Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

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CellTrans

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Proposed Indication

- [Donislecel] is an allogeneic pancreatic islet cellular therapy indicated for the treatment of brittle Type 1 diabetes (labile diabetes) in adults whose symptoms are not well controlled despite intensive insulin therapy.

Diabetes

- Type 1 Diabetes Mellitus (T1DM) results from autoimmune destruction of pancreatic islet cells
  - Hyperglycemia
    - Short-term
    - Long-term complications
  - Hypoglycemia

Brittle Diabetes

Brittle diabetes represents the most severe phenotype of high glucose variability. Historically, brittle diabetes was defined as severe instability of blood glucose levels with frequent and unpredictable episodes of hypoglycemia and/or diabetic ketoacidosis (DKA) that disrupt life activities, often requiring frequent and/or prolonged hospitalizations. Given the imprecision of the term "brittle" diabetes, it is no longer commonly used, and instead, clinicians focus on the individual problem, recurrent DKA or severe hypoglycemia.

https://www.uptodate.com/contents/approach-to-the-adult-with-brittle-diabetes-or-high-glucose-variability?search=brittle%20diabetes&source=search_result&selectedTitle=1~19&usage_type=default&display_rank=1

Severe Hypoglycemic Event (SHE)

An event with symptoms compatible with hypoglycemia in which the patient required the assistance of another person, and that was associated with either a blood glucose level < 50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration

Clinical Studies

UIH-001 (Phase 1/2) and UIH-002 (Phase 3)

- The primary evidence for clinical efficacy and safety comes from 2- single arm open-label studies

- Comparisons are made to the natural history of type 1 diabetes and experience with whole pancreas transplantation as external controls.

Inclusion Criteria

UIH-001

- Reduced awareness of hypoglycemia, and
- Metabolic lability/instability, characterized by 2 or more episodes of documented severe hypoglycemia

OR

- 2 or more hospital visits for DKA over the last year, and
- Despite efforts at optimal glucose control, progressive secondary complications of diabetes

UIH-002

- At least 1 episode of severe hypoglycemia in the past 3 years, and
- Reduced awareness of hypoglycemia

Endpoints

UIH-001

- Success – insulin independence
- Partial success – reduction in insulin requirement, HbA_{1c}, hypoglycemic episodes
- Failure – absence of insulin secretion

UIH-002

- Primary composite – $HbA_{1c} \leq 6.5\%$ at Day 365 and free of severe hypoglycemic events (SHE) from Day 23-365, following the first and last transplant
- Secondary – absence of exogenous insulin injection reported at Day 365

Results

Subjects

- Type 1 Diabetes
- Female (80%)
- Caucasian
  - 1 Native American
- 1 Hispanic

Baseline Diabetes Characteristics

UIH-001 (N = 10)	Mean	SD	Min	Max
Age at diagnosis (years)	18.4	13.5	6	53
Time since diagnosis (years)	28	9.8	10	41
Age at treatment (years)	46.4	10.2	35	63
Baseline insulin (units/kg/day)	0.52	0.14	0.25	0.68

UIH-002 (N = 20)	Mean	SD	Min	Max
Age at diagnosis (years)	17.4	13	1	39
Time since diagnosis (years)	29.4	13.4	9	53
Age at treatment (years)	46.9	12.5	21	67
Baseline insulin (units/kg/day)	0.47	0.14	0.14	0.78

Number of Transplants Received

Number of Transplants Subject Received	UIH-001 Subjects N=10	UIH-002 Subjects N=20	Total Transplants
1	3	8	**11**
2	2	10	**24**
3	5	2	**21**
Total	-	-	**56**

Total Duration of Follow-up

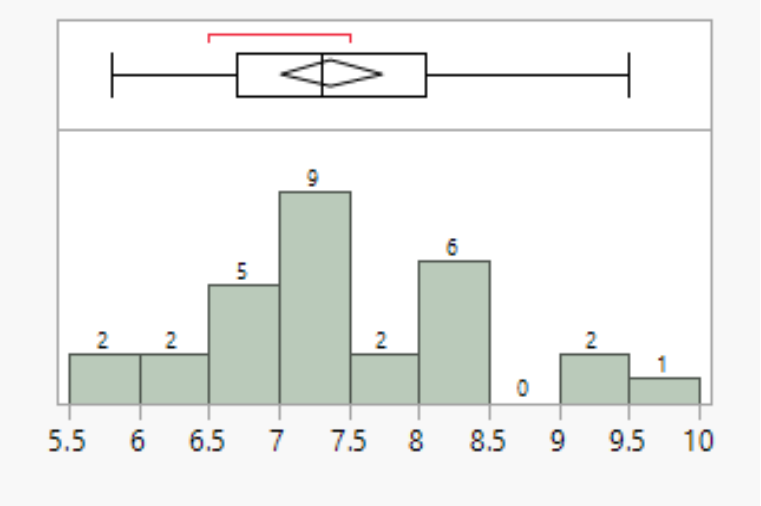
Total Duration Subjects Followed (years)	N	Mean	Min	Max
UIH-001	10	7.8	1.5	13
UIH-002	20	4.7	0.3	10.7

Efficacy

Applicant's Primary Efficacy Endpoint

Outcome	Main Group N=30
Success n (%)	19 (63.3)
Success ($HbA_{1c} \leq 6.5\%$ + Free of SHE) 95% C.I.	44, 80
Failure $HbA_{1c} > 6.5\%$ n (%)	5 (16.7)
Failure Any SHE n (%)	7 (23.3)

HbA_{1c} (%) prior to the First Transplant



N[a]	Mean	Min	Max
29	7.4	5.8	9.5

[a] One subject did not have a baseline HbA_{1c} reported

Severe Hypoglycemic Event (SHE)

An event with symptoms compatible with hypoglycemia in which the patient required the assistance of another person, and that was associated with either a blood glucose level < 50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration

SHE Events Prior to First Transplant

UIH-001 and UIH-002

# SHE	# Subjects N=30
0	25
1	2
2	1
3	1
4	1
Total	**30**

Goal of Islet Cell Transplant

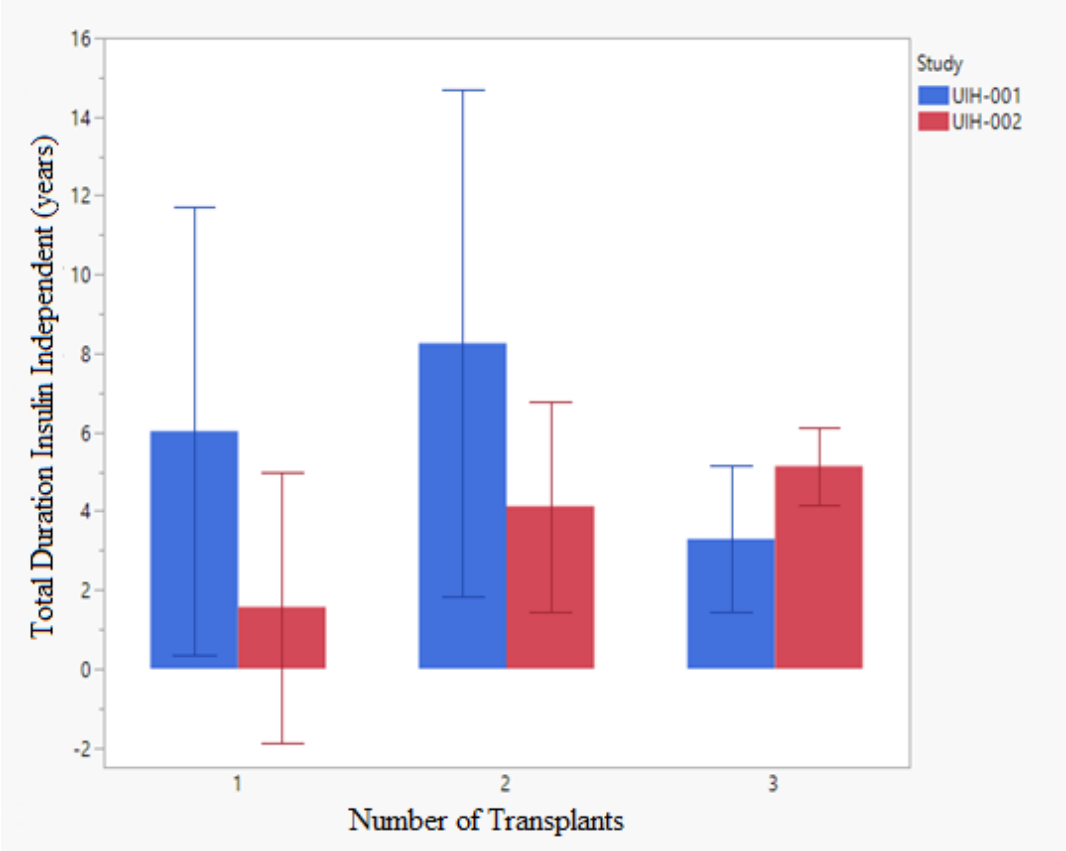
- Restitution of endogenous insulin
- Improvement or normalization of glycemic control

Total Duration of Insulin Independence

Total Duration Insulin Independent (years)	**N**	**Mean**	**Min**	**Max**
UIH-001	10	5.1	0.24	12.8
UIH-002	20	3.2	0	9.9

Insulin Independence by Number of Transplants

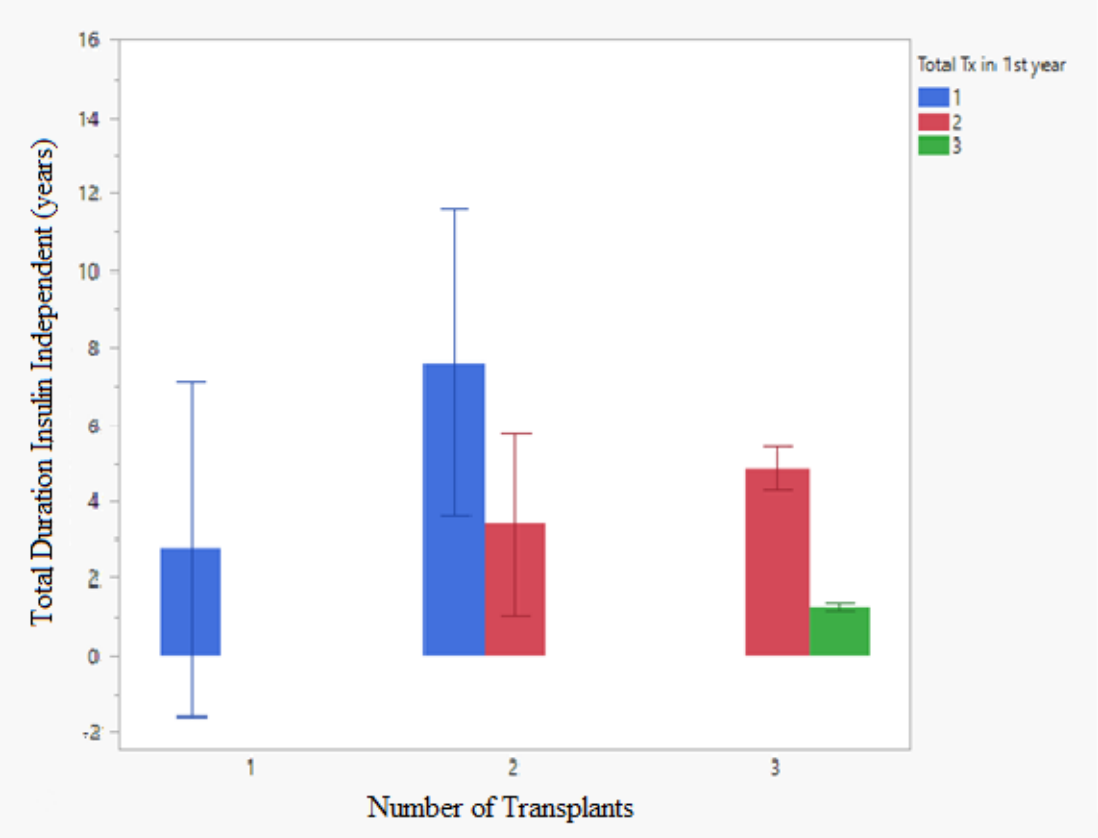
Comparison by Number of Transplants in 1st Year



Mean ± SD

Insulin Independence by Number of Transplants

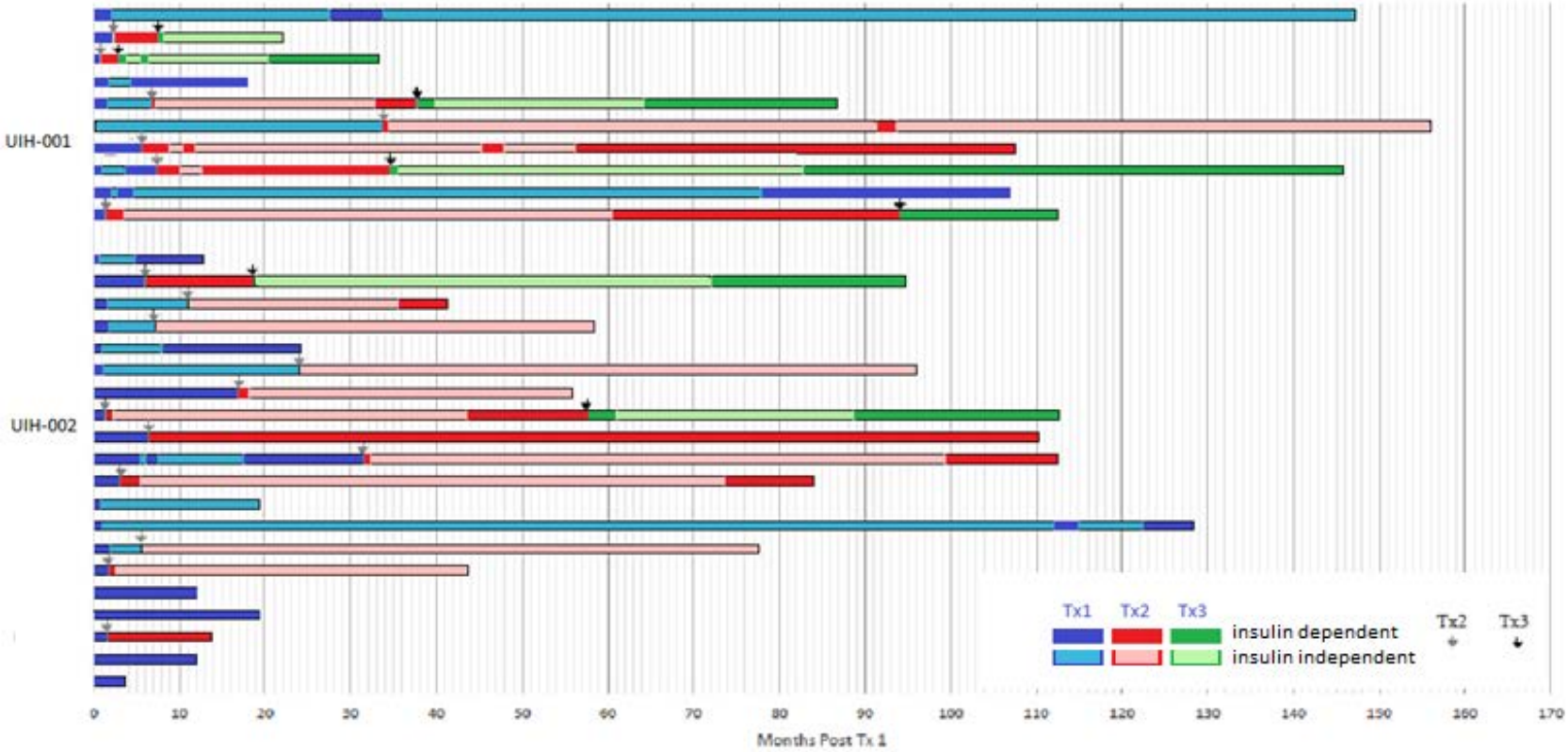
Comparison by Number of Transplants in 1st Year



Mean ± SD

Outcome

Individual Subjects



Efficacy Conclusion

- Insulin independence for > 1 year in 21 of 30 subjects
- Expected benefit of absence of SHE during period of insulin independence

Safety

Adverse Events

Adverse Event Severity	UIH-001	UIH-002	Total
Death	0	1	**1**
Life-Threatening	4	7	**11**
Severe	46	78	**124**
Moderate	161	259	**420**
Mild	513	831	**1344**
“Missing”	92	50	**142**

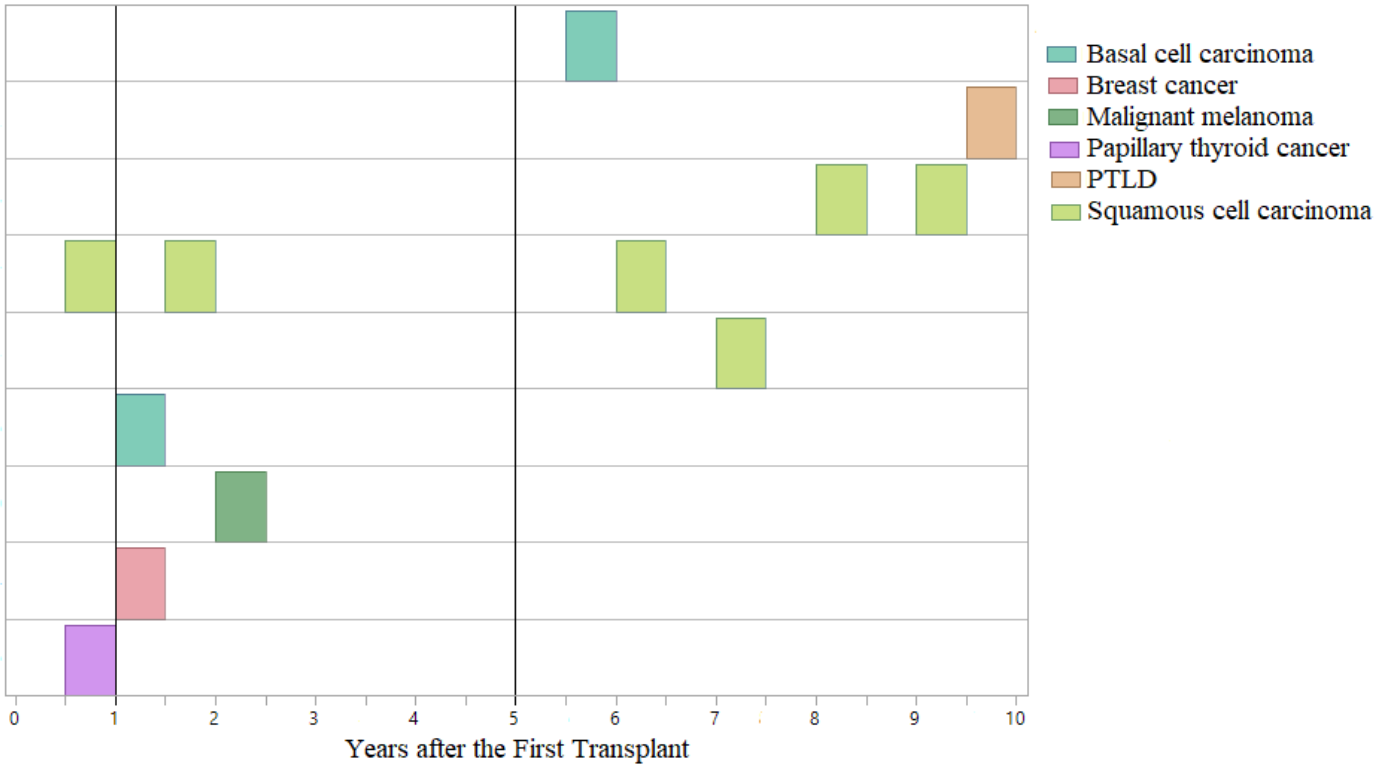
Procedural Complications

- 3 of 30 subjects (10%) experienced 4 serious procedure-related adverse events
  - 1 liver laceration and vascular injury during 2nd surgery requiring emergency surgery
  - 2 hepatic hematomas

- 2 of 56 transplants (3.6%) with reported elevated portal pressures
  - 1 subject had a final portal pressure of 22 mmHg, the procedure was completed
  - 1 subject had an elevated portal pressure during the procedure and did not receive the entire transplant

Adverse Events Associated with Immunosuppression

Time from First Transplant to Detection of Cancer



Infections

- 1 subject (3%) who received only one transplant, died from sepsis and multi-organ failure in the second year after transplant

- 178 AEs of infection were reported for 26 of 30 subjects (86.7%): 1 life-threatening (urosepsis), 12 severe, 94 moderate, 59 mild, and 12 without attribution (missing) that included 2 episodes of pneumonia, 2 of herpes, and 1 of cellulitis

Renal Function

- 6 (20%) of 30 subjects had a persistent decrease in renal function from mild to moderate, using eGFR at 1 year after the first transplant.

- 6 (20%) of 30 subjects had new onset microalbuminuria, and 3 (10%) had new onset macroalbuminuria at 1 year after the first transplant.

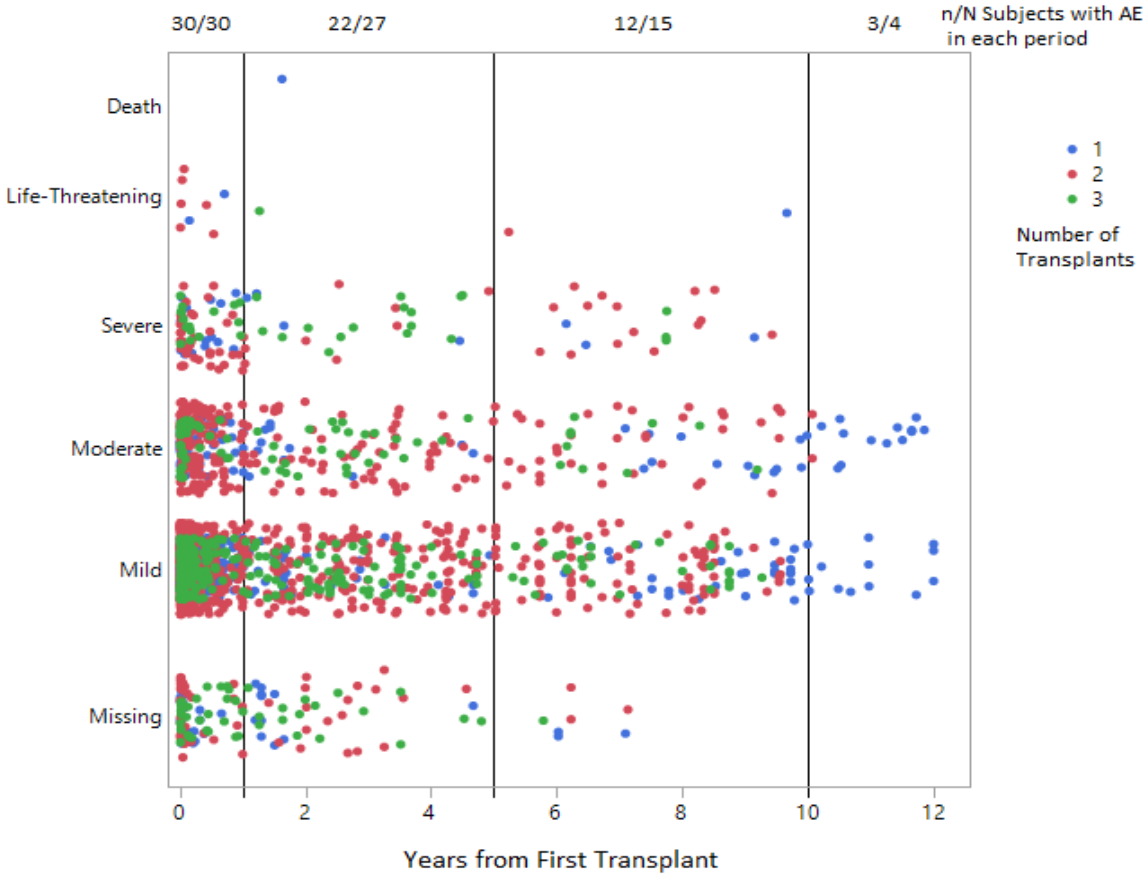
All Adverse Events

- A total of 1,319 adverse events occurred during the first year after the first transplant: 8 life-threatening, 75 severe, 240 moderate, 906 mild, and 90 not specified.

- In Years 2 through 5 after the first transplant, there were a total of 452 adverse events: 1 death, 1 life-threatening, 28 severe, 106 moderate, 271 mild, and 45 not specified. Twenty-four (24) subjects contributed data to the safety data base after the first year.

- Five (5) or more years after the first transplant, there was a total of 271 adverse events: 2 life-threatening, 21 severe, 74 moderate, 167 mild, and 7 not specified. Twelve (12) subjects contributed to the safety data base after 5 years.

Occurrence of Adverse Events



Safety Conclusion

- Procedurally related adverse events were not unexpected and were consistent with those described for other islet cell programs.

- Immunosuppression related adverse events were not unexpected and were consistent with those described for patients receiving whole pancreas transplantation.

Support for Benefit Assessment Based on Insulin Independence

- Using objective versus subjective measures
  - Stated as an alternative endpoint in 2009 Guidance
- Primary efficacy endpoint for UIH-001, secondary for UIH-002
- Product requires donated cadaveric pancreata
- Studies took decades – not likely to be redone
- Orphan indication

Benefit-Risk