

I concur with this review. M. Serabian 07/19/21

I concur with this review. S. Sanduja 07/19/21

FOOD AND DRUG ADMINISTRATION
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PRODUCT:	Donislecel-jujn; LANTIDRA (Purified allogeneic islets of Langerhans for transplant)
APPLICANT:	CellTrans Inc.
PROPOSED INDICATION:	Treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia (neuroglycopenia requiring active intervention from a third party) despite intensive diabetes management.
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EXECUTIVE SUMMARY:

LANTIDRA (donislecel-jujn) is a cell suspension consisting of purified allogeneic pancreatic islets of Langerhans formulated in supplemented transplant medium. The purported mechanism of action of LANTIDRA is pulsatile secretion of multiple

hormones by endocrine cells within the islets in response to increases and decreases in blood glucose (BG) levels.

No nonclinical studies were conducted with LANTIDRA. Instead, the applicant referenced multiple publications and one manuscript in the BLA submission that evaluated biological activity, local (liver) distribution, and the local (liver) safety of transplanted allogeneic or syngeneic islets in combination with various immunosuppressive agents in diabetic rodent (mice, rats) and nonhuman primate (NHP) models. Data from selected citations are summarized in this review memo. The findings of these studies support inclusion of immunosuppression as a critical component for successful islet engraftment and survival following transplant in diabetic animals. The administration of various FDA-approved immunosuppressive agents that constitute the Edmonton Protocol regimen, as well as other concomitant medications prescribed in the proposed label, provided support for the survival and subsequent biological activity of the transplanted islets.

No genotoxicity, carcinogenicity, or developmental and reproductive toxicity (DART) studies were conducted with LANTIDRA.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

There are no nonclinical deficiencies identified in this submission. There are no outstanding requests for additional nonclinical data for evaluation of LANTIDRA. The nonclinical information provided in the BLA submission supports approval of the licensure application.

Formulation and Chemistry:

LANTIDRA (donislecel-jujn) is a cellular therapy comprised of islets of Langerhans obtained from the pancreas of deceased adult human donors. The islets contain the following endocrine cell subtypes: glucagon-producing α -cells (b) (4) insulin-producing β -cells (b) (4) pancreatic peptide-producing (PP)-cells and somatostatin-producing δ -cells (b) (4) and ghrelin-producing ϵ -cells (b) (4). The drug product is a suspension of purified allogeneic islets of Langerhans formulated in Connaught Medical Research Laboratories (CMRL) 1066 Transplant solution supplemented with 2-[4(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES; 10 mM) and human serum albumin (0.5% final concentration). LANTIDRA is packaged in a sterile, single-use infusion bag and is administered within 6 hours from the time of product release.

Abbreviations

ALG	Anti-Lymphocyte Globulin
AUC	Area under the Curve
BG	Blood Glucose
FK506	Tacrolimus
GLP-1	Glucagon-Like Peptide-1
GTT	Glucose Tolerance Test
HbA1c	Glycosylated Hemoglobin A1c
IE	Islet Equivalent
IM	Intramuscular
IP	Intraperitoneal
IV	Intravenous
IV-GTT	Intravenous Glucose Tolerance Test
IP-GTT	Intraperitoneal glucose tolerance test
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
ROS	Reactive Oxygen Species
STZ	Streptozotocin
T1DM	Type 1 Diabetes Mellitus

Related File(s)

IND #9336; ‘Allogeneic Islet Cells (Human, NIAID/DAIT) Administered via Intraportal Infusion; and Immunosuppressive Therapy’; National Institute of Allergy and Infectious Diseases (NIAID); Type 1 Diabetes Mellitus; ACTIVE

IND #11228; ‘Allogenic Islets Cells (Human, University of Chicago) Administered via Intraportal Infusion; and Immunosuppressive Therapy’; Piotr Witkowski, MD, PhD (UC, Chicago); Type 1 Diabetes Mellitus; ACTIVE

IND#11807; ‘Allogeneic Islet Cells (Human, University of Illinois) Administered via Intraportal Infusion; and Immunosuppressive Therapy’; CellTrans Inc.; Type 1 Diabetes Mellitus; ACTIVE

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INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) results from autoimmune destruction of the insulin-producing β -cells within the pancreatic islets of Langerhans^{1,2}. As a result of β -cell loss, secondary abnormalities in glucagon-secreting cells occur, which can cause metabolic instability and extreme glycemic variability. Short-term complications from an inadequate amount of insulin include hyperglycemia and diabetic ketoacidosis which can result in diabetic coma and/or death. Long-term, persistent hyperglycemia is associated with microvascular disease and the development of retinopathy, neuropathy, and nephropathy. The current standard-of-care for treatment of patients with T1DM is exogenous insulin replacement therapy^{3,4}.

Although insulin replacement is the standard of care for this clinical population, continuous monitoring is necessary to maintain tight glycemic control and avoid hypoglycemia and other potential life-threatening complications. Intrahepatic transplantation of allogeneic islets has resulted in restoration of the critical insulin producing β -cells^{5,6,7}. The Edmonton Protocol, in which human cadaveric islets were transplanted via the hepatic portal vein in patients with T1D that were exposed to an immunosuppression regimen of daclizumab for induction and sirolimus and tacrolimus for maintenance, was a significant advance in the transplantation field.⁸ Of note is that in

¹ Pathak V, et al. Therapies for type 1 diabetes: current scenario and future perspectives. *Clinical Medicine Insights: Endocrinology and Diabetes* 2019; 12:1-13.

² McCall AL and Farhy LS. Treating type 1 diabetes: from strategies for insulin delivery to dual hormonal control. *Minerva Endocrinol* 2013; 38:145-163.

³ Steffes MW, et al. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care* 2003; 26:832-836.

⁴ The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993. 329(14): 977-86.

⁵ Bottino R, et al. The Future of islet transplantation is now. *Front Med* 2018; 5: 2175-2184.

⁶ Moede T, et al. Alpha cell regulation of beta cell function. *Diabetologia* 2020; 63:2064-2075

⁷ Rickels MR. Recovery of endocrine function after islet and pancreas transplantation. *Curr Diab Rep*. 2012; 12(5):587-596.

⁸ Shapiro AJ, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen (Daclizumab, Sirolimus and Tacrolimus). *N Engl J Med* 2000; 343:230-238.

March 2018, daclizumab was voluntarily withdrawn from the global market due to reports from Europe of severe encephalitis observed in patients with multiple sclerosis⁹. Based on these clinical data, this Protocol was modified to include an immunosuppression regimen of basiliximab, sirolimus, and tacrolimus¹⁰. The applicant reported that they successfully reproduced the efficacy data observed with use of the Edmonton Protocol, showing functional islet engraftment, and resulting in long-term sustained glycemic control in this patient population^{5,11,12}.

NONCLINICAL STUDIES

PHARMACOLOGY STUDIES

Summary List of Pharmacology Studies

No pharmacology studies with LANTIDRA were conducted. The applicant provided publications and one manuscript in Module 4 of the BLA that report the findings from nonclinical pharmacology studies evaluating the biological activity of allogeneic islets alone or in combination with one or more clinically relevant immunosuppression agents. In addition to the manuscript, this reviewer has summarized selected publications that support the overall purported mechanism of action and biological activity of LANTIDRA.

In vitro Studies

Study Number	Publication/Manuscript Citation
1	(b) (4) <i>Unpublished Manuscript</i> Note: This manuscript summarizes <i>in vitro</i> and <i>in vivo</i> studies.

⁹ <https://www.fda.gov/drugs/drug-safety-and-availability/fda-working-manufacturers-withdraw-zinbryta-market-united-states>

¹⁰ <https://clinicaltrials.gov/ct2/show/NCT00566813>.

¹¹ Gangemi A, et al. Islet transplantation for brittle type 1 diabetes: The UIC Protocol. *Am J Transplant* 2008; 8:1250-1261.

¹² Qi M, et al. Five-year follow-up of patients with type 1 diabetes transplanted with allogeneic islets: The UIC experience. *Acta Diabetol* 2014; 51: 833-843.

In vivo Studies

Study Number	Publication/Manuscript Citation
1	(b) (4) <i>Unpublished Manuscript</i> Note: This manuscript summarizes <i>in vitro</i> and <i>in vivo</i> studies.
2	Yasunami Y et al. FK506 as the Sole Immunosuppressive Agent for Prolongation of Islet Allograft Survival in the Rat. <i>Transplantation</i> 1990; 49:682-686
3	B Scharp DW et al. Transplantation of Islets of Langerhans in Diabetic Rhesus Monkeys. <i>Surgery</i> 1975; 77:100-5
4	Qi M et al. Implementation of a Simplified Method of Islet Isolation for Allogeneic Islet Transplantation in Cynomolgus Monkeys. <i>Pancreas</i> 2014; 43: 226-235
5	Gray BN and Watkins E Jr. Prevention of Vascular Complications of Diabetes by Pancreatic Islet Transplantation. <i>Arch Surg</i> 1976; 111: 254-257

Overview of Pharmacology Studies

Overview of in vitro Studies

(b) (4)

1 page has been determined to be not releasable: (b)(4)

Overview of in vivo Studies

Study #1

(b) (4)

unpublished manuscript

(b) (4)

Study #2

Yasunami Y et al. FK506 as the Sole Immunosuppressive Agent for Prolongation of Islet Allograft Survival in the Rat. Transplantation 1990; 49:682-686

Objective: To determine the effect of tacrolimus on islet allografts in a diabetic rat model.

Methods: A total of 1500 fresh islets isolated from WKA/Qdj (RT1^u) rats were transplanted into the liver of Lewis rats (RT1^l) exposed to STZ via the portal vein. Following transplant, the rats were subcutaneously injected with tacrolimus (0, 0.1, 0.32, 1.0, or 3.2 mg/kg/day) for seven consecutive days. Islet function was determined by non-fasting (NF) glucose levels and body weights collected at pre- and post-transplant. Rejection of islet allograft was considered to have occurred when two consecutive plasma glucose levels exceeded 250 mg/dL, with associated weight loss. When more than two consecutive plasma glucose levels exceeded 400 mg/dL post-transplant the animal was sacrificed. Sections of the liver were examined microscopically for overall structure (hematoxylin-eosin staining), as well as for presence of insulin, glucagon, and somatostatin (markers of islet engraftment and function).

Note:

- The proposed product label specifies (at the discretion of the physician) administration of a calcineurin inhibitor, such as tacrolimus (1 mg/patient by mouth) immediately pre-transplant. The label also specifies that the "... maintenance immunosuppression regimen should be steroid-free and typically should include a combination of a calcineurin inhibitor and an mTOR inhibitor or appropriate alternatives, at the discretion of the physician. Maintenance immunosuppression must be continued permanently to prevent islet graft rejection. Trough levels of maintenance immunosuppressant drugs should be monitored at the discretion of the physician and adjustments in dose should be made to maintain appropriate levels in the blood."

Results:

Transplanted/no tacrolimus - The mean survival time (MST) of the islet allografts was 4.4 ±1.1 days (n=5)

Transplanted/0.1 mg tacrolimus/kg/day - The MST of the islet allografts was 7.2 ±0.8 days (n=5).

Transplanted/0.32 mg tacrolimus/kg/day - The MST of the islet allografts was 45.3 ±23.1 days (n=6). The islet allografts in 4/6 animals survived; the rats were normoglycemic for greater than 60 days post-transplant. Following sacrifice at 60 (n=2) or 120 (n=2) days, the allogeneic islets were present in the liver of all animals, and mononuclear cells were occasionally detected adjacent to the allograft. Immunohistochemical staining revealed well-granulated β-cells in all allografts. The transplanted islet allografts survived 9 days in one animal (1/6) and 23 days in one animal (1/6).

Transplanted/1.0 mg tacrolimus/kg/day - The MST of the islet allografts was 54.4 ± 8.8 days (n=5). Allograft rejection occurred in 2/5 animals at 40 days and 52 days post-transplant, with plasma glucose levels ranging from 150 and 350 mg/dL. The remaining 3/5 animals were sacrificed at 60 days post-transplant; the allograft morphology was similar to the 60-day findings in the animals administered 0.32 mg tacrolimus/kg/day.

Transplanted/3.2 mg tacrolimus/kg/day - The MST of the islet allografts was 14.3 ± 6.5 days (n=3). The plasma glucose levels for all animals returned to pre-transplant levels by 21 days post-transplant. Allogeneic islets were present in the liver of all animals, with no mononuclear cell infiltration. Immunohistochemical staining revealed weaker staining for insulin, and glucagon, and somatostatin.

The authors conclude that these data suggest that short-term administration of tacrolimus at dose levels of 0.32 or 1.0 mg/kg/day post-transplant result in significant allograft survival. However, higher dose levels of tacrolimus (3.2 mg/kg/day) were deleterious to allograft survival.

Reviewer's Comment:

- The conclusion of the authors is reasonably supported by the reported data. These data provide overall support for the administration of a calcineurin inhibitor, such as tacrolimus, in the target patient population.

Study #3

Scharp DW et al. Transplantation of Islets of Langerhans in Diabetic Rhesus Monkeys. Surgery 1975; 77:100-5

Objective: To evaluate the feasibility of intraportal transplant of allogeneic islet cells in a nonhuman primate (NHP) diabetic model.

Methods: Islets were isolated using a digestion-filtration technique from pancreata collected from healthy rhesus NHPs. Recipient NHPs (n=5) underwent a 70% distal pancreatectomy (including a splenectomy), followed by IV infusion of STZ. Fasting blood samples were collected daily to monitor the development of diabetes. When repeat IV-GTT testing confirmed the diabetic status of the animal (ketoacidosis half-time [KT $\frac{1}{2}$] of less than 1.0 %/min)¹³, purified islets (islet number was not specified) were administered via the portal vein. The recipient NHPs also received rabbit anti-monkey lymphocyte globulin (10 mg/kg/day) in combination with either methylprednisolone (0.8 mg/kg/day) or azathioprine (2.5 mg/kg/day).

Results: Compared to their diabetic state pre-transplant, all recipient NHPs exhibited decreased polyphagia, polydipsia, polyuria, and hyperglycemia and no decrease in body weight immediately post-transplant. IV-GTT testing results showed that nine normal monkeys demonstrated a biphasic insulin release pattern similar to man (mean KT $\frac{1}{2}$ of

¹³ KT $\frac{1}{2}$ - the percent decrease in the BG level per minute. Per the publication, the KT $\frac{1}{2}$ for healthy NHPs is 3.6%/min.

glucose responses: 3.6%/min). IV-GTT testing, performed at one week post-transplant, showed that peripheral insulin levels remained low but exhibited an early response to the glucose challenge in all recipient NHPs (mean $KT^{1/2}$ of glucose responses: 1.52%/min) compared to their pre-transplant diabetic state (mean $KT^{1/2}$ of glucose responses: 0.71%/min). In longer follow-up of three transplanted NHPs, one NHP was reported to be normoglycemic at 6 weeks post-transplant, and a repeat IV-GTT testing at 4 weeks post-transplant showed a slight improvement compared to the Week 1 value. Two NHPs were normoglycemic at 3 weeks post-transplant; however, one of these animals died due to bronchopneumonia (time of death post-transplant was not specified).

Note:

- A total of five NHPs were evaluated; however, the follow-up/survival for only three NHPs was reported.

The authors conclude that these data suggest that intraportal transplant of allogeneic islets using a digestion-filtration technique, similar to an aspect of the commercial manufacturing process, resulted in normoglycemia in the NHP recipients with diabetes.

Reviewer's Comment:

- Although the study duration was not specified, the parameters appear to be evaluated at different earlier time points post-transplant. In addition, the number of islets transplanted into each animal was not provided. Thus, it is unclear whether the determination of graft viability and function long-term was characterized. Additional missing information included: the sex, age, and initial body weight of each donor and recipient NHP. However, this was a preliminary study, thus the resulting data supported the feasibility of using this diabetic animal model to further assess allogeneic islet transplantation.

Study #4

Qi M et al. Implementation of a Simplified Method of Islet Isolation for Allogeneic Islet Transplantation in Cynomolgus Monkeys. *Pancreas* 2014; 43: 226-235

Objective: To evaluate intraportal allogeneic islet cell transplants in an NHP diabetic model.

Methods: Islets were isolated using a digestion-filtration technique from pancreata collected from healthy cynomolgus NHPs (10 males and 1 female). STZ-induced diabetic NHPs (2 males and 3 females) with persistent hyperglycemia (greater than 250 mg/dL within 48 hours after IV infusion of STZ) were transplanted via the mesenteric vein, followed by administration of the Edmonton Protocol immunosuppression regimen (daclizumab [1 mg/kg], sirolimus [24-hour target blood drug level of 10-15 ng/mL], and tacrolimus [24-hour target blood drug level of 4-6 ng/mL]). Blood samples were collected at various time points for measurement of each immunosuppression agent.

The islet cell dose level (IE/kg) was 8000 (Recipient #1), 18,000 (Recipients #2-3), 22,000 (Recipient #4), and 21,875 (Recipient #5). IV-GTT testing was performed: 1) at baseline (pre-diabetic, Recipients #1-5), 2) after STZ infusion (Recipients #1-5), and 3) at 60 days post-transplant (Recipients #2-4). Graft dysfunction was defined as a NF BG level greater than 200 mg/dL for two consecutive days. Liver biopsies (right lobe) were obtained at different time points post-transplant from several animals for histopathology: Recipient #1 at Week 1 and Month 1, Recipient #2 at Day 103, and Recipient #3 at Month 6). Histopathology included assessment of morphology (hematoxylin-eosin staining), islet engraftment and function (insulin-glucagon staining), and immune cell infiltration (CD11b⁺, CD3⁺ and CD8⁺ cells). A biopsy of the pancreas was collected from Recipient #4 at Month 6 to confirm the toxic effect of STZ on the islets of the native pancreas.

Notes:

- Per the publication, the Edmonton Protocol immunosuppression regimen, which included daclizumab, was administered in clinical trials conducted under IND #11807^{8,9}. However, since daclizumab is no longer commercially available, the proposed product label specifies that a non-depleting monoclonal anti-IL-2 receptor antibody (e.g., basiliximab) should be administered pre-transplant and post-transplant.
- A total of five NHPs were included in the study. However, it appears that since Recipient#5 displayed allograft rejection by Day 57, no other biopsy data were collected. In addition, the survival interval for each animal was not specified.

Results: All five recipient monkeys displayed BG levels greater than 250 mg/dL within 48 hours after STZ injection. Based on the AUC data from the IV-GTT profile, Recipient #1 displayed normal BG levels on Day 1 post-transplant but became hyperglycemic and required exogenous insulin by Day 10. Immunohistochemical assessment of the Week 1 liver biopsy collected from this animal showed insulin- and glucagon-positive islets; however, degenerated islets and inflammatory CD3⁺ CD11b⁺ cell infiltrates were detected in the Month 1 biopsy. This animal was sacrificed 30 days post-transplant.

Recipients #2-5 achieved prolonged normoglycemia (57-232 days), with positive C-peptide secretion, post-transplant. The AUC data from the IV-GTT testing showed a normal BG clearance profile and C-peptide secretion in Recipients #2-4 at Day 6 post-transplant. Recipient #2 demonstrated stable allograft survival (insulin- and glucagon-positive islet allograft with minimal peri-islet inflammatory infiltration at Day 103, without administration of exogenous insulin, up to Day 210 before graft rejection was observed. Recipients #3 and #4 achieved prolonged allograft survival (Days 231 and 171, respectively) post-transplant. Histopathology confirmed a well-granulated insulin-positive islet allograft in the liver of both NHPs, but no insulin-positive islets in the native pancreas were detected in Recipient #4 at Month 6. Recipient #5 exhibited

allograft rejection at Day 57; per the authors, this possibly was due to the low blood levels of tacrolimus.

The authors conclude that these data suggest that intraportal transplant of sufficient numbers of allogeneic islets in diabetic NHPs exposed to the Edmonton Protocol immunosuppression regimen resulted in restoration of normoglycemia.

Reviewer's Comment:

- The conclusion of the authors is reasonably supported by the reported data. These data provide overall support for the safety assessment of LANTIDRA using the Edmonton Protocol original immunosuppression regimen in the early-phase clinical trials conducted under IND#11807, and for an appropriate immunosuppression regimen in combination with intraportal transplantation of LANTIDRA in the target patient population.

Study #5

Gray BN and Watkins E Jr. Prevention of Vascular Complications of Diabetes by Pancreatic Islet Transplantation. Arch Surg 1976; 111: 254-257

Objective: To evaluate the effect of transplanted islet allografts on prevention of renal and ophthalmic complications in a diabetic rat model.

Methods: Allogeneic islets were isolated from male Wistar-Lewis rats. Male Fischer rats were IV injected with STZ (65 mg/kg) to induce a diabetic state. Transplantation (600 intact islets) into the liver (route not specified) was performed at 2-4 weeks after the induction of diabetes. The following groups were included in the study (10 animals/group). The animals were sacrificed at 9 months post-transplant.

Group 1 - Diabetic rats – non-transplanted

Group 2 - Diabetic rats – transplanted in combination with low-dose (4 rats) or high-dose (6 rats) rabbit anti-rat lymphocyte serum

Group 3 - Age-matched healthy male Fischer rats

Following sacrifice, the eyes and kidneys were collected from Groups 1 and 2 (all rats) and the eyes (all rats) and kidneys (three rats) were collected from Group 3.

Histopathology of the eyes determined the presence of new vessel formation and the degree of capillary dilation in the retina. Histopathology of the kidney evaluated: 1) the amount of Periodic Acid Schiff (PAS)-positive material (i.e., basement membranes of glomerular capillary loops and tubular epithelium) deposited in the glomerular mesangium, 2) the degree of thickening of the glomerular afferent arteriole wall and the parietal layer of the Bowman capsule, and 3) renal glomerular diameter.

Results:

Group 1 - 1) NF serum glucose levels were consistently greater than 400 mg/100 mL, 2) increased new vessel formation, significantly greater numbers of retinal capillaries and

vessel dilation in the stratum opticum were observed, 3) subcapsular cataracts were observed, 4) notably increased amounts of PAS-positive material in the glomerular mesangium and a thicker glomerular afferent arteriole wall were observed compared to Groups 2 and 3. In addition, the mean glomerular diameter was considerably larger compared to Group 2.

Groups 2 and 3 - 1) NF serum glucose levels were in the normal range, 2) no significant changes in the retina or kidney were observed, and 3) allogeneic β -cells were detected in the liver in the Group 2 animals compared to Group 3. No cataract formation was detected in the eyes of Groups 2 and 3 animals.

The authors conclude that the transplanted diabetic animals did not exhibit adverse microscopic changes in the retina and kidney that were observed in the non-transplanted diabetic animals.

Reviewer's Comment:

- The conclusion of the authors is reasonably supported by the reported data. These data provide overall support for the intraportal transplantation of LANTIDRA in the target patient population.

SAFETY PHARMACOLOGY STUDIES

No safety pharmacology studies with LANTIDRA were conducted.

PHARMACOKINETIC STUDIES (Intrahepatic Distribution/Persistence of the Graft)

Summary List of Pharmacokinetic Studies

No distribution studies with LANTIDRA were conducted. The applicant provided publications that assessed the distribution and persistence of allogeneic islets in the liver following intraportal transplant in Module 4 of the BLA. This reviewer has summarized selected publications that support the overall purported *in vivo* distribution profile of LANTIDRA following intraportal transplantation.

In vivo Studies

Study Number	Publication Citation
6	Franklin WA, et al. The Fate of Transplanted Pancreatic Islets in the Rat. <i>Am J Pathol</i> 1979; 94:85-96
7	Hirshberg B, et al. Histopathological Study of Intrahepatic Islets Transplanted in the Nonhuman Primate Model using Edmonton Protocol Immunosuppression. <i>J Clin Endocrinol Metab</i> 2002; 87:5424-9
8	Eich T, et al. Positron Emission Tomography: A Real-Time Tool to Quantify Early Islet Engraftment in a Preclinical Large Animal Model. <i>Transplantation</i> 2007; 84: 893-8

Study #6

Franklin WA, et al. The Fate of Transplanted Pancreatic Islets in the Rat. Am J Pathol 1979; 94:85-96

Objective: To assess the distribution and persistence of allogeneic islets in the liver in the absence of immunosuppression agents following intraportal transplantation in diabetic rats.

Methods: The allogeneic islets were obtained from Wistar Furth (WF) rats (donors; 175-225 g). One group of STZ-induced immunocompetent diabetic ACI rats (recipients; 150-175 g) with persistent hyperglycemia (greater than or equal to 400 mg/dL) was administered approximately 1200-1500 islets/rat via intraportal injection. The BG levels were monitored daily until physiologic evidence of allograft rejection was observed (considered as 100 mg/dL higher than the lowest BG level post-transplant).

To determine the time-point post-transplant at which allograft rejection occurred and the effect of islet rejection on liver morphology, the ACI rats (n=2-3) were sacrificed daily in the first week post-transplant, weekly for one month, and at Month 3.

Results:

The transplanted animals were normoglycemic (BG less than 200 mg/dL) within 24 hours; however, hyperglycemia recurred by Day 5 post-transplant. Allogeneic islets were detected in the lumina of the small portal veins at Day 1 post-transplant. By Day 2, small lymphocytes had infiltrated the allograft. These lymphocytes rapidly increased in size and number, and by Day 5 (designated as the time of graft rejection) the allografts appeared to be compressed by large numbers of mononuclear cells with relatively abundant cytoplasm and occasional mitotic figures. These lymphoid infiltrates gradually disappeared and by 4 weeks post-transplant small focal mononuclear cell infiltrates and some fibrous nodules were detected in the portal tracts. At Month 3 post-transplant, inflammatory changes were absent and only rare fibrous nodules were detected in the portal tracts.

The authors conclude that the transplanted allogeneic islets were detected in the lumina of small portal veins by Day 1 post-transplant; however, allograft rejection occurred quickly (by Day 5), possibly as a result of a cell-mediated immune response due to the lack of an immunosuppression regimen.

Reviewer's Comment:

- The conclusion of the authors is reasonably supported by the reported data. These data provide overall support for inclusion of an appropriate immunosuppression regimen in combination with intraportal transplantation of LANTIDRA in the target patient population.

Study #7

Hirshberg B, et al. Histopathological Study of Intrahepatic Islets Transplanted in the Nonhuman Primate Model Using Edmonton Protocol Immunosuppression. J Clin Endocrinol Metab 2002; 87:5424-9

Objective: To determine the distribution profile of allogeneic islets in the liver of immunosuppressed rhesus macaques following intraportal transplantation.

Methods: Allogeneic islets were isolated from rhesus NHPs. Five rhesus NHP recipients underwent a total pancreatectomy, followed by transplantation of approximately 44,000-93,000 IEs via the portal vein¹⁴. The immunosuppression regimen consisted of daclizumab (2 mg/kg), sirolimus (24-hour target trough levels of 10-15 ng/mL), and tacrolimus (24-hour trough levels of 4-6 ng/mL). Islet function was assessed by measurement of daily BG levels and periodic serum arginine-stimulated C-peptide levels. The animals were considered insulin-independent if the BG and C-peptide levels were in the normal range as compared to non-diabetic NHPs and there was no requirement for exogenous insulin.

Each animal was sacrificed upon allograft rejection, as determined by 1) BG levels greater than 200 mg/dL and negative C-peptide levels for 4 consecutive weeks, 2) failure to thrive for any reason, 3) weight loss greater than 15%, or 4) the authors' determination that the animal should be sacrificed. Liver sections were stained with hematoxylin-eosin to enable detection of islets and the presence of peri-islet inflammatory cells, lymphocytes, neovascularization, and other pathological changes. Immunohistochemistry was performed to identify insulin, somatostatin, glucagon, and pancreatic polypeptide in the transplanted islets.

Notes:

- The authors cited other publications for the procedure used to isolate the allogeneic islets, as well as the methods used to induce diabetes and transplant the islets^{14,15}.
- The authors state that the C-peptide secretory response to arginine provides an accurate reflection of β -cell mass.

Results:

Fate of each NHP: 1) one animal died on Day 5 post-transplant due to aspiration pneumonia (NHP #1); 2) one normoglycemic animal was sacrificed on Day 30 post-transplant due to wasting (NHP #2); 3) one animal displayed graft rejection at 2 months

¹⁴ Hirshberg B et al. 2002. Pancreatic islet transplantation using the nonhuman primate (rhesus) model predicts that the portal vein is superior to the celiac artery as the islet infusion site. *Diabetes* 2002; 51:2135-2140.

¹⁵ Kenyon NS et al. Long-term survival and function of intrahepatic islet allografts in rhesus monkeys treated with humanized anti-CD154. *Proc Natl Acad Sci USA* 1999; 96:8132-8137.

post-transplant (NHP #3); and 4) the remaining animals were sacrificed at 3 and 7 months post-transplant (NHPs #4 and #5, respectively).

Islet distribution in the liver: The islets were evenly distributed among the hepatic lobes (right lateral lobe, left lateral lobe, large central lobe, left medial fragment, gallbladder proximal fragment, right medial fragment). The authors reported that one animal displayed even distribution of the allogeneic islets throughout the portal vascular bed. Additional observations included:

NHP #1: No evidence of neovascularization in the liver was noted; cellular degeneration was evident (cytosolic hyalinization, pyknotic nuclei).

NHP #2: An abundant capillary supply and occasional mitotic cells (cell types undergoing mitosis were unknown) were observed in the graft. Intrahepatic islets stained for insulin, pancreatic polypeptide, glucagon, and somatostatin.

NHP #3: Allograft rejection was associated with low tacrolimus levels. A few surviving endocrine cells within a lymphohistiocytic inflammation lesion and a prominent capillary network were observed.

NHP #4: A well-established capillary network in the graft was observed. The allogeneic islets were often adjacent to the portal vein, with a thin endothelial layer separating the islets from the portal vein lumen.

NHP #5: Islet vascularity could not be assessed because the islets were small and sparse. Within the portal triad, there was an islet cell cluster with adjacent localized hepatocellular glycogenosis and alterations in hepatocellular morphology that only occurred in hepatic cords extending from this portal islet to the central vein. The authors state that the long-term consequence of the glycogenosis is unclear.

The authors conclude that: 1) there was even distribution of the allogeneic islets throughout the portal vascular bed and the liver lobes; 2) the allografts developed an abundant vascular supply within 30 days post-transplant; and 3) by 3 months post-transplant, islets had become essentially extra-portal.

Reviewer's Comment:

- The conclusion of the authors is reasonably supported by the reported data. These data provide overall support for inclusion of the (revised) Edmonton Protocol immunosuppression regimen in combination with intraportal transplantation of LANTIDRA in the target patient population.

Study #8

Eich T, et al. Positron Emission Tomography: A Real-Time Tool to Quantify Early Islet Engraftment in a Preclinical Large Animal Model. Transplantation 2007; 84:893-8

Objective: To develop an imaging technique to monitor the survival of transplanted islets in the peri-transplant and early post-transplant phase in immunocompetent, non-diabetic pigs.

Methods:

In vitro study: A total of 300-900 IEs collected from healthy Swedish Landrace pigs were labeled with 2-deoxy-2 (^{18}F fluoro-D-glucose [^{18}F -FDG]) for one hour. The labeled islets were first exposed to different concentrations of glucose (0, 2.7, 5.5 and 11 mM), followed by measurement of the radioactivity (using a well-counter). The radioactivity concentration in islets/radioactivity concentration in the buffer was determined (termed enrichment).

In vivo study: Ten immunocompetent hybrid piglets (13-18 kg) received the ^{18}F -FDG labeled islets (7000 IEs/kg) through the portal vein. A mean 96-min dynamic positron emission tomography and computed tomography (PET/CT) scanning sequence (General Electric; n=5) was acquired in 2D to include the liver (initiated at the start of the transplant and continued for one hour), followed by a 2D whole-body examination to determine any extrahepatic distribution of radioactivity. A 5-minute 3D examination of the liver was then performed, and CT was used for attenuation correction and anatomical correction of the PET findings. Whole-body IV contrast-enhanced CT of the liver was performed after completion of the PET examination protocol.

In addition, a 60-minute 2D scan (Hamamatsu PET scanner; n=5) was performed to include the liver, followed by a 5-minute static examination of the head and bladder. Transmission scans (10-30 minutes) were acquired before each emission scan using a rotating ^{68}Ge point source. Images were reconstructed using a 4-mm Henning filter.

At the end of the examination, the piglets were sacrificed.

Results:

In vitro study: The isolated islets were macroscopically intact, with a purity of greater than 95%. The autoradiogram showed that the islets contained ^{18}F -FDG, but the medium was free of radioactivity. No difference in insulin release was detected between labeled and unlabeled islets. The uptake of ^{18}F -FDG was competitively inhibited by glucose in the incubation medium. The mean enrichment of ^{18}F -FDG into the islets was 0.99 ± 0.32 . The *in vitro* retention of ^{18}F -FDG in the islets was approximately 50% at 2.5 hours.

In vivo study: Imaging evaluations of the liver showed that more than 95% of the radioactivity was confined to the islets at the time of transplant. The mean peak radioactivity within the liver was $54 \pm 5.1\%$ at the end of the transplantation procedure. The distribution of labeled islets in the liver was heterogenous, and primarily in the posterior and anterior lobes. Whole-body 2D imaging showed that at 60-200 minutes

after the start of the transplantation procedure there was no accumulation of radioactivity in the lungs, heart, or brain. This finding suggests that the residual radioactivity detected in these organs was possible released from lysed islet cells in the form of ^{18}F -FDG-6P, but not the native ^{18}F -FDG. Radioactivity in the blood samples was below the detection limit.

The authors conclude that this imaging technology allowed for real-time measurement of islet survival and distribution. The distribution of the ^{18}F -FDG-labeled islet cells in the liver was found to be heterogeneous. No accumulation of radioactivity was detected in non-hepatic tissues.

Reviewer's Comment:

- The conclusion of the authors is reasonably supported by the reported data. These data provide overall support for the intraportal transplant of LANTIDRA in the target patient population.

TOXICOLOGY STUDIES

Summary List of Toxicology Studies

No toxicology studies with LANTIDRA were conducted. The applicant provided publications assessing the overall safety of islet allografts following intraportal transplantation in Module 4 of the BLA. This reviewer has summarized one selected publication that support the administration of an immunosuppression regimen in combination with LANTIDRA. Please also refer to other publications summarized in this review memo regarding this concept.

Toxicology Studies:

Study Number	Publication Citation
9	Melzi R, et al. Intrahepatic Islet Transplant in the Mouse: Functional and Morphological Characterization. <i>Cell Transplant</i> 2008; 17:1361-70

Study #9

Melzi R et al. Intrahepatic Islet Transplant in the Mouse: Functional and Morphological Characterization. *Cell Transplant* 2008;17:1361-70

Objective: To evaluate islet allograft survival and effect on liver morphology following intraportal transplantation in diabetic mice.

Methods: Pancreatic islets were isolated from C57BL/6 or BALB/C mice (9 weeks old, 20-22 g). STZ-induced diabetic BALB/C (n=47) or C57BL/6 (n=12) recipient mice (males, 9 weeks old, 20-22 g) with persistent hyperglycemia (NF BG of 439 ± 95 mg/dL) were transplanted with 400 allogeneic islets via the portal vein. The BG levels were measured at 15, 30, and 60 minutes post-transplant; once daily for the first week; then

every second day. Animal deaths within the first 7 days post-transplant was attributed to the surgical procedure. Primary nonfunction was defined as the inability to reach NF BG levels less than 250 mg/dL for two consecutive measurements, and rejection was defined as two successive BG levels greater than 250 mg/dL.

Notes:

- BALB/C mice are T-helper (Th)2-type inflammatory-prone and C57BL/6 mice are Th1-type inflammatory-prone. For evaluation of graft morphology, animals (2 animals/time point) were sacrificed immediately and at Days 1, 3, 5, 7, 9, 11, and 14 post-transplant. Liver sections were stained with hematoxylin-eosin and microscopically evaluated for islet cell presence, morphology, and any adverse findings (e.g., embolism, vessel thrombosis, focal areas of liver necrosis). Immunohistochemistry was used to determine leukocyte infiltration and the presence of insulin within islets.
- Per the publication, the increased frequency of transplantation failure was due to a higher number of deaths attributed to the surgical procedure (15/59). The results were reported for animals that survived to scheduled sacrifice.

Results: The median survival time of the allografts was 7 ± 0.22 days (C57BL/6 islets in BALB/C recipients; n=24) and 4 ± 0.2 days (BALB/C islets in C57BL/6 recipients; n=7). Islet function (BG concentration of less than 250 mg/dL within 5 days post-transplant) was observed in 24/47 (51.1%) BALB/C mice transplanted with C57BL/6 islets and in 6/12 (50%) C57BL/6 mice transplanted with BALB/C islets.

Histopathology data for the BALB/C recipient mice showed the following:

- 1) Immediately post-transplant, the allogeneic islets localized in the blood vessels of hepatic portal spaces, appeared to be healthy, and stained strongly for insulin. However, intravascular thrombi around the islets and hepatocyte necrosis in the ischemic region were also observed.
- 2) On Day 1 post-transplant the islets appeared to be trapped in the blood vessel of the liver portal spaces, resulting in disruption of the downstream blood supply. The hepatocytes in the ischemic region were of abnormal shape and texture. Necrotic wedge-shaped regions appeared around the islets.
- 3) By Day 3 post-transplant, leukocyte infiltrates had colonized the necrotic hepatic regions; however, the islets were relatively healthy.
- 4) By Days 9-14 post-transplant, mononuclear leukocytes had infiltrated the colonized islets, starting as peri-islet, and becoming intra-islet, with progressive endocrine tissue destruction and loss of the insulin staining.

The authors conclude that these data suggest that in the absence of an immuno-suppression regimen, adverse findings such as emboli, thrombosis, and numerous focal

areas of necrosis around the transplanted islets, were detected in the liver. These findings were observed on Day 1, progressed to necrotic regions surrounded by multifocal leucocyte infiltrates by Day 3, with progressive mononuclear leukocyte infiltration of the colonized islets (from peri-islet to intra-islet), leading to islet destruction by Days 9-14. In addition, significant differences in the median survival time of the allografts between the C57BL/6 and the BALB/C recipient mice were observed.

Reviewer's Comment:

- The conclusion of the authors is reasonably supported by the reported data. Following intraportal transplantation of the allograft, the liver toxicity was more severe in the Th1-type inflammatory-prone C57BL/6 recipient mice compared to the Th2-type inflammatory-prone BALB/C recipient mice. These data suggest that an immunosuppression regimen is necessary for islet survival post-transplant and provide overall support for use of the (revised) Edmonton Protocol with intraportal transplantation of LANTIDRA in the target patient population.

Developmental and Reproductive Toxicology Studies (DART):

No DART studies with LANTIDRA were conducted.

Genotoxicity Studies:

No genotoxicity studies with LANTIDRA were conducted.

Carcinogenicity/Tumorigenicity Studies:

No carcinogenicity/tumorigenicity studies with LANTIDRA were conducted. The applicant cited two publications that examined the potential for hepatic carcinogenicity following intraportal transplantation of allogeneic islets in diabetic rats. The applicant states that the carcinogenic risk of LANTIDRA in transplanted patients is low.

Study Number	Publication Citation
10	Grotting JC, et al. The Fate of Intraportally Transplanted Islets in Diabetic Rats. A Morphologic and Immunohistochemical Study. <i>Am J Pathol</i> 1978; 92: 653-70
11	Dombrowski FC, et al. Hepatocellular Neoplasms Induced by Low-Number Pancreatic Islet Transplants in Autoimmune Diabetic BB/Pfd Rats. <i>Cancer Res</i> 2006; 66:1833-1843

Study #10

Grotting JC, et al. The Fate of Intraportally Transplanted Islets in Diabetic Rats. A Morphologic and Immunohistochemical Study. *Am J Pathol* 1978; 92: 653-70

Objective: To study the morphology and survival of syngeneic islet allografts following intraportal transplantation in diabetic rats.

Methods: Donor islets were isolated from 6-8 day old Lewis rats (sex not specified). STZ (50 mg/kg)-induced diabetic inbred female Lewis rats (180-250 g) were transplanted via the portal vein (n=12; number of islets was not specified) or non-transplanted (controls; n=2). The transplanted rats were sacrificed at 24 and 48 hours (n=2 animals/time point) and at Weeks 1 (n=2), 2 (n=2), 4 (n=2), 39 (n=1), and 65 (n=1) post-transplant. One control animal was sacrificed at Week 4 and the other at Week 16. Hematoxylin-eosin staining and aldehyde-fuchsin staining were used to identify the presence of islet cells. Immunohistochemical staining was used to identify cells containing insulin, glucagon, somatostatin, and pancreatic polypeptide.

Results:

- 1) All STZ-induced diabetic recipients except one became normoglycemic by Day 9 post-transplant. All animals gained weight and plasma insulin levels increased.
- 2) Liver histopathology:
 - (a) 24 hours post-transplant (n=2): Embolized pancreatic tissue, composed of approximately 80% acini and 20% islets, was distributed throughout the liver, primarily in the terminal branches of the portal system. Endothelial cells and lymphocytes were found in small clusters of islet cells (positive for insulin, glucagon, somatostatin, and pancreatic polypeptide), contributing to formation of thrombus. Many islet thrombi were surrounded by microinfarcts in the hepatic parenchyma.
 - (b) Week 1 post-transplant(n=2): Progressively larger thrombi were observed.
 - (c) Week 39 post-transplant (n=1): The islet thrombi were present. While most of the islet morphology recapitulated that of normal adult rat islet cells, a few strands of islet cells were coursing between the cords of hepatocytes. These strands were composed primarily of insulin- or glucagon-positive cells and resembled the gyriform growth pattern observed in some human α - and β -cell neoplasms¹⁶.

Week 65 post-transplant (n=1): Insulin-, glucagon-, somatostatin-, or pancreatic polypeptide-positive cells were identified within large complex islet structures. Strands of glucagon- or insulin-positive islet cells were detected. Relatively large portions of the liver were replaced by cystic tumors ranging in size from single microscopic dilated spaces to massive fluid-filled cavities. These tumors were lined by a single layer of well-differentiated ductal epithelium without inflammatory infiltrates, resembling biliary cystadenomas in humans.

The authors conclude that STZ caused the abnormal liver histopathology, noting that such tumors have been previously reported in untransplanted rats administered the same dose level of STZ¹⁷ and tumors have never been reported in nondiabetic animals transplanted with islets via the portal vein.

¹⁶ Greider MH et al. The human pancreatic islet cells and their tumors. II. Ulcerogenic and diarrheogenic tumors. *Cancer* 1974; 33:1423-1443.

¹⁷ Feldman S et al. Streptozotocin induced liver tumors. *Transplantation* 1977; 24:152-154.

Reviewer's Comment:

- No conclusion can be drawn from this published study due to the extremely small numbers of transplanted rats evaluated at each time point, as well as the lack of:
1) adequate numbers of concurrent STZ-injected untransplanted control animals at each time point and 2) concurrent non-diabetic transplanted control animals.

Study #11

Dombrowski FC, et al. Hepatocellular Neoplasms Induced by Low-Number Pancreatic Islet Transplants in Autoimmune Diabetic BB/Pfd Rats. Cancer Res 2006; 66:1833-1843

Objective: To exclude STZ as a causative factor in the development of hepatic neoplasms in hepatic carcinogenicity in diabetic, transplanted rats.

Methods:

- 1) Syngeneic islets were isolated from non-diabetic BB/Pfd littermate donor rats.
- 2) Spontaneous autoimmune-diabetic BB/Pfd rats that re-established long-lasting self-tolerance were transplanted via the portal vein with a low number (450 islets/rat; n=148) or a high number (1200 islets/rat; n=86) of islets. Additional untransplanted spontaneous autoimmune-diabetic BB/Pfd rats (n=40) served as concurrent controls.
- 3) Non-diabetic BB/Pfd rats rendered diabetic with STZ (65 mg/kg), were transplanted via the portal vein with a low number (450 islets/rat; n=144) or a high number (1200 islets/rat; n=118) of islets. Additional untransplanted STZ-induced diabetic BB/Pfd rats (n=40) served as concurrent controls.
- 4) Untransplanted non-diabetic BB/Pfd rats (n=165) served as the concurrent normoglycemic control group.

The presence of: 1) clear cell focus or clear cell preneoplastic foci of altered hepatocytes (CCF), 2) hepatocellular adenoma (HCA), 3) hepatocellular carcinoma (HCC), or 4) mixed cell focus (MCF) in the liver was evaluated at the following time points post-transplant: 0-3, 3-6, 6-9, 9-12, 12-15, and 15-28 months.

Notes:

- Per the publication, BB/Pfd rats are an inbred Pfd substrain of the BB rat. Some BB/Pfd rats spontaneously become diabetic due to an autoimmunologic disorder similar to human T1DM, which is not completely understood but involves mutations of the lyp locus on chromosome 4, lymphopenia, and dysregulation of inflammatory cells, leading to insulinitis and β -cell destruction. The authors state that approximately 78% of spontaneous autoimmune-diabetic BB/Pfd rats can reestablish long-lasting self-tolerance to native β -cells. Thus, these animals can tolerate transplanted syngeneic islets in the absence of immunosuppression. In this study, approximately 22% of the BB/Pfd rats failed to reestablish long-lasting self-tolerance, thus displayed β -cell destruction following transplant. The reported results did not include the findings from these animals.

- The number of untransplanted spontaneous autoimmune-diabetic BB/Pfd rats that reestablished long-lasting self-tolerance could not be determined because these animals did not receive the syngeneic islets.

Results:

- 1) Transplantation of low islet numbers: The autoimmune- and STZ-diabetic BB/Pfd recipient rats displayed mild hyperglycemia. Liver histopathology consisted of the following:
 - a) 0-3 months post-transplant: Liver acini downstream of the transplanted islets showed insulin-induced alterations (e.g., glycogen and/or fat accumulation; translocation of the insulin receptor; increased expression of insulin-like growth factor I [IGF-I]¹⁸, IGFII/mannose-6-phosphate receptors [MPRs]¹⁹, and insulin receptor substrate-1 [IRS-1]²⁰, Raf-1²¹, and Mek-1²²).
 - b) 6-12 months post-transplant: Altered liver acini progressed to other types of 'preneoplasia' structures (i.e., mixed cell foci and basophilic cell foci).
 - c) 12-15 and 15-18 months post-transplant: A total of 52% and 100% of the animals exhibited single or multiple HCAs or HCCs, respectively. Most HCAs and HCCs were composed of a mixed population of clear and basophilic cells.
- 2) Transplantation of high islet numbers: The autoimmune- and STZ-diabetic BB/Pfd rats were normoglycemic. No hepatic neoplasms were detected.

¹⁸ IGF-I and IGF-II have structural homology to insulin and similar metabolic actions. They are functionally related to insulin but have higher growth-promoting activity.

¹⁹ MPRs are transmembrane glycoproteins that target lysosomal enzymes in vertebrates.

²⁰ IRS-1 is an intracellular signaling adaptor protein that transmits signals from the insulin and IGF-I receptors to phosphoinositide 3-kinase (PI3K)/Protein kinase B (PKB) and extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathways.

²¹ Raf-1 is a proto-oncogene, serine/threonine kinase that can phosphorylate serine and threonine residues on Mek-1 in the RAS-RAF-MEK-ERK signaling pathway to transmit mitogenic, differentiative and oncogenic signals.

²² Mek-1 is a dual recognition kinase that can phosphorylate a tyrosine and threonine on MAPK, which is required for MAPK activation.

²³ Dombrowski F, et al. Hyperproliferative liver acini after intraportal islet transplantation in streptozotocin-induced diabetic rats. *Lab Invest* 1994; 71:688-699.

²⁴ Dombrowski F, et al. Hepatocellular neoplasms induced by low-number pancreatic islet transplants in streptozotocin diabetic rats. *Am J Pathol* 1997; 150:1071-1087.

- 3) Untransplanted diabetic controls: No hepatic neoplasms were detected in the autoimmune- and STZ-diabetic BB/Pfd rats.
- 4) Untransplanted non-diabetic controls: A total of 4/25 non-diabetic BB/Pfd rats developed a single CCF at 15-18 months.

The authors conclude that these data confirm their previously reported findings in STZ-diabetic Lewis rats, identifying hyperinsulinism and hyperglycemia as a ‘carcinogenic mechanism’ in diabetic rats. They note that tumors were also detected in spontaneous autoimmune-diabetic BB/Pfd rats, thus independent of STZ.

Reviewer’s Comment:

- The conclusion of the authors is reasonably supported by the reported data. However, while the applicant acknowledges the data, they also note that the lesions occurred only in animals transplanted with a low number of islets^{23,24,25,26}. This combination of islet number, hyperinsulinism, and hyperglycemia resulted in liver tumors. Transplantation of high numbers of islets did not result in hepatic neoplasms. Per the proposed label, the recommended minimum clinical dose level for the target population is 4000-5000 EIN/kg. In addition, the translation of these rodent data (rodent donors and recipients) to the clinical scenario is not well understood. Thus, the carcinogenic risk of LANTIDRA in transplanted patients is considered low.

Other Safety/Toxicology Studies

No safety/toxicology studies were conducted to evaluate the additional concomitant medications specified in the proposed product label, including: 1) the immunosuppression medications (e.g., basiliximab, etanercept, sirolimus, tacrolimus, anti-thymocyte globulin and mycophenolate mofetil); 2) a GLP-1 receptor agonist (e.g., exenatide); 3) a TNF- α receptor antagonist (e.g., etanercept); 4) antimicrobials (e.g., trimethoprim, sulfamethoxazole, valganciclovir, pentamidine, and cefazolin); 5) anticoagulants (heparin during transplant and enoxaparin afterwards); and 6) local anesthetics. Per the applicant, each of these drug products is approved by the FDA. Please refer to the package insert/prescribing information for each respective product.

²⁵ Scharf JG, et al. Analysis of the IGF axis in preneoplastic hepatic foci and hepatocellular neoplasms developing after low-number pancreatic islet transplantation into the livers of streptozotocin diabetic rats. *Lab Invest* 2000;80:1399-411.

²⁶ Evert M et al. Insulin receptor, insulin receptor substrate-1, Raf-1, and Mek-1 during hormonal hepatocarcinogenesis by intrahepatic pancreatic islet transplantation in diabetic rats. *Cancer Res* 2004;64: 8093-100.

APPLICANT'S PROPOSED LABEL

- Subsections 8.1-8.3 of Section 8 ('Use in Specific Populations') should be revised to comply with 21 CFR 201.56(d)(1), 201.57(c)(9), and 201.57(c)(14), as applicable²⁷.
- Section 13 ('Nonclinical Toxicology') was not provided because nonclinical studies with LANTIDRA were not conducted. This is acceptable.

CONCLUSION OF NONCLINICAL STUDIES

Review of the nonclinical studies in the published literature provided overall support for the purported mechanism of action of LANTIDRA and the need for an immunosuppressive regimen. The nonclinical data support approval of the license application.

KEY WORDS/TERMS

Donislecel-jujn; LANTIDRA; allogeneic islets; brittle Type 1 Diabetes Mellitus; β -cells; insulin; hyperglycemia; hypoglycemia; pancreas; liver; streptozotocin-induced diabetes; STZ; nonhuman primates; islet allograft; intraportal transplantation; immunosuppression; Edmonton Protocol; mechanism of action; pharmacology; distribution; toxicology

²⁷ Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products - Content and Format, at: <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm450636.pdf>