasting and stimulated glucose, fasting and stimulated C-peptide levels.

Figure 2. Blood Glucose Levels from Baseline through 1 Year after First Transplant (Combined UIH-001 & UIH-002)



Source: [ISS Table 14.3.15](#).

Reviewer Comments: There is no adequate information on extrinsic factors (e.g. PK of co-administered drugs such as GLP-1 agonists and immunosuppressive drugs) therefore it is difficult to evaluate the impact of these factors on the PD parameters and success of islet cell transplantation.

6.3. Immunogenicity Assessments

Human leukocyte antigen (HLA) sensitization also called development of donor-specific antibodies following islet transplantation is considered a potential risk as it might be a barrier against future transplantation (either islet or whole organ such as future kidney transplantation). HLA sensitization can be as a result of the use of multiple islet infusions to achieve enough engrafted islet mass that may expose an islet recipient to several mismatched HLA alleles. In studies #UIH-001 and UIH-002, panel-reactive antibodies (PRA) was determined by analysis of anti-human antibodies. T1DM autoimmunity was assessed by measuring antibodies against islet antigens or insulin.

For the combined UIH-001 & 002, 6 out of 28 (21%) patients transitioned from PRA (either Class I, Class II, or both) <20% at baseline to $\geq 20\%$ following islet transplant (Table 2 & Table 3). Overall, 3/6 (50%) patients developed Class I only, 2/6 (33%) patients developed Class II only, and 1/6 (17%) patients developed both Class I and II antibodies. Two out of the 3 (67%) patients who transitioned from Class II PRA <20% at baseline to $\geq 20\%$ posttransplant did so only after receiving more than one transplant (second infusion in both cases). The Applicant states that clinical impact of HLA sensitization is not fully known. The development of post-transplant PRA $\geq 20\%$ did not appear to impact islet graft function, as 5/6 (83%) patients who transitioned from PRA <20% at baseline to $\geq 20\%$ posttransplant achieved HbA1c $\leq 6.5\%$ at 1 year post-last transplant. Antibodies against islet cell, glutamic acid decarboxylase 65 (GAD65), islet antigen 2 (IA2) and insulin were also evaluated. Islet transplantation did not appear to increase the level of autoantibodies at 48 weeks after last transplant as compared to the baseline levels (Table 4).

Reviewer Comments: There appears to be a slight increased risk for PRA (either Class I or II) with multiple vs single infusion. For example, about 11%, 25% and 29% of subjects transitioned to $\geq 20\%$ PRA when infused with one, two or three islet transplantation, respectively. However, caution is needed in interpretation of the PRA and T1DM autoantibodies results due to the small sample size, the transient nature of the antibodies in some subjects and the arbitrary threshold for immunogenicity risk assessment. Also,

the long-term clinical impact of HLA sensitization both on islet function and risk related to future transplantation (islet or whole organ) are not fully evaluated.

Table 2. Transition from Baseline PRA <20% to ≥20% for Studies UIH-001 and UIH-002 by the Total Number of Transplants Received

| Total Transplants Received | PRA Class | Transition to PRA ≥20%, N/N (%) |
|----------------------------|-----------|---------------------------------|
| Overall | Any | 6/28 (21) |
| | Class I | 4/28 (14) |
| | Class II | 3/28 (11) |
| 1 | Any | 1/9 (11) |
| | Class I | 1/9 (11) |
| | Class II | 1/9 (11) |
| 2 | Any | 3/12 (25) ^a |
| | Class I | 1/12 (8) ^a |
| | Class II | 2/12 (17) ^a |
| 3 | Any | 2/7 (29) ^b |
| | Class I | 2/7 (29) ^b |
| | Class II | 0 |

Source: [Listing 16.2.10](#) (UIH-001) and [Listing 16.2.10](#) (UIH-002)

Table 3. Number of Patients at 0%, 1-19%, and ≥20% PRA (Class I and II) by Transplant Number at the Time of Assessment and Time Post-Transplant (#UIH-001 and UIH-002)

| Transplant # at Assessment | Time of Assessment ^a | Class I PRA | | | Class II PRA | | |
|-------------------------------|---------------------------------|---------------|------------------|-----------------|---------------|------------------|-----------------|
| | | 0% N/N (%) | 1-19% N/N (%) | ≥20% N/N (%) | 0% N/N (%) | 1-19% N/N (%) | ≥20% N/N (%) |
| – | Baseline | 29/30 (97) | 0 | 1/30 (3) | 27/30 (90) | 1/30 (3) | 2/30 (7) |
| 1 | 6 Months (Week 24) | 21/22 (95) | 0 | 1/22 (5) | 20/22 (91) | 0 | 2/22 (9) |
| | 1 Year (Week 48/56) | 10/13 (77) | 0 | 3/13 (23) | 11/13 (85) | 0 | 2/13 (15) |
| 2 | 6 Months (Week 24) | 16/16 (100) | 0 | 0 | 14/16 (88) | 0 | 2/16 (12) |
| | 1 Year (Week 48/56) | 17/17 (100) | 0 | 0 | 15/17 (88) | 0 | 2/17 (12) |
| 3 | 6 Months (Week 24) | 4/5 (80) | 1/5 (20) | 0 | 5/5 (100) | 0 | 0 |
| | 1 Year (Week 48/56) | 6/7 (86) | 1/7 (14) | 0 | 7 (100) | 0 | 0 |

Source: [Listing 16.2.10](#) (UIH-001) and [Listing 16.2.10](#) (UIH-002)

Table 4. Islet Cell, GAD65, IA2, and Insulin Antibodies at Baseline and Week 48 after Last Transplant (#UIH-001 and UIH-002)

| | Islet Cell | GAD65 | IA2 | Insulin |
|--------------------------|----------------------------|----------------|----------------|-------------------|
| Baseline | | | | |
| n | 23 | 26 | 25 | 21 |
| Mean (SD); % | NC | 48 (78.5) | 1.0 (0.49) | 16.5 (19.2) |
| Median (Min, Max); units | <1:4 (<1:4, 1:256) [titer] | 5 (1, 250) | 0.8 (0.8, 2.8) | 5.6 (0.4, 50.0) |
| BLQ, n | 19 (<0.4) | 6 (<1), 7 (<5) | 19 (<0.8) | 2 (<0.4), 1 (<1) |
| ALQ, n | 0 | 2 (>250) | 0 | 4 (>50) |
| Week 48 | | | | |
| n | 28 | 28 | 29 | 25 |
| Mean (SD); % | NC | 43 (72.7) | 0.9 (0.32) | 6.1 (11.0) |
| Median (Min, Max); units | <1:4 (<1:4, 1:32) [titer] | 5 (1, 250) | 0.8 (0.8, 2.1) | 1.0 (0.4, 50.0) |
| BLQ, n | 25 (<1:4) | 2 (<1), 9 (<5) | 20 (<0.8) | 10 (<0.4), 2 (<1) |
| ALQ, n | 0 | 2 (>250) | 0 | 1 (>50) |

Source: UIH-001 CSR [Listing 16.2.8d](#), UIH-002 CSR [Listing 16.2.8d](#)

7. Appendix

7.1. Study#1- Islet Transplantation in Type 1 Diabetic Patients Using the Edmonton Protocol of Steroid Free Immunosuppression (UIH-001)

Objective: The primary objective of the study was to demonstrate the safety of allogeneic islet transplantation in type 1 diabetic (T1D) patients, as performed at University of Illinois (UI) Health. The secondary efficacy objectives include assessments of pharmacodynamic (PD) endpoints such as HbA1c, insulin, c-peptide and glucose test.

Overall Study Design: This was a Phase 1/2, open-label, single-center study of allogeneic islet transplantation in patients with brittle T1DM. Ten subjects received up to 3 islet transplantations to assess safety and to gather initial efficacy data. All potential donors were screened for safety and for organ quality. A minimum number of islets of about 10,000 islet equivalents (IE)/kg of recipient body weight was used for engraftment and confirmed C-peptide expression based on the Edmonton protocol. Participants in the trial received immunosuppression (daclizumab, sirolimus, tacrolimus, and etanercept) to prevent allotransplant rejection. During the course of Study UIH-001, daclizumab was removed from the market and was replaced with basilixumab (Protocol A7, August 2012). In addition, subjects received prophylactic anti-infective medications including valganciclovir, trimethoprim/sulfamethoxazole, and cefazolin; heparin and enoxaparin (low molecular weight heparin) to reduce coagulation risk; and filgrastim as needed for treatment of neutropenia. Subjects also received chronic treatment with exenatide (GLP-1 agonist) to enhance insulin secretion by the transplanted islet cells.

Route of Administration and Dosing Regimen: Islets were delivered to the portal vein via either transvenous or percutaneous transhepatic access under fluoroscopic and ultrasound guidance. Eligible subjects were planned to receive one to three transplants to reach the target minimum total of 10,000 IE/kg of recipient body weight. Additional transplants were indicated if the first transplant failed to reach the desired minimum number of islets, and if after the first transplant and following withdrawal of insulin therapy, pre- or post-prandial blood glucose levels repeatedly exceeded 10 mmol/L. No maximum number of delivered islets was specified if packed cell volume did not exceed 10 mL per transplant.

Primary Efficacy Endpoint (Insulin Independence): Transplant was considered a success when, beginning two weeks after their last transplant, patients were not using insulin and achieved

an HbA1c $\leq 6.5\%$. During the year after last transplant, a patient was still considered a success if an intercurrent illness or other event caused a patient to require insulin use for a period not exceeding a total of 14 days. Thus, a durable period of insulin independence from 2 weeks up to each point of evaluation during the 1 year follow-up after last transplant was considered a success at that time point.

Secondary Efficacy Parameters (Pharmacodynamic Endpoints): The secondary efficacy parameters are surrogate markers of islet mass and islet function, specifically:

- HbA1c levels: reaching normal values of less than 6.1% by Day 90 \pm 14 days, Day 180 \pm 21 days and Day 365 \pm 35 days following the first transplant (denoting the day of first transplant as Day 0) and continuing for 365 days following their final transplant (by Day 365 \pm 35 days, denoting the day of last transplant as Day 0, if patient has more than one transplant) were to be considered a success.
- Oral glucose tolerance: to be judged normal if blood glucose levels were lower than 7.8 mmol/L (140 mg/dL) after a 2-hour oral glucose tolerance test, as impaired if blood glucose levels were between 7.89 and 11.1 mmol/L (140 and 199 milligrams mg/dL) and as diabetic if blood glucose levels were higher than 11.1 mmol/L (199 mg/dL).
- Mixed meal test (glucose and C-peptide levels): Acute C-peptide response and blood glucose level to a standard mixed meal test was to be used to compare values at enrollment to values at 12 months following final transplant.
- The acute C-peptide response to the glucagon stimulation test: The fold-increase in C-peptide levels 6 minutes after glucagon injection was to be evaluated
- Intravenous glucose tolerance: Glucose disappearance rate constant was to be evaluated. The acute insulin response to an intravenous glucose challenge (AIR-IVGGT) was to be calculated as indicator of islet mass.

Bioanalytical Methods: The bioanalytical methods used to assess PD markers and immunogenicity risk were developed under “fit-for-purpose” approach in which each method was considered suitable for its intended purpose.

Demographics and Patient Baseline Characteristics

A total of 10 patients (1 male and 9 female) enrolled and completed the study. The average age was 46.4 years (range 35 to 63 years) the average weight was 62.4 kg (range 55.6 to 71.4 kg),

the average height was 166.6 cm, and the average BMI was 22.5 kg/m² (range 20.9-24.1). The patient population were 100% non-Hispanic Caucasian.

Analysis of Pharmacodynamic Endpoints

A summary of mean pharmacodynamic parameters at baseline and at 1 year after last transplant is provided in Table 1. Relative to baseline, fasting and stimulated glucose were reduced at 1 year after islets transplant. The fasting and stimulated C-peptide were increased at 1 year after last transplant. Mean HbA1c was reduced <6 % from baseline at 1 year after last transplant (Table 5).

Table 5. Pharmacodynamic Parameters and Responses at Baseline and 1 Year after Last Transplant – Study UIH-001

| Parameter | | Baseline | 1 Year after Last Transplant |
|----------------------------------|--------------|------------------|------------------------------|
| HbA1c % | | | |
| | Mean (SD); n | 7.21 (1.205); 10 | 5.72 (0.282); 10 |
| MMTT | | | |
| Glucose mg/dL (fasting) | Mean (SD); n | 143.3 (87.87); 9 | 103.5 (21.73); 10 |
| Glucose mg/dL (90-min) | Mean (SD); n | 312.1 (94.18); 9 | 163.2 (58.30); 10 |
| C-peptide ng/mL (fasting) | Mean (SD); n | 0.00 (0.000); 9 | 1.41 (0.375); 10 |
| C-peptide ng/mL (90-min) | Mean (SD); n | 0.01 (0.033); 9 | 4.02 (1.156); 10 |
| GST | | | |
| C-peptide fold increase | Mean (SD); n | 1.00 (0.000); 8 | 1.80 (0.491); 10 |
| IVGTT ^a | | | |
| kG | Mean (SD), n | – | -0.00915 (0.003664); 10 |
| AIR _{glu} | Mean (SD), n | – | 19.712 (19.9048); 9 |
| OGTT ^a | | | |
| Normal (glucose <140 mg/dL) | n (%) | – | 4 (40) |
| Impaired (glucose 140-199 mg/dL) | n (%) | – | 1 (10) |
| Diabetic (glucose >199 mg/dL) | n (%) | – | 5 (50) |
| Missing | n (%) | – | 1 (10) |

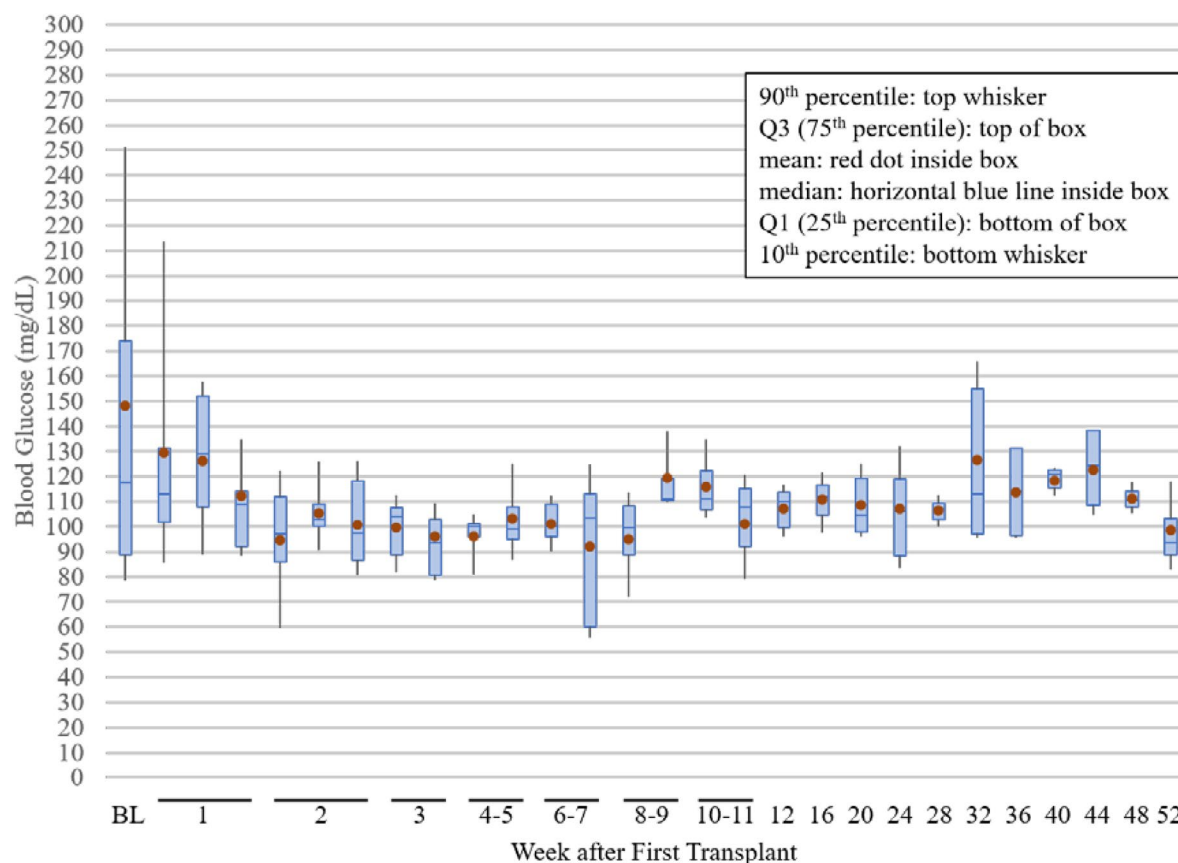
AIR_{glu} = Acute insulin response to glucose; kG = Glucose disappearance rate constant;

^aPretransplant IVGTT and OGTT were not performed for safety reasons, as C-peptide negative T1D patients would exhibit exceedingly high glucose levels during these tests.

Source: UIH-001 CSR Table 14.1.3, 14.2.2b and Listing 16.2.6a

A longitudinal assessment of fasting blood glucose is provided in Figure 1. Fasting blood glucose levels decreased with the first 3 weeks following initial islet transplant and generally maintained over time, with some fluctuation (Figure 3).

Figure 3. Blood Glucose Levels from Baseline through 1 Year after First Transplant – Study UIH-001



Source: UIH-001 CSR [Table 14.3.15](#) and [Listing 16.2.8b](#)

Reviewer Comments: The mean %HbA1c level at 1 year after islet transplant reduced to 5.72% (~21% lower than baseline). The mean level of C-peptide was higher than the proposed target level of 0.5 ng/mL for 9 out of 10 subjects. One subject who did not achieve target C-peptide level received below the recommended dose of 10000 IE/kg (refer to Dose-Response Analysis below). A reduction of the mean fasting blood glucose level within the first two weeks following islet transplantation was observed. Although there is higher inter-subject variability fasting blood glucose level remain lower than baseline at 1 year after the last transplantation.

Dose-Response Analysis

The summary of administered total dose and number of transplants with islets is provided in Table 2. Overall, 10 patients were treated up to 1 to 3 allogeneic islets transplant. Three patients (30%) underwent single transplant, two patients (20%) underwent two separate transplants, and the

remaining five (50%) were infused on three separate occasions. The mean overall administered dose was 16824 IE/kg. The average total dose for subject treated with single, double and triple infusion of islet was 5770 IE/kg, 12632 IE/kg and 21748 IE/kg, respectively (Table 6). In each case, the decision to transplant additional islets beyond the first infusion was based on clinical outcomes.

Table 6. Summary of Administered dose (UIH-001)

| Dosing Regimen | Mean Total Administered Dose (IE/kg) |
|--------------------------------|---|
| Single transplant (n=3) | 5770 (4208-6605) |
| 2 transplants (n=2) | 12632 (12247-13017) |
| 3 transplants (n=5)* | 21748 (16941-29404) |
| Overall patients (N=10) | 16824 (4208-29404) |

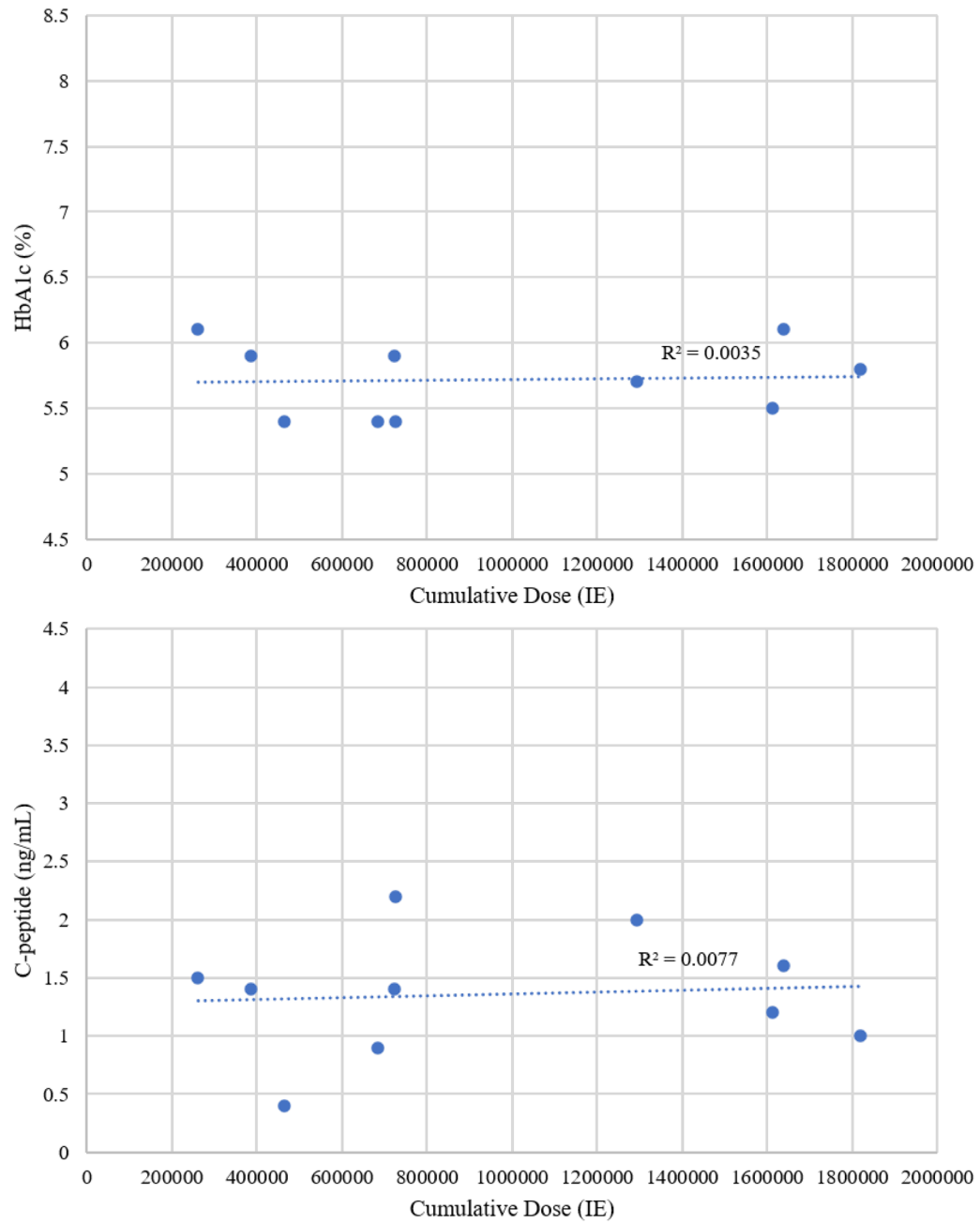
*One subject in this study received the third transplant as part of study UIH-002 study and dosing and inter-dose interval is calculated here.

Source: Prepared by Reviewer

HbA1c percentage and C-peptide levels at 1 year after last transplant are summarized by dose in Figure 2. There was no apparent dose-response related to HbA1c and C-peptide levels (Figure 4). All patients at all dose levels had achieved target HbA1c levels ($\leq 6.5\%$) and all but 1 patient had achieved target C-peptide levels (≥ 0.5 ng/mL) at 1 year after last transplant (Figure 5).

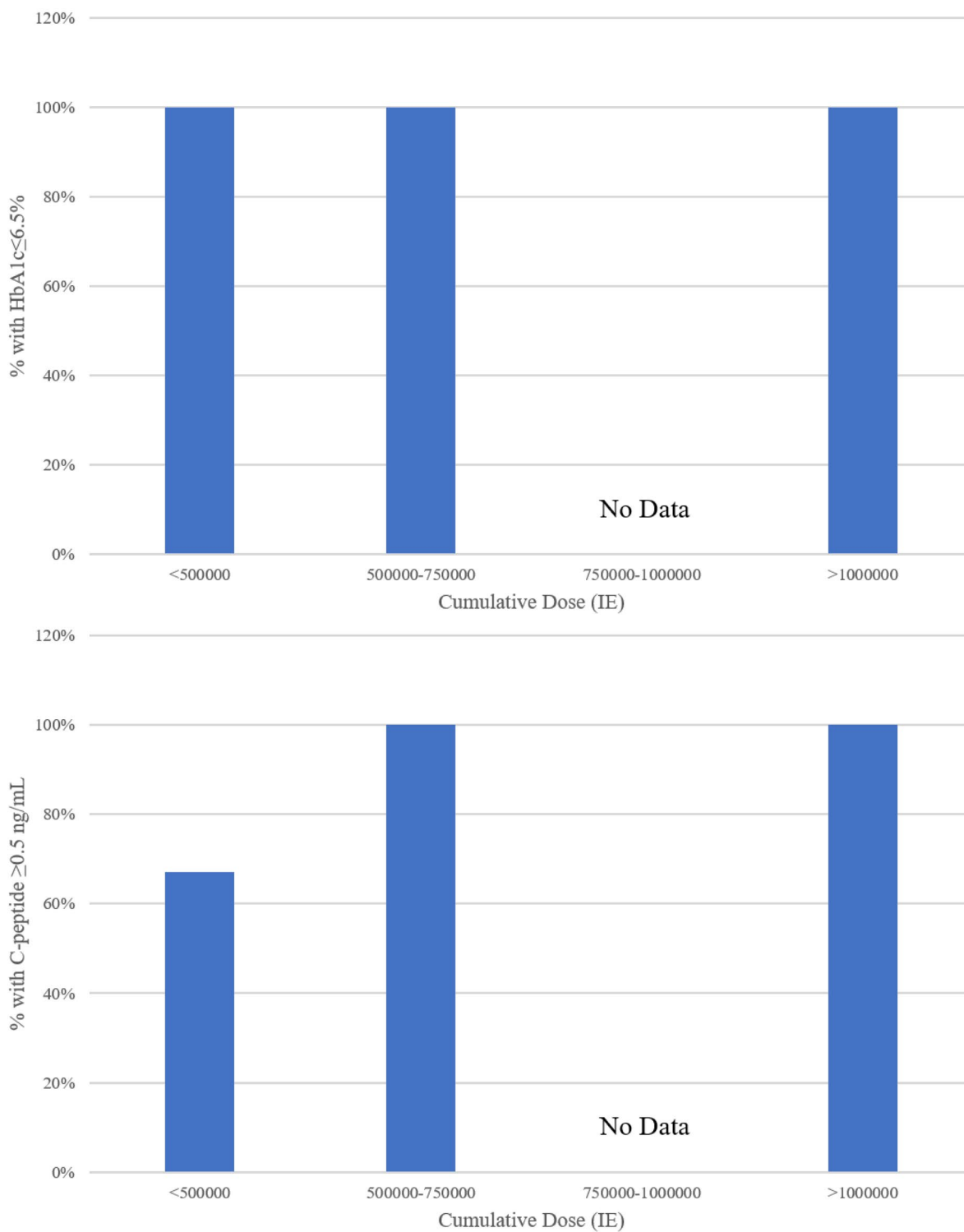
Reviewer Comments: For patient who received multiple infusion, the average inter-dose interval between the first and the second infusion was 253 ± 352 days (range 25 to 1029 days), and inter-dose interval between the second and third infusion was 399 ± 1108 days (range 62-2815 days). These data indicate a highly variable dosing frequency. Also, no dose-response relationship for both HbA1c and C-peptide level was established. It should be note that there were only 10 subjects in this study and one subject from this study received the third infusion as part of UIH-002 study protocol after ~7 years from the second infusion. For integrated dose-response and immunogenicity analysis refer to comprehensive clinical pharmacology review section.

Figure 4. HbA1c (%) and C-Peptide Level at 1 Year after Last Transplant, by Dose (Study UIH-001)



Source: UIH-001 Listings [16.2.6a](#) and [16.2.6](#)

Figure 5. Percentage of Patients Achieving HbA1c $\leq 6.5\%$ or C-Peptide ≥ 0.5 ng/mL at 1 Year after Last Transplant, by Dose (Study UIH-001)



Source: UIH-001 Listings [16.2.6a](#) and [16.2.6d](#)

7.2. Study#2- Islet Transplantation in Type 1 Diabetic Patients Using the UIC Protocol, Phase 3 (UIH-002)

Objective: The primary objective of this study was to demonstrate the safety and efficacy of allogeneic islet transplantation in type 1 diabetic patients performed at UIC.

Overall Study Design: This was a Phase 3, nonrandomized, single-center study in which at least 50 study patients with brittle T1DM were planned for 1 to 3 allogeneic pancreatic islet transplants per patient. Potential organ donors were screened against safety and organ quality criteria. Pancreatic islet cells were isolated in clean room facilities at the Cell Isolation Laboratory at UI Health and injected into the portal vein by transvenous or percutaneous transhepatic access under fluoroscopic and ultrasound guidance. A target islet concentration of 10,000 islet equivalents (IE)/kg recipient body weight was based on findings associated with the previously established Edmonton Protocol for allogeneic islet transplantation. One to three transplants were planned for each patient to reach the target of 10,000 IE/kg. Once subject in this trial received two previous islet transplantation as part of the UIH-001 and the third infusion as part of UIH-002. Patients received corticosteroid-free immunosuppression to prevent allotransplant rejection. The immunosuppressive regimen included treatment with basiliximab, sirolimus, tacrolimus, and etanercept. Patients who had pre-formed antibodies against human leukocyte antigens (HLA) received anti-T-cell antibody (anti-thymocyte globulin (ATG); Thymoglobulin®) instead of basiliximab. Mycophenolate mofetil was administered to patients who did not tolerate sirolimus or tacrolimus. In addition, patients received prophylactic anti-infective medications such as trimethoprim/sulfamethoxazole and valganciclovir, heparin to reduce coagulation risk, and filgrastim as needed for treatment of neutropenia. Patients also received chronic treatments with exenatide (glucagonlike peptide-1 [GLP-1] agonist) to enhance insulin secretion by the transplanted islet cells.

Pharmacodynamic Assessment: For PD analysis blood samples were collected at the Clinical Research Center as follows:

- 2-3 times a week for the first 4 weeks
- Weekly until week 12 after transplantation, followed by monthly monitoring during the first year. Additional visits may be necessary until the last visit (52 weeks).

Additional evaluations were allowed if medical conditions presented during the study period; in these cases, each patient was evaluated according to best medical practice. When a second or third transplant was performed on a single patient, the follow-up visit schedule was restarted to

permit careful follow-up during the immediate post-operative period. In the event a second transplant was not needed due to successful engraftment, insulin independence, and stable blood glucose levels, the follow-up schedule was maintained at monthly intervals following week 12 through the first year study period according to the protocol. The following PD markers/efficacy were evaluated:

- Glycated hemoglobin (HbA1c),
- C-peptide level,
- Blood glucose level,
- Insulin-secretory capacity (intravenous glucose tolerance test [IVGTT], glucagon stimulation test [GST], oral glucose tolerance test [OGTT], and mixed meal tolerance test [MMTT]) were measured to provide detailed information about graft functionality.

Demographics and Patient Baseline Characteristics

A total of 20 patients (5 male and 15 female) were enrolled. Nineteen out of the 20 patients (95%) completed the study through 1 year after their last transplant. The average age was 47 years (range 21 to 67 years), weight was 65 kg (range 53 to 83 kg), and body mass index (BMI) was 24 kg/m² (range 21-27). The patient population were 100% non-Hispanic Caucasian.

Analysis of Pharmacodynamic endpoints

A summary of mean pharmacodynamic parameters at baseline and at 1 year after last transplant is provided in Table 7. Relative to baseline, fasting and stimulated glucose were reduced and fasting and stimulated C-peptide were increased at 1 year after last transplant. Mean HbA1c was reduced from 7.37% (baseline) to 6.12 % (1 year after last transplant) (Table 7). A longitudinal assessment of fasting blood glucose is provided in Figure 6.

Table 7. Pharmacodynamic Parameters at Baseline and 1 Year after Last Transplant (Study UIH-002)

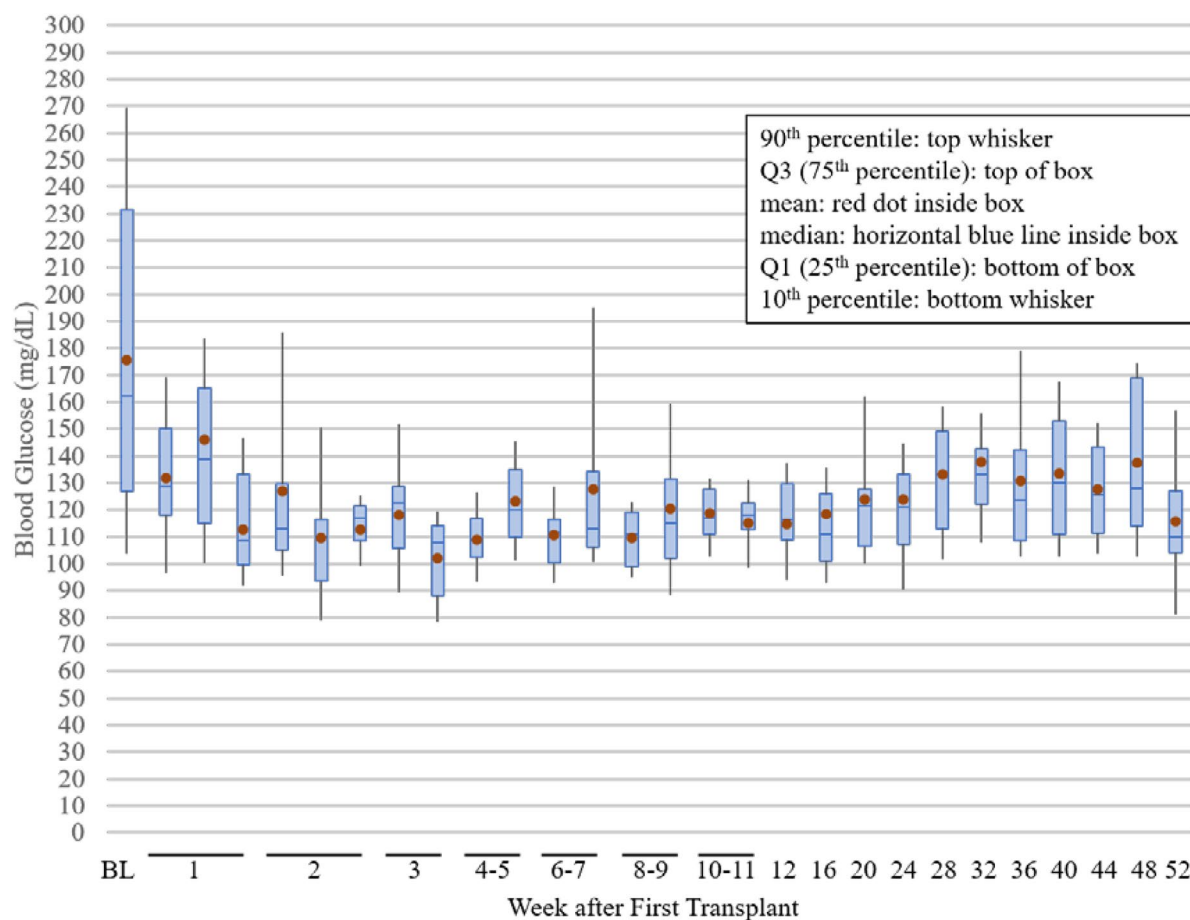
| Parameter | | Baseline | 1 Year after Last Transplant |
|----------------------------------|--------------|-------------------|------------------------------|
| HbA1c % | | | |
| | Mean (SD); n | 7.37 (0.867); 21 | 6.12 (0.836); 19 |
| MMTT | | | |
| Glucose mg/dL (fasting) | Mean (SD); n | 171.8 (61.18); 20 | 106.9 (18.37); 16 |
| Glucose mg/dL (90-min) | Mean (SD); n | 368.4 (69.90); 20 | 147.2 (53.39); 16 |
| C-peptide ng/mL (fasting) | Mean (SD); n | 0.09 (0.018); 20 | 1.23 (0.701); 16 |
| C-peptide ng/mL (90-min) | Mean (SD); n | 0.14 (0.184); 20 | 3.49 (2.008); 16 |
| GST | | | |
| C-peptide fold increase | Mean (SD); n | 1.05 (0.224); 20 | 2.08 (0.654); 15 |
| IVGTT | | | |
| kG | Mean (SD), n | – | -1.71 (0.692); 16 |
| AIR _{glu} | Mean (SD), n | – | 16.97 (19.292); 16 |
| OGTT | | | |
| Normal (glucose <140 mg/dL) | n (%) | – | 4 (19) |
| Impaired (glucose 140-199 mg/dL) | n (%) | – | 7 (33.3) |
| Diabetic (glucose >199 mg/dL) | n (%) | – | 5 (23.8) |
| Missing | n (%) | – | 5 (23.8) |

Source: UIH-002 CSR Tables 14.1.3 and Listing 16.2.6a

Dose-Response Analysis

The summary of administered total dose and number of transplants with islets is provided in Table 4. Overall, 20 patients were treated up to 1 to 3 allogeneic islets transplant.. Eight patients (40%) underwent single transplant, 10 patients (50%) underwent two separate transplants, and the remaining two (10%) were infused on three separate occasions. The mean overall administered dose was 12014 IE/kg. The average total dose for subject treated with single, double and triple infusion of islet was 7049 IE/kg, 13157 IE/kg and 23701 IE/kg, respectively (Table 8). There is no clear dose-response relationship for HbA1c and C-peptide (Figure 7). Most patients at all dose levels had achieved target HbA1c levels ($\leq 6.5\%$) and all but 1 patient had achieved target C-peptide levels (≥ 0.5 ng/mL) at 1 year after last transplant.

Figure 6. Blood Glucose Levels from Baseline through 1 Year after First Transplant (Study UIH-002)



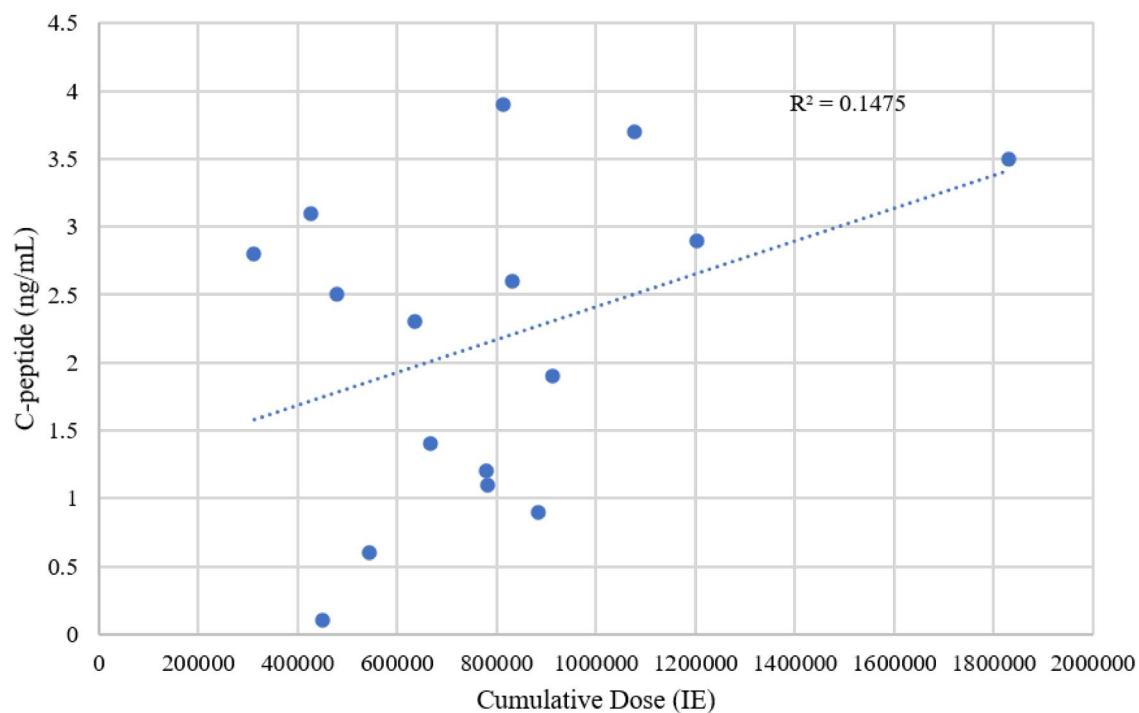
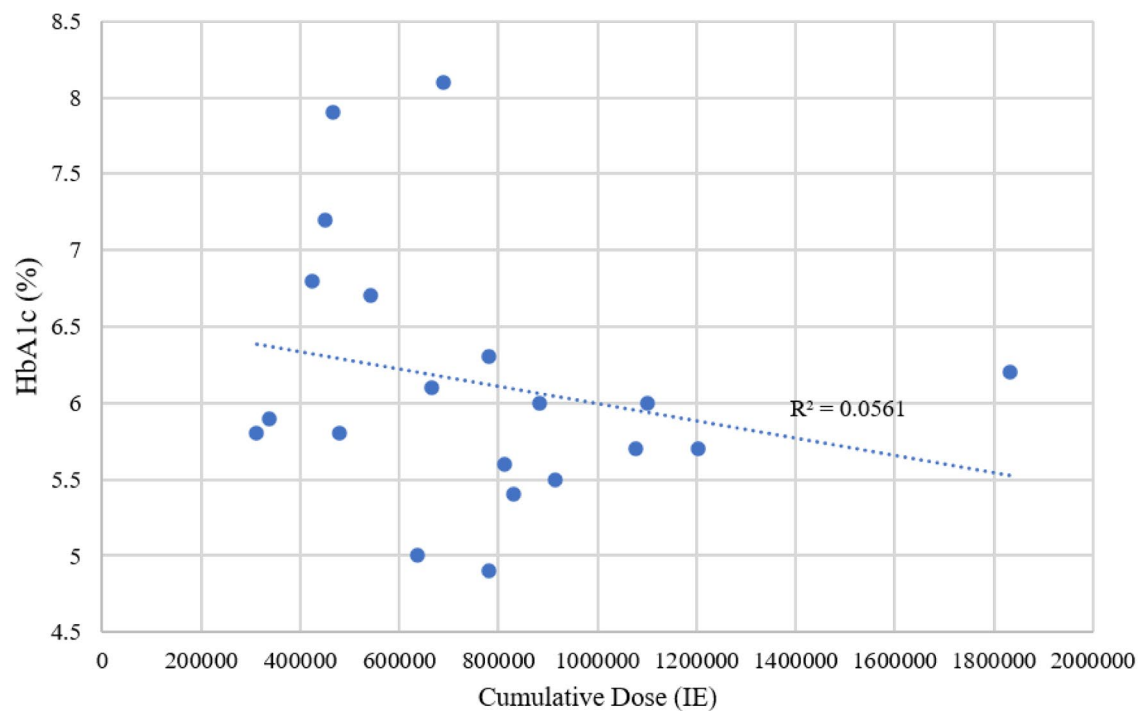
Source: UIH-002 CSR [Table 14.3.15](#) and [Listing 16.2.8b](#)

Table 8. Summary of Administered dose (UIH-002)

| Dosing Regimen | Mean Administered Total Dose (IE/kg) |
|-------------------------|--------------------------------------|
| Single transplant (n=8) | 7049 (5097-9579) |
| 2 transplants (n=10) | 13157 (10250-16850) |
| 3 transplants (n=2) | 23701 (19002-28400) |
| Overall patients (N=20) | 12014 (5097-28400) |

Source: Prepared by Reviewer

Figure 7. HbA1c (%) and C-Peptide Level at 1 Year after Last Transplant, by Dose (Study UIH-002)



Source: UIH-002 Listings [16.2.6a](#) and [16.2.6d](#)

Reviewer Comments: For patient who received multiple infusion, the average inter-dose interval between the first and the second infusion was 304 ± 293 days (range 39 to 955 days), and inter-dose interval between the second and third infusion was 1046 ± 940 days (range 381-1710 days). The mean %HbA1c level at 1 year after islet transplant reduced to 6.12% (~18% lower than baseline). The mean level of fasting C-peptide was higher than the proposed target level of 0.5 ng/mL. A weak trend for dose-response relationship was noted for C-peptide and Hb1Ac. A higher inter-patient variability and no strong dose-response relationship is observed in this clinical study.