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UNIVERSITY OF UTAH
L. S. SKAGGS PHARMACY INSTITUTE

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DONISLECEL-JUJN (LANTIDRA)

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Drug Regimen Review Center

Monet Luloh, PharmD, Clinical Pharmacist
Lauren Heath, PharmD, MS, Clinical Pharmacist
Valerie Gonzales, PharmD, Clinical Pharmacist
Kristin Knippenberg, MFA, Administrator and Editor
Jacob Crook, MS, Data Analyst
Joanne LaFleur, PharmD, MSPH, Director and Associate Professor

University of Utah College of Pharmacy, Drug Regimen Review Center

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ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
AAFP	American Academy of Family Physicians
ABCD	Association of British Clinical Diabetologists
ADA	American Diabetes Association
AE(s)	Adverse event(s)
AID	Automated insulin delivery
BMI	Body mass index
CGM	Continuous glucose monitor(ing)
CMV	Cytomegalovirus
CSII	Continuous subcutaneous insulin infusion
DKA	Diabetic ketoacidosis
DUR	Drug Utilization Review
EASD	European Association for the Study of Diabetes
EIN	Equivalent islet number
FDA	US Food and Drug Administration
FPG	Fasting plasma glucose
GAD(65)	Glutamic acid decarboxylase
GLP-1	Glucagon-like peptide 1
(Hb)A1c	Glycosylated hemoglobin or hemoglobin A1c
IA-2	Islet tyrosine phosphatase 2 or islet antigen-2
ICER	Institute for Clinical and Economic Review
IE	Islet equivalent(s)
MDI(s)	Multiple daily injection(s)
NICE	National Institute for Health and Care Excellence
OGTT	Oral glucose tolerance test
OPTN	Organ Procurement and Transplantation Network
PA	Prior authorization
PCP	*Pneumocystis jirovecii* pneumonia
RCT(s)	Randomized controlled trial(s)
SGLT-2	Sodium-glucose cotransporter 2
SR(s)	Systematic review(s)
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
UIH	University of Illinois Hospital and Health Sciences System or UI Health
UK	United Kingdom
UNOS	United Network for Organ Sharing
US	United States
ZnT8	Zinc transporter 8

1.0 INTRODUCTION

Type 1 diabetes mellitus (T1D) is characterized by destruction (usually autoimmune-mediated) of insulin-producing pancreatic β-cells, ultimately resulting in absolute endogenous insulin deficiency.[1-6] T1D is attributable to roughly 5%−10% of all diabetes cases, and onset can occur any time from childhood to adulthood.[1,4,6] In the absence of chronic exogenous insulin therapy, T1D is life-threatening.[1,7] Currently, the administration of exogenous insulin, either by multiple daily injections (MDI) or an insulin pump, is the mainstay of treatment for T1D.[7] However, even with adherence to insulin treatment, some individuals with T1D may fail to attain the glycemic targets required to prevent or delay the onset of diabetes-related complications.[8,9]

Donislecel-jujn (Lantidra) was approved by the United States (US) Food and Drug Administration (FDA) in June 2023 as the first, allogeneic (deceased donor-derived), pancreatic islet cellular treatment for *adults* with T1D who fail to achieve glycated hemoglobin (HbA1c) goals due to recurrent severe hypoglycemic episodes, despite intensive diabetes management and education.[9,10] Donislecel was designated as an orphan drug, allowing for 7 years of market exclusivity.[11,12] Donislecel approval was based on 2 single-arm studies in adults, following decades of clinical experience using islet cell transplantation in patients with T1D.[10,13-17]

Donislecel contains several endocrine cell types other than β-cells that are responsible for glucose homeostasis (eg, α-cells, ε-cells), but it is believed that its therapeutic effect is primarily by insulin secretion from the transplanted functional β-cells.[10] Treatment with donislecel entails a *single infusion* of the transplant islet cells and *may be given up to 2 additional times* to patients a) who still require exogenous insulin within 1 year of a previous infusion, or b) within 1 year after losing exogenous insulin independence (regardless of duration from the prior infusion). It must be administered by a healthcare provider specialized in islet cell transplantation, within a controlled aseptic environment (eg, radiology suite, operating suite). Treated patients require continuation of exogenous insulin until reaching insulin independence which, though highly variable, may be as short as several weeks after the donislecel infusion.[10]

The objective of this report is to provide evidence on the safety and efficacy of donislecel to assist the Utah Medicaid Drug Utilization Review (DUR) board in assuring safe and appropriate use.

2.0 METHODS

The following US- and United Kingdom (UK)-based organization websites were searched for clinical practice guidelines and/or position/consensus statements on islet cell transplantation for the treatment of T1D in adults, published within the past 5 years (2018−2023):

- American Diabetes Association (ADA): https://diabetes.org/
- American Association of Clinical Endocrinologists (AACE): https://www.aace.com/
- American Academy of Family Physicians (AAFP): https://www.aafp.org/home.html
- National Institute for Health and Care Excellence (NICE): https://www.nice.org.uk/
- Association of British Clinical Diabetologists (ABCD): https://abcd.care/

The Institute for Clinical and Economic Review (ICER) website (https://icer.org/) was also searched for evidence-based reports on the use of donislecel. Donislecel prescribing information (ie, package insert) and FDA review documents were obtained from the following website: https://www.fda.gov/vaccines-blood-biologics/lantidra.

A systematic literature search for randomized controlled trials (RCTs) and systematic reviews (SRs) of RCTs addressing the efficacy and/or safety of donislecel was conducted in Ovid-Medline and Embase using search terms for donislecel. Due to the paucity of published evidence on donislecel, we also conducted a literature search in Ovid-Medline using free-text terms and controlled vocabulary for recent (2020−2023) reviews on islet cell transplantation. Additionally, we searched for registered, unpublished clinical trials of donislecel on ClinicalTrials.gov. See **Appendix A** for the complete search strategies used in each database.[1-5]

3.0 BACKGROUND

T1D is a heterogeneous, endocrine condition characterized by destruction (usually autoimmune-mediated) of insulin-producing pancreatic β-cells, ultimately causing absolute exogenous insulin deficiency.[1-6] Complications associated with T1D are both acute (eg, severe hypoglycemia, ketoacidosis), and chronic (eg, microvascular or macrovascular disease).[18] T1D represents about 5%−10% of all diabetes cases.[1,6] T1D onset typically occurs during childhood, but can manifest at any stage of life.[1,5,6] While there are 3 stages of T1D (see **Table 1**), islet cell transplantation is used in patients who are dependent on exogenous insulin (ie, patients with clinical T1D or stage 3 T1D), rather than stage 1 or 2 T1D in which patients are typically asymptomatic and do not yet have overt hyperglycemia required for diagnosis of clinical T1D.[4,6,19] For information related to the diagnosis of T1D, see **Appendix B**.

Table 1. Type 1 Diabetes Stages[4,6]

Features	Stage 1	Stage 2	Stage 3 (Clinical T1D)
Presence of ≥2 pancreatic autoantibodies	✓	✓	✓ (May be absent)
Dysglycemia[a]	Absent	✓	✓ Overt hyperglycemia
Symptoms	Asymptomatic	Asymptomatic	✓ Usually symptomatic

[a] According to the ADA, examples that meet the criterion for Stage 2 dysglycemia, identified as either IFG and/or IGT, include FPG of 100 to 125 mg/dL, 2-hour PG of 140 to 199 mg/dL, or A1C of 5.7% to 6.4% or an A1C increase of ≥10%.[4] Overt hyperglycemia for Stage 3 meets the diagnostic criteria for T1D.[4]

Abbreviations: A1C, glycosylated hemoglobin or hemoglobin A1c; ADA, American Diabetes Association; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PG, plasma glucose; T1D, type 1 diabetes mellitus

Among the 1.2 million people with T1D in the US, about 25% experience hypoglycemia unawareness[20] and 66% have recurrent severe hypoglycemic episodes.[16] Notably, approximately 70,000 patients with T1D fail to experience improvements in hypoglycemia, even after participating in structured educational programs and utilizing advanced technologies to help avoid hypoglycemia.[16] Although there have been notable advancements in insulin pumps and continuous glucose monitors (CGMs) over the years, hypoglycemic episodes continue to pose a substantial challenge for patients with T1D, attributing to

approximately 40,000 emergency department visits annually.[16] Prior to donislecel approval, β-cell replacement by islet cell (as an experimental procedure in the US) or pancreas transplantation have been studied and used in clinical practice for decades to restore endogenous insulin production and mitigate T1D sequela.[1,7,16,17] Islet cell transplantation, such as donislecel, and pancreas transplantation require *life-long* immunosuppression to mitigate the risk of allogeneic graft rejection and/or the resurgence of immune-mediated destruction of islet cells.[1,7,10]

Donislecel is a single company's (CellTrans, Chicago, Illinois) preparation of an allogeneic (deceased donor-derived) islet cellular transplant product.[12] Unlike other regions of the world where allogenic islet cell transplantation has evolved into a standard-of-care procedure for certain patients with T1D, its extensive adoption in the US has been restricted by the FDA regulation process and classification of islet transplant (ie, as cellular therapy rather than transplant organ) despite its development over the past 2 decades.[12,15-17] Prior to the newly approved product, donislecel, islet cell transplantation was considered an investigational procedure in the US, only to be conducted for research purposes in clinical trials, and therefore usually non-reimbursable by health insurance payors.[15,16,21]

From 2016 to 2019, 11 patients with T1D received an islet cell transplantation in the US (potentially including donislecel as part of its clinical trials)[*], a rapid decline from previous years possibly due to higher procedural costs and less research funding.[15,16] While the approval of donislecel has increased patient accessibility to islet cell transplantation outside of a clinical trial setting, some transplant surgical organizations and lawmakers believe the outdated regulatory classification of islet cell transplantation, and therefore donislecel, as a biologic drug instead of as a transplant organ limits the utility of this life-changing therapy and hinders therapy development.[12,15,16,22] Thus, there are hopes to shift the regulatory purview of islet cell transplantation, and consequently donislecel, from the FDA to the United Network for Organ Sharing (UNOS) and Organ Procurement and Transplantation Network (OPTN).[15,16,22] Donislecel (and islet transplantation in general) differ from other investigational treatments such as stem cell-derived human islets (eg, VX-880) that may be used to overcome traditional islet cell transplantation limitations (eg, donor supply shortage).[21,23]

Islet cell transplantation, including donislecel, may have limited therapeutic utility due to the shortage of donated pancreases suitable for islet cell transplantation and the requirement for *life-long* immunosuppression, with the latter associated with adverse effects such as neoplasia, nephrotoxicity, and increased risk of infections.[13,21,24-27] It should be noted that unlike typical drug products, biologics, particularly cell products like donislecel, often do not achieve precise dosing.[14] Moreover, the use of delivery devices can damage or alter the amount of islets, thereby potentially affecting the efficacy.[14]

4.0 DONISLECEL MECHANISM OF ACTION AND PHARMACODYNAMICS

Pancreatic islets play a pivotal role in regulating blood glucose levels by releasing multiple hormones, especially insulin, in response to fluctuations in blood glucose.[10] Although donislecel contains multiple different endocrine cells (eg, α-cells, ε-cells), it is believed that the therapeutic and pharmacodynamic effects of donislecel are primarily attributed to the delivery of functional donor β-cells, thereby

[*] The donislecel clinical trials included UIH-001 and UIH-002 (see **Section 7.0**); in UIH-001, the first transplant took place on January 11, 2005, while the last transplant in UIH-002 was performed on July 15, 2016.[14]

potentially eliminating the need for exogenous insulin delivery. The pharmacodynamic characteristics of donislecel on blood glucose regulation are most evident in patients who achieve insulin independence.[10]

5.0 DONISLECEL ADMINISTRATION AND MONITORING

Donislecel is an islet cellular suspension infused over approximately 30 minutes into the hepatic portal vein; according to prescribing information, up to 2 additional infusions may be given for patients a) who still require exogenous insulin within 1 year of a previous infusion, or b) within 1 year after losing exogenous insulin independence (regardless of duration from the prior infusion).[10] Each donislecel lot is prepared from a single donor that is intended for a specific recipient.[28] Healthcare providers specializing in islet cell transplantation, including interventional radiologists and surgeons, should oversee the administration of donislecel within a controlled aseptic environment (eg, radiology suite, operating suite).[10] After the infusion, patients should be monitored in the hospital for at least 24 hours. Patients are expected to continue insulin treatment until the transplant takes effect. Notably, not all recipients of donislecel achieve insulin independence; for some, insulin independence may take several weeks to occur or may not be maintained long-term.[10]

Donislecel should be used with steroid-sparing immunosuppressive therapy, including pre-procedurally 30 to 360 minutes before the infusion (eg, with an anti-interleukin-2 receptor antibody, tumor necrosis factor inhibitor) and *life-long* post-infusion (eg, with a calcineurin inhibitor and a mammalian target of rapamycin inhibitor) to minimize the risk of islet graft rejection and maintain islet cell viability (see **Section 10.3** for clinical scenarios that warrant discontinuing immunosuppressive therapy).[10] Notably, specific immunosuppression regimens may be selected at the discretion of the treating physician who is knowledgeable about islet cell transplantation. Antibiotic prophylaxis should be administered during the periprocedural period; specifically immediately after the infusion, prophylaxis for *Pneumocystis jirovecii* pneumonia (PCP) and cytomegalovirus (CMV) should be administered, and continued as directed according to the anti-infective's prescribing information (see **Appendix C** for recommended pre- and post-infusion medication regimens).[10]

Table 2 summarizes the FDA approved indication for donislecel and directions for use, including dosing information, according to prescribing information.

Table 2. Donislecel (Lantidra) FDA-approved Indication and Directions for Use[10]

FDA-approved indication
Treatment of T1D in adults who have failed to reach HbA1c targets due to recurrent hypoglycemic episodes despite intensive diabetes management (eg, insulin and devices) and education. Immunosuppressive therapy (eg, mTOR inhibitor) should be used before and life-long after the infusion[a]; avoid the use of systemic steroids. Limitations on use: • No evidence of benefit for patients with well-controlled diabetes on insulin treatment, or those with hypoglycemia unawareness capable of preventing repeated severe hypoglycemic episodes (neuroglycopenia that requires outside intervention) while using intensive management. • Patients with a history of portal thrombosis should not receive repeated intraportal infusions (*exception: if the thrombosis occurred in the second- or third-order branches of the portal vein*). • No evidence to support use in patients with liver disease, renal failure, or those who have received a renal transplant.
Dosing and administration information[b]

• The dosage strength varies based on the product batch, but is represented on the container label[c] and does not exceed $1x10^6$ EIN per bag (10 mL of packed islet tissue)
  ○ Minimum dose for initial infusion: 5,000 EIN/kg
  ○ Repeat infusion(s): 4,500 EIN/kg
• Each dose consists of 2 infusion bags aseptically connected to each other: 1 bag (1,000 mL) contains donislecel (up to a maximum of $1x10^6$ EIN); and the other bag (750 mL) is used to rinse the infusion line and donislecel bag to ensure all islet cells have been transferred
• Infused approximately over 30 minutes at a rate of ≤25 mL/kg/h into the hepatic portal vein; may reduce rate if fluid load is intolerable
• Repeat infusions (up to an additional 2)[d] may be administered to patients:
  ○ Who still require exogenous insulin within 1 year of a previous infusion, or
  ○ Within 1 year after losing exogenous insulin independence (regardless of duration from the prior infusion)

Dosage storage
• Donislecel should be disposed if it is not used within 6 hours of "product release", or should not be used if temperature is not controlled between 15°C and 25°C • Do not irradiate

[a] *Note that there may be certain clinical scenarios that warrant discontinuing immunosuppression (see* ***Section 10.3****).*

[b] *No specific dosage adjustments are provided in the prescribing information for renal or hepatic impairment.*

[c] *The islet number and other additional information is also included on the Final Islet Product Certificate of Analysis.*

[d] *There is no efficacy or safety data available for more than 3 infusions in a single patient.*

Abbreviations: EIN, equivalent islet number; FDA, US Food and Drug Administration; h, hour; HbA1c, glycosylated hemoglobin or hemoglobin A1c; kg, kilogram; mL, milliliter; mTOR, mammalian target of rapamycin; T1D, type 1 diabetes mellitus; US, United States

Physicians should monitor specific parameters (ie, portal pressure, blood glucose, formation of a portal vein thrombosis) during and/or after the donislecel infusion.[10] **Table 3** summarizes the recommended monitoring during and after the donislecel infusion, according to prescribing information.

Table 3. Recommended Monitoring During and After Donislecel Therapy, per Product Labeling[10]

Parameter	During infusion		Acute period after the infusion	
	Monitor	Recommendation	Monitor	Recommendation
Portal pressure	✓	• Pause: >22 mmHg; may restart once <18 mmHg • STOP: >22 mmHg for >10 minutes		
Blood glucose	✓	• Every 15 minutes • Treat if <70 mg/dL	✓	• Every 30 minutes during the initial 4 to 8 hours post infusion • Continue to monitor as needed after 4 to 8 hours (*using BGMs and CGMs approved for hospital use while the patient is hospitalized*), and treat accordingly • Treat if <70 mg/dL
Portal vein thrombosis	✓	• Systemic heparinization may help mitigate clot propagation, but may increase the risk of intra-abdominal hemorrhage	✓	• Perform hepatic examination using Doppler and abdominal ultrasound after removing the catheter; repeat at minimum on days 1 and 7 after the infusion

Abbreviations: BGM(s), blood glucose meter(s); CGM(s), continuous glucose monitor(s); dL, deciliter; mg, milligram; mmHg, millimeter of mercury

6.0 GUIDELINE RECOMMENDATIONS FOR TREATING TYPE 1 DIABETES MELLITUS (T1D)

Treatment of T1D primarily relies on exogenous insulin replacement, in addition to physical activity, dietary management, education, and social and psychological support, to maintain blood glucose levels near a physiological target and prevent diabetes-related complications (see **Appendix D** for recommended glycemic goals from reviewed US guidelines).[1,29,30] Reviewed guidelines and consensus/position statements recommend MDI, including both prandial and basal insulin, or continuous subcutaneous insulin infusion (CSII) via an insulin pump for most patients with T1D, including adults and children, typically starting at the time of diagnosis.[1,7,29-31]

The ADA/EASD consensus report highlights that the choice of insulin regimen should be individualized to the patient, based on preferences, capabilities, and circumstances, whereas NICE (2022) and ABCD (2020) prefer MDI as the initial insulin regimen and reserve insulin pump therapy for select patients with T1D (eg, inadequate HbA1c levels [≥8.5%; 69 mmol/mol] despite optimal care with MDI).[1,29,31,32]

Although insulin therapy is essential for patients with T1D, achieving optimal glycemic targets solely through insulin treatment can be challenging due to the associated risks of hypoglycemia.[1] According to the ADA/EASD consensus report, the use of adjunctive therapies, such as metformin, glucagon-like peptide 1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 (SGLT-2) inhibitors[†], and pramlintide can be considered on a case-by-case basis depending on the risks and benefits.[1] Of these, pramlintide (Symlin) is the only non-insulin agent approved in the US for adults with T1D,[1,7,30] indicated for those on mealtime insulin who are not achieving glycemic targets despite optimal insulin use[‡].[33]

While the ADA (2023) and AACE (2022) do not provide formal recommendations on the use of adjunctive therapies in patients with T1D, they cite evidence on the use of metformin, liraglutide (a GLP-1 receptor agonist), and SGLT-2 inhibitors in this population.[7,30] Generally, these adjunctive therapies have demonstrated modest improvements in diabetes-related outcomes (eg, weight loss, HbA1c reduction, insulin requirements) among patients with T1D, but concerns of adverse effects have limited their utilization.[1,7,30] For example, SGLT-2 inhibitors reduce HbA1c and body weight and improve blood pressure, among other outcomes, but are associated with a considerable increased risk (absolute rate of approximately 4% annually) of diabetic ketoacidosis (DKA) in patients with T1D, warranting careful use.[1,7,29,30] Therefore, the ABCD (2020) cautiously recommends SGLT-2 inhibitors as adjuncts to insulin for certain adults with T1D (eg, those who are not prone to ketosis or underweight).[29] The only adjunctive agent recommended by NICE (2022) is metformin, specifically for adults with T1D who have a BMI ≥25 kg/m^2 and desire to reduce their insulin dosage while improving blood glucose control.[31]

6.1 Islet cell transplantation

Reviewed clinical practice guidelines and consensus/position statements predate FDA-approval of donislecel; therefore, they do not comment on its use.[1,7,29-31] Yet, because donislecel is a islet cell transplant, guidance regarding islet cell transplantation is applicable.[10,12,14] Several recent guidelines and consensus/position statements provide general guidance on islet cell transplantation (see **Table 4**).[1,7,29,31]

The decision to perform a islet cell transplantation must consider the surgical risks, metabolic requirements, and the patient's preferences.[1] Due to the potential adverse effects associated with life-long immunosuppressive treatment, the ADA (2023) emphasizes that suitable candidates for *pancreas* transplantation, and presumably islet cell transplantation, are patients with T1D who have severe metabolic complications (eg, severe hypoglycemia, recurrent ketoacidosis) despite optimal management, or those simultaneously undergoing or who have received a renal transplant.[7] Notably, patients undergoing a renal transplant may be more likely to receive a simultaneous pancreas transplant, given it is the gold-standard for patients with T1D and severe diabetic chronic kidney disease.[1,34] In addition to severe metabolic complications[§] and severe diabetic chronic kidney disease

[†] Although SGLT inhibitors are not approved in the US for the management of T1D, low-dose dapagliflozin (5 mg) and sotagliflozin (200 mg) are approved in Europe as adjuncts to insulin for patients with T1D who have a BMI ≥27 kg/m^2.
[‡] Prescribing information does not recommend using pramlintide (Symlin) in pediatric patients due to the potential for severe hypoglycemic events and insufficient evidence for its use in the pediatric population.
[§] Severe metabolic complications include "hypoglycemia, hypoglycemia unawareness, ketoacidosis, incapacitation problems with exogenous insulin therapy, and failure of insulin-based management to prevent acute complications"[1] (page 2613).

(for those also receiving a kidney transplant) as indications for β-cell therapy (ie, islet cell or pancreas transplantation), the ADA/EASD (2021) specifically states that islet cell transplantation is indicated for those with recurrent level 3 hypoglycemia** and excessive glycemic lability.[1]

Because islet cell transplantation is a less invasive procedure than whole-pancreas transplantation, the ADA/EASD (2021) consensus report and experts state that islet cell transplantation may be suitable for patients who are ineligible for a pancreas transplant, including older adults, frail patients, or those with coronary artery disease.[1,34]

The 2020 ABCD position statement provides explicit candidacy criteria for islet cell transplantation alone among adults with T1D.[29]

- Candidates who may be suitable include adults with T1D (including those who have undergone a renal transplant) with one of the following characteristics despite optimal management:
    - Hypoglycemia unawareness, or
    - At least 2 episodes of severe hypoglycemia (defined as a hypoglycemic episode that required outside assistance for recovery) within the previous 2 years
- Ideally, it is preferred for patients to have previously trialed an insulin pump and CGM before determining suitability for islet transplantation, but this is not required.

Candidates who may *not* be suitable for islet cell transplantation alone include adults with T1D whose daily insulin requirements exceed 0.7 units/kg, have a weight >85 kg, or have kidney dysfunction (generally defined as a glomerular filtration rate of <60 mg/min).[29] Note that the position statement mentions that a simultaneous pancreas and kidney transplant can be considered for patients who need a renal transplant.[29]

** Level 3 hypoglycemia is defined as any instance of hypoglycemia where an individual experiences mental and/or physical status changes that requires treatment assistance from another person.

Table 4. Guideline and Consensus/Position Statement Guidance on Islet Cell Transplantation in Patients with Type 1 Diabetes Mellitus

Professional organization and guideline; publication year	Key guidance points[a]
United States Guidelines/Consensus Statements	
American Diabetes Association (ADA) Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes Guideline; 2023[7]	Target age group/population for recommendations: children and adults with diabetes[35] • Pancreas transplantation, and presumably islet cell transplantation, should be selectively considered for patients with T1D who have severe metabolic complications (eg, severe hypoglycemia, recurrent ketoacidosis) despite optimal management, or those simultaneously undergoing or who have received a renal transplant. • Patients undergoing islet cell or pancreas transplantation require *life-long* immunosuppression to mitigate the risk of allogeneic graft rejection and/or the resurgence of immune-mediated destruction of islet cells.

American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)
 	
The Management of Type 1 Diabetes in Adults: A Consensus Report; 2021[1]
	Target age group/population for recommendations: adults with T1D
	• β-cell therapy (ie, islet cell or pancreas transplantation) is indicated in (a) patients with severe metabolic complications, or (b) patients with severe diabetic chronic kidney disease (GFR <30 mL/min/1.73 m^2) receiving a kidney transplant (per figure 7, simplified overview of indications for β-cell therapy).
	  ○ Severe metabolic complications included "hypoglycemia, hypoglycemia unawareness, ketoacidosis, incapacitating problems with exogenous insulin, and failure of insulin-based therapy to prevent acute complications"[1] (page 2613).
	  ○ Pancreas or islet cell transplantation can be performed simultaneously or after a whole organ kidney transplant in those also indicated for a kidney transplant.
	• Islet cell transplantation is indicated for patients with "…excessive glycemic lability and frequent level 3 hypoglycemia[b] despite optimal medical therapy…"[1] (page 2615)

United Kingdom Guidelines/Position Statements	
National Institute for Health and Care Excellence (NICE)[c] Type 1 Diabetes in Adults: Diagnosis and Management; 2022[31]	Target age group/population for recommendations: adults (≥18 years) with T1D • Consider a referral for islet cell and/or pancreas transplantation for adults with T1D suffering from recurrent severe hypoglycemia that is unresponsive to appropriate management. • For adults with T1D who have inadequate diabetes control, and who have undergone a renal transplant and are taking immunosuppressive therapy, consider islet cell or pancreas transplantation.

Association of British Clinical Diabetologists (ABCD)
 	
Standards of Care for Management of Adults with Type 1 Diabetes Position Statement; 2020[29]
	Target age group/population for recommendations: adults with T1D
	• Patients should be referred to a specialized center for islet transplantation if they have persistent hypoglycemia despite optimal management, including with technological devices.
	• Adults with T1D (including those who have undergone a renal transplant) may be suitable for islet transplantation if they experience any of the following despite optimal management:
	  ○ Hypoglycemia unawareness
	  ○ At least 2 episodes of severe hypoglycemia (defined as a hypoglycemic episode that requires outside assistance for recovery) within the previous 2 years
	• Adults with T1D may *not* be suitable for islet transplantation if their daily insulin requirements exceed 0.7 units/kg, have a weight >85 kg, or have kidney dysfunction (generally defined as a GFR <60 mL/min).
	  ○ Note that a simultaneous pancreas and kidney transplant can be considered for patients who need a renal transplant.

[a] *Reviewed clinical practice guidelines and consensus/position statements predate FDA-approval of donislecel-jujn (Lantidra); therefore, they do not comment on its use.* ***Notably, only the NICE guideline provided guidance on the strength of recommendation, whereas guidance points from other reviewed guidelines and consensus/position statements were not made at the level of formal graded recommendations with level of evidence ratings****.*

[b] *Level 3 hypoglycemia is defined as any instance of hypoglycemia where an individual experiences mental and/or physical status changes that require treatment assistance from another person.*

[c] *NICE recommendation strength: Consider: generally indicates a weak recommendation for the intervention, implying that the intervention should be used for certain patients if the benefits outweigh the risks.*[36]

Abbreviations: ABCD, Association of British Clinical Diabetologists; ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; GFR, glomerular filtration rate; kg, kilogram; NICE, National Institute for Health and Care Excellence; T1D, type 1 diabetes mellitus

7.0 DONISLECEL CLINICAL TRIALS (UIH-001 AND UIH-002)

The systematic literature searches performed on November 8, 2023 found no randomized controlled trials (RCTs) for donislecel (see **Appendix A**).

The FDA approval of donislecel was based on 2 non-randomized, prospective, single-arm, open-label trials, including a phase I/II study (UIH-001; NCT00566813) and a phase III study (UIH-002; NCT00679042).[10,13,14] UIH-001 was started in 2004 and UIH-002 in 2007; both trials were conducted at a single center (University of Illinois Hospital & Health Science System).[13,14] Because both trials were methodologically similar, it allowed for a pooled analysis of the safety and efficacy outcomes.[14]

Each study included a minimum **follow-up duration of 1 year after the previous infusion, with the option for additional follow-up at 5 and 10 years**.[13,14] For UIH-001 and UIH-002, the targeted minimum islet dose for the initial infusion was around 10,000 islet equivalent (IE)/kg (higher than the FDA-approved minimum recommended dose of 5,000 equivalent islet number [EIN]/kg for the initial infusion, as stated in product labeling[10]), with no maximum islet number specified, provided packed cell volume did not exceed 10 mL.[13,14] For subsequent infusions in both donislecel trials, the delivered islet number must have surpassed 10,000 IE/kg after receiving 2 infusions, and be below 10 mL of packed cell volume for each infusion.[13]

Both UIH-001 and UIH-002 are currently unpublished in peer-reviewed journals. Details regarding the inclusion/exclusion criteria and study outcomes were obtained from the donislecel package insert and relevant FDA review documents.[10,13,14]

7.1 Study population

Across both studies, a total of 30 adults (UIH-001, N=10; UIH-002, N=20) with T1D received at least one donislecel infusion, up to a maximum of 3 infusions (56 total infusions were administered).[10,13] To be eligible for either study, participants had to be at least 18 years of age and have T1D for at least 5 years.[13,14] Despite intensive insulin management efforts, UIH-002 also required participants to experience at least one episode of severe hypoglycemia within the previous 3 years and have a history of hypoglycemia unawareness, whereas UIH-001 required at least one of the following: a) hypoglycemia unawareness, b) ≥2 episodes of severe hypoglycemia or ≥2 DKA-related hospital visits within the previous year, or c) progressive diabetes-related microvascular complications (ie, retinopathy, nephropathy, or neuropathy).[14,37,38] **Table 5** summarizes key inclusion criteria for these donislecel clinical trials. Although exclusion criteria across both studies were generally similar, UIH-002 had a unique exclusion criterion of known family history of medullary cancer of the thyroid or multiple endocrine neoplasia type 2.[13] Complete inclusion criteria and exclusion criteria for both studies are provided in **Appendix E**.

Demographics of the included patient population across both trials were a median age of 46.5 years, mostly female (80%), and predominantly non-Hispanic Caucasian.[10,14] Baseline characteristics were similar across both trials: the mean time since T1D diagnosis was 28 years in UIH-001 and 29.4 years in UIH-002; the mean baseline HbA1c was 7.3 in UIH-001 and 7.4 in UIH-002; and the mean frequency of severe hypoglycemic events over 1 year was 0.1 in UIH-001 and 0.5 in UIH-002.[13,14] While most

participants in UIH-001 had T1D-related microvascular complications, 6 participants (30%) in UIH-002 also had retinopathy and/or neuropathy.[13]

Table 5. Key Inclusion Criteria for Donislecel Clinical Trials (UIH-001 and UIH-002)[14,37,38]

Key Inclusion Criteria	UIH-001 Study	UIH-002 Study
Age	18 to 65 years	18 to 75 years
T1D duration	>5 years	>5 years
	AND at least one of the following:	**AND both of the following:**
Episodes of metabolic instability[a]	• ≥2 episodes of severe hypoglycemia, or • ≥2 DKA-related hospital visits within the previous year	• ≥1 episode of severe hypoglycemia[b] in the previous 3 years
Metabolic complications[a]	• Hypoglycemia unawareness[c]	• Hypoglycemia unawareness[c]
Progressive diabetes-related microvascular complications[a]	• Retinopathy[d], or • Nephropathy[e], or • Neuropathy[f]	

[a] *Experienced by the participant despite optimal efforts to control glucose with intensive insulin management*

[b] *Defined as an episode showing consistent symptoms of hypoglycemia, necessitating aid from another person, and either a blood glucose value <50 mg/dL or rapid resolution following the administration of glucose, carbohydrates, or glucagon.*

[c] *Defined as a self-reported lack of appropriate autonomic symptoms when blood glucose levels decrease below 54 mg/dL*

[d] *Retinopathy progression is defined by at least a three-step advancement (based on ETDRS grading), or a comparable result as determined by an ophthalmologist experienced in diabetic retinopathy*

[e] *Nephropathy progression is defined as an increase in microalbuminuria of ≥72 mg/24 hours (50 µg/min) over at least a 3-month period (starting at any point within the previous 2 years), despite ACE inhibitor therapy*

[f] *Defined as persistent or worsening autonomic neuropathy (eg, gastroparesis, postural hypotension), or severe peripheral neuropathic pain unresponsive to standard treatments (eg, gabapentin).*

Abbreviations: ACE, angiotensin-converting enzyme; DKA, diabetic ketoacidosis; dL, deciliter; ETDRS, Early Treatment Diabetic Retinopathy Study; mg, milligram; min, minute; T1D, type 1 diabetes mellitus; µg, microgram

7.1.1 Donislecel administration

The criteria for subsequent infusions differed between both trials but generally included signs of declining islet cell function (eg, increased blood glucose levels) in the absence of exogenous insulin administration following the previous infusion.[10,13] The phase III trial (UIH-002) specifically allowed for subsequent islet infusions at any time during the 5-year follow-up period in patients who initially achieved insulin independence (ie, glycemic control without exogenous insulin requirement) for at least 30 days.[13]

Of the combined 30 participants enrolled in UIH-001 and UIH-002, 11 (37%) received 1 infusion, 12 (40%) received 2 infusions, and 7 (24%) received 3 infusions.[10,14] Most infusions (initial and repeat infusions) occurred within the first year of the participant's entry into the study, with 21 participants

receiving all eligible infusions within the first year.[13] The median islet number administered *per infusion* (initial and repeat infusions) was 399,178 EIN, representing a median islet dosage of 6,570 EIN/kg.[10]

7.1.2 Immunosuppressive regimen

Concomitant immunosuppression in both studies consisted of a steroid-sparing regimen (modified Edmonton Protocol) to prevent steroid-related β-cell toxicity and to improve engraftment and islet graft function.[10,14,17] In general, the immunosuppressive agents used were the same in both clinical trials, and included a combination of any of the following: anakinra, daclizumab (no longer available on the market), basiliximab, mycophenolate mofetil, etanercept, everolimus, sirolimus, tacrolimus, cyclosporine, and anti-thymocyte immunoglobulin[10]; it appears that life-long immunosuppression primarily included combination regimens with a calcineurin inhibitor and an mammalian target of rapamycin inhibitor.[13] Across both trials, all participants received tacrolimus and sirolimus, but the proportions of participants receiving additional agents varied.[10]

Other agents were permitted to be used such as anticoagulants (ie, heparin, enoxaparin), and prophylactic antibiotics (eg, valganciclovir, trimethoprim/sulfamethoxazole) to prevent procedural- or transplant-related complications.[14] Exenatide, a GLP-1 receptor agonist, was also permitted for use in both clinical trials; most participants had this as add-on therapy (6 participants [60%] in UIH-001 and 20 participants [100%] in UIH-002).[10]

A considerable confounding factor of these trials is the undocumented adherence of exenatide (eg, dose changes, discontinuation, initiation) and use of other undocumented diabetes medications that the FDA reviewers discovered participants were using during the study, which were not mentioned in the protocol.[14] Given the diverse patterns of exenatide utilization in both clinical studies, there is insufficient data to substantiate the use of exenatide in patients treated with donislecel.[10]

7.2 Efficacy outcomes

All participants in UIH-001 and 18 participants (90%) in UIH-002 completed the minimum follow-up at 1 year after the previous infusion.[14] Of the 2 participants that withdrew during the initial year in UIH-002, one withdrew due to immunosuppression-related adverse effects, and the other became non-compliant to the immunosuppression therapy, with neither participant achieving insulin independence.[14] The total duration of follow-up after the first infusion varied among enrolled participants across both clinical trials: 12 participants were followed for 1 to 5 years, 12 participants for 5 to 10 years, and 4 participants for more than 10 years.[14]

According to the FDA advisory review, the FDA review team decided the main efficacy endpoint (post-hoc) was the occurrence of insulin independence (ie, no longer requiring exogenous insulin for glycemic control) as determined by an integrated analysis across both trials.[13] While this constituted the primary endpoint in UIH-001, it was a pre-defined secondary endpoint in UIH-002. This outcome on insulin independence was deemed to be a stronger indicator of clinical benefit for UIH-002 instead of the original proposed composite efficacy primary endpoint for absence of severe hypoglycemic events and a HbA1c ≤6.5%.[13]

Overall, 25 participants (83%) achieved *any duration* (ranging from 4 days to 12.9 years) of insulin independence (defined as no longer requiring exogenous insulin treatment) after receiving 1 to 3 infusions of donislecel.[10,14] Of the 5 participants who did not achieve insulin independence (all enrolled in UIH-002), 4 received 1 infusion, and the remaining participant received 2 infusions.[14] For the 25 participants who attained insulin independence, 4 participants sustained insulin independence for <1 year, 12 participants for 1 to 5 years, and 9 participants for >5 years.[10] As of April 24, 2023, 4 participants have maintained insulin independence, ranging from 11.0 to 17.6 years from their first infusion.[14] The duration of insulin independence did not appear to be influenced by baseline demographic factors such as duration of diabetes, number of severe hypoglycemic events, HbA1c, sex, or age.[13,14]

At the time of their second infusion, 6 of the 19 participants had achieved insulin independence.[10] Overall, 11 participants did not undergo a second infusion: 4 were insulin independent, 3 lacked a donor, and 4 were either intolerant to the immunosuppression therapy or had withdrawn from the study. All 7 participants who received a third infusion achieved insulin independence. One participant was unable to receive a third infusion due to infection.[10]

Table 6 provides the mean duration of insulin independence, according to the total number of donislecel infusions in all participants, for each of the clinical trials. Importantly, the results suggest that a patient's response to donislecel (ie, attaining insulin independence) cannot be estimated based on the overall number of infusions.

Table 6. Duration of Insulin Independence by Number of Donislecel Infusions Received, According to the Clinical Trial (UIH-001 or UIH-002)[10,13,14]

Total number of infusions	UIH-001			UIH-002		
	Number of participants		Mean duration of insulin independence (years; SD)[a]	Number of participants		Mean duration of insulin independence (years; SD)[a]
	Achieving insulin independence	Total		Achieving insulin independence	Total	
1	3	3	6.0 (5.7)	4	8	1.6 (3.4)
2	2	2	8.3 (6.4)	9	10	4.1 (2.7)
3	5	5	3.3 (1.9)	2	2	5.1 (1.0)

[a] *The numbers for the mean duration of insulin independence were obtained from 'Alternative Text 1' located in Appendix 5 of the FDA advisory committee review.*[13]

Abbreviations: FDA, US Food and Drug Administration; SD, standard deviation; UIH, University of Illinois Hospital and Health Sciences System or UI Health; US, United States

7.3 Safety outcomes

The safety analysis[††] from the FDA included all participants enrolled in both donislecel clinical trials (UIH-001 and UIH-002; 30 total participants; encompassing 56 total infusions), followed for a mean duration of 6.5 years.[13,14] In both clinical trials, donislecel was administered to participants at different time points, making a direct comparison of adverse events (AEs) rates challenging, which was further compounded by the lack of a control group.[13,14] Additionally, the rate of AEs may have varied based on the total number of donislecel infusions received.[9]

In total, 27 participants (90%) experienced at least 1 serious AE, usually caused by the infusion procedure or concomitant immunosuppressive therapy, and 8 participants (27%) experienced at least 1 life-threatening AE.[10] The most common immunosuppression-related AEs that resulted in a serious reaction were infections (87%) and malignancy (37%). Certain serious AEs (eg, infections, malignancies) necessitated the cessation of immunosuppressive agents, either temporarily or permanently, in 8 participants. As a result, these participants eventually experienced islet cell function loss and insulin non-independence (if insulin independence was achieved), but the exact timeframe of losing islet cell viability upon discontinuing immunosuppressive therapy is unclear. Anemia was also a commonly reported AE (any severity, 80% of participants) that may have been due to immunosuppression or possibly procedural-related complications associated with bleeding. The main causes of a serious infusion procedure-related reaction were liver laceration, hematoma, intra-abdominal bleeding, and hemorrhage (occurring in a combined total of 13% of participants), and increased portal pressure (7% of participants), which was often transient. Overall, the most commonly reported AEs (occurring in 80−90% of participants), from the initial infusion through 1 year after the final infusion, were fatigue, nausea, anemia, and diarrhea.[10]

According to the FDA review memorandum, at 1 year post-initial infusion, 6 participants (20%) experienced a sustained decline from mild to moderate renal impairment, and 1 participant (3%) experienced a transient decline from moderate to severe renal impairment.[14] No participants exhibited a persistent decline to severe renal impairment or progressed to end-stage renal disease.[14]

Donislecel may increase the development of panel reactive antibodies (PRA), which can adversely influence the eligibility of a patient for a renal transplant (see **Section 10.2** for *warnings and precautions*).[10] Across both clinical trials, 6 participants (of the 28 who had PRA findings; 21%) had a Class I PRA ≥20% after being treated with donislecel: 1 participant received 1 infusion, 3 participants received 2 infusions, and 2 participants received 3 infusions.[10]

Two deaths were reported, both occurring in UIH-002: 1 participant died from multi-organ failure due to sepsis (1.6 years following their first and only infusion), and the other participant died from global atrophy, progressive confusion, and micro-ischemic disease (9.7 years following their first infusion; received a total of 2 infusions).[10,14] At or up to the time of the event, both participants were taking concomitant immunosuppressive therapy.[10,14]

[††] Refer to **Section 10.0** for additional safety information from these trials, as reported by prescribing information.

Table 7 provides an overview of select AEs that occurred over the total duration of follow-up, unless otherwise noted, in the pooled population across UIH-001 and UIH-002.

Table 7. Select Combined Safety Outcomes, per Clinical Trials (UIH-001 and UIH-002)[a 10,14]

Immunosuppression-related adverse events (AEs):

- Infections: 211 events (26 participants)
  - 22 events were severe, 115 events were moderate, and 1 was life-threatening
  - 1 participant died from multi-organ failure due to sepsis (1.6 years following their first and only infusion)
- Malignancies: 16 events (11 participants)
  - 3 events were life-threatening
  - 12 skin cancers, 1 lymphoproliferative disease, 1 breast cancer, and 1 thyroid cancer
- Anemia[b]: 90 events (24 participants)
  - 9 events were severe (Hgb 6.5 to <8 g/dL), 27 were moderate (8 to <10 g/dL), and 1 was life-threatening (Hgb <6.5 g/dL)
    - Severe and life-threatening AEs required transfusion: 5 transfusions were given to 5 participants
    - Procedural-related complications: 3 transfusions (number of participants: not reported)
    - Non-procedure related complications: 2 transfusions (number of participants: not reported)
- Renal impairment from baseline to 1 year after the first infusion:
  - 6 participants experienced a sustained decline from mild (eGFR 60 to 89 mL/min/1.73 m^2) to moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2)
  - 1 participant experienced a transient decline from moderate to severe (eGFR 15 to 30 mL/min/1.73 m^2) renal impairment
  - No participants exhibited a persistent decline to severe renal impairment or progressed to ESRD

Procedural-related adverse events (AEs):

- Liver laceration: 1 event (life-threatening)
- Intraabdominal hemorrhage: 1 event
- Perihepatic hematomata: 2 events that required prolonged hospitalization
- Increased portal pressure (≥22 mmHg):
  - Necessitating stopping the procedure: 2 participants
  - Incomplete donislecel delivery: 1 participant

Panel reactive antibodies (PRA):

- Shift from baseline class I PRA <20% to ≥20% post treatment with donislecel: 6 participants (of 28 total)
  - 1 infusion: 1 participant (of 9 total; 11%)
  - 2 infusions: 3 participants (of 12 total; 25%)
  - 3 infusions: 2 participants (of 7 total; 29%)

[a] The total number of participants is 30 unless otherwise noted. Reflects AEs over the total follow-up period (mean of 6.5 years).

[b] In addition to immunosuppression, anemia may also be caused by procedure-related complications (eg, bleeding).

Abbreviations: AE(s), adverse event(s); dL, deciliter; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; g, gram; Hgb, hemoglobin; m, meter; min, minute; mL, milliliter; mmHg, millimeters of mercury; PRA, panel reactive antibodies

8.0 PLACE IN THERAPY

The exogenous delivery of insulin, either from MDI or an insulin pump, is essential for patients with T1D.[7,14] However, some patients with T1D experience challenges with preventing hyperglycemia, a potentially life-threatening condition, even with the use of advanced insulin pump devices and appropriate blood glucose monitoring.[14]

Except for whole-pancreas transplantation or clinical studies for other experimental procedures (eg, stem-cell transplant), islet cell transplantation, such as donislecel, is currently the only therapy in the US that can potentially restore endogenous insulin secretion and physiologic glycemic control for patients with T1D.[14,15,39,40] Donislecel is approved for adults with T1D who fail to achieve HbA1c goals due to recurrent severe hypoglycemic episodes, despite intensive diabetes management and education.[10] For these patients, donislecel offers a less invasive procedure (compared to whole-organ pancreas transplantation) that can potentially eliminate the need for exogenous insulin administration.[1,14] However, it is important to consider that the sustained effectiveness of donislecel is likely contingent upon continued immunosuppression, which carries its own risks (eg, infections, malignancies).[10,14] Nonadherence or discontinuation of immunosuppressive therapy may lead to the deterioration of islet cell viability, compromising any attained insulin independence.[14] Therefore, the use of donislecel should be reserved for a subset of patients with T1D who are able to tolerate immunosuppressive therapy and for whom intensive diabetes management fails to prevent recurrent severe hypoglycemic episodes,[10,14] which is generally in alignment with recent guidance from guidelines and consensus/position statements for islet cell transplantation (see **Table 4**).[1,7,29,31]

9.0 SPECIAL POPULATIONS

Patients with concurrent medical conditions, including pregnancy, should not receive donislecel if they are contraindicated to the infusion procedure or specific immunosuppression regimen.[10] Although the risks of donislecel administration during pregnancy, including procedure-related risks, have not been evaluated in human or animal studies, certain immunosuppressive agents required for concomitant use of donislecel have been associated with fetal malformations. Therefore, a negative pregnancy test is required before starting donislecel in patients who may become pregnant. Additionally, effective contraception is recommended before starting donislecel and chronically thereafter, provided the patient continues to be of reproductive potential. Notably, fertility (male and female) may be affected by certain immunosuppressive agents.[10] If pregnancy occurs, the patient should be advised to contact their transplant healthcare provider immediately and immunosuppression should be discontinued due to the risk of severe AEs (eg, fetal malformations, prematurity).[10,13]

The effects of donislecel on a breastfed infant are unknown.[10] However, certain concomitant immunosuppressive agents may be present in breast milk. Therefore, patients receiving donislecel should consider the risks and benefits of breastfeeding.[10]

According to product labeling, donislecel has not been studied in pediatric patients with T1D.[10] Additionally, an insufficient number of older adults (>65 years of age) were enrolled in the clinical trials of donislecel. Consequently, there is a lack of data to ascertain whether the safety and efficacy of donislecel varies between older and younger adults.[10]

No specific dosage adjustments for donislecel are provided in the product labeling (ie, package insert) for patients with hepatic or renal impairment.[10] There is insufficient evidence to support the safe and effective use of donislecel in patients with hepatic disease or renal failure, or those who have undergone a renal transplant. Consideration must be taken in patients who may require a renal transplant as donislecel has the potential to develop or elevate PRAs, which can negatively influence the ability to obtain a donor match, and thereby, renal transplant candidacy (see **Section 10.2** for donislecel *warnings and precautions*).[10]

Table 8 provides an overview of donislecel use in special populations, according to prescribing information.

Table 8. Recommendations for Donislecel Use in Special Populations[a] [10]

Special population	Key considerations

Pregnant patients	• Pregnancy is a contraindication to donislecel due to the need for concomitant immunosuppression. A negative pregnancy test is required before starting donislecel in patients who may become pregnant due to the need for long-term immunosuppression
	  ○ Certain immunosuppressive agents have been associated with fetal malformations
	• Effective contraception is recommended before starting donislecel and chronically thereafter
	• Immunosuppression should be discontinued if pregnancy occurs
	• There is no human or animal data on the use of donislecel during pregnancy
	  ○ The clinical trials of donislecel (UIH-001 and UIH-002) excluded pregnant patients likely due to the potential harm from concomitant immunosuppressive therapy required with donislecel treatment.[13,14]

Patients who are breastfeeding	• Effects of donislecel on a breastfeed infant are unknown • It is unknown if donislecel is excreted in breast milk[41] • Patients receiving donislecel should consider the risks and benefits of breastfeeding, especially given the need for long-term immunosuppressive agents, which may be present in breast milk, following donislecel use
Pediatric patients	• Donislecel has not been studied in the pediatric population (<18 years old)
Older adults	• The maximum enrollment age permitted in UIH-001 and UIH-002 was 65 years and 75 years, respectively.[14] However, an insufficient number of older adults were enrolled to ascertain whether the safety and efficacy of donislecel varies between older and younger adults.
Patients with renal or hepatic impairment	• Insufficient evidence exists to support the safe and effective use of donislecel in patients with hepatic disease or renal failure, or those who have undergone a renal transplant ○ The clinical trials of donislecel (UIH-001 and UIH-002) excluded patients with renal disease (defined as macroalbuminuria, serum creatinine >1.5 mg/dL, or creatinine clearance <80 mL/min/1.73 m^2), and those who received a prior transplant (except for islet cell transplantation, for UIH-002).[13,14] • No specific dosage adjustments for donislecel are provided in the product labeling

[a] Most of the information reported in the table was obtained from the prescribing information (ie, package insert)[10]; supplemental information was obtained from relevant FDA review documents regarding the clinical trials (UIH-001 and UIH-002) for donislecel approval.[13,14]

Abbreviations: dL, deciliter; m, meter; mg, milligram; mL, milliliter; min, minute; UIH, University of Illinois Hospital and Health Sciences System or UI Health

10.0 SAFETY

Below is a summary of reported adverse events (AEs), and warnings and precautions, as reported in the donislecel prescribing information. Notably, donislecel should not be given to patients with conditions that are contraindicated to immunosuppressive therapy (eg, pregnancy) or the infusion procedure.[10] **Section 10.3** outlines specific considerations for discontinuing immunosuppressive therapy after receiving donislecel.

10.1 Adverse events[‡‡]

Owing to the variations in follow-up duration, number of infusions, and timing between infusions across the two donislecel clinical trials (UIH-001 and UIH-002), AEs were reported for the overall duration of each participants follow-up period, which ranged from 0.3 to 14.5 years after the initial infusion.[10] Across both UIH-001 and UIH-002, 27 participants (90%) experienced at least one *serious* AE, most often attributed to the infusion procedure or immunosuppression.[10] For the infusion procedure, the most common causes of a serious AE were liver laceration/hematoma, intra-abdominal bleeding, and hemorrhage (combined total of 4 participants; 13%), and portal hypertension (2 participants; 7%). Notably, anemia may have been due to immunosuppression or possibly procedural-related complications associated with bleeding. Severe and life-threatening reactions necessitated transfusions, with a total of 5 transfusions administered to 5 participants. Of these, 3 transfusions were associated with procedural complications, while the remaining 2 were non-procedure related. Most of the serious AEs for immunosuppression were attributed to infections (26 participants; 87%) and malignancy (11 participants; 37%).[10]

The most common AEs (50−90% of participants) of any severity, occurring after the initial infusion through 1 year after the final infusion, were nausea, fatigue, anemia, diarrhea, abdominal pain, asthenia, headache, hyponatremia, increased transaminases, upper respiratory tract infection, vomiting, and urinary tract infection.[10] AEs of Grade 3 or higher[§§] experienced by the greatest percentage of treated participants, from the first infusion to 1 year after the final infusion, were increased low density lipoprotein (37%), anemia (27%), pneumonia (17%), diarrhea (13%), hyponatremia (13%), and urinary tract infection (10%).[10]

10.2 Warnings and precautions

Product labeling for donislecel includes the following warnings and precautions[10]:

- **Concomitant immunosuppression risks:** To maintain islet cell viability, *life-long* immunosuppression is required in patients receiving donislecel. However, prolonged immunosuppression increases the risk of infections, severe anemia, and malignancies. Therefore, patients should receive appropriate vaccinations, particularly live vaccinations, before being treated with donislecel. Prophylaxis for *Pneumocystis jirovecii* pneumonia (PCP) and cytomegalovirus (CMV) should be administered

[‡‡] Refer to **Section 7.3** for additional safety information from UIH-001 and UIH-002.
[§§] Grade 3 events were severe, but not immediately life-threatening, that required hospitalization or resulted in disability or limited activities of daily living; Grade 4 events posed a threat to life or required urgent intervention; and Grade 5 events were related to death.

immediately after the donislecel infusion, and continued as directed according to the anti-infective's prescribing information. Patients should be monitored for signs of infection, anemia, and malignancy following donislecel treatment.

- **Procedural complications:** Following the administration of donislecel, liver laceration, intra-abdominal bleeding, and hemorrhage have occurred. Portal blood pressure, bleeding, and the potential development of portal vein thrombosis should be monitored during and immediately after the donislecel infusion (see **Table 3**).
- **Increased risk of islet graft rejection:** Patients exhibiting a positive T- and B-cell crossmatch between donor lymphocytes and recipient serum may undergo rapid rejection of the islet cells. The T- and B-cell crossmatch assay operates in a binary manner, necessitating negativity for both T- and B-cells to minimize the risk of rejection.
- **Transmission of donor-derived infections:** Donislecel is associated with the potential risk of transmitting communicable diseases from the donor to the recipient. After donislecel treatment, patients should be monitored for signs of active infection, and if infection is suspected, treated appropriately.
- **Panel reactive antibodies (PRA):** The administration of donislecel may result in an increase in PRA levels, potentially affecting the eligibility of the patient for a renal transplant. The benefit-risk profile of donislecel should be carefully weighed when considering use in a patient who may undergo a renal transplant in the future.

10.3 Considerations for discontinuing immunosuppressive therapy

Although immunosuppressive therapy should be continued permanently after receiving donislecel, the following are clinical scenarios that warrant discontinuing immunosuppressive therapy, per the donislecel prescribing information[10]:

- The patient develops a fatal malignancy or infection, and the prescribed treatment necessitates the cessation of immunosuppressive therapy
- The patient becomes pregnant
- The patient has relied on exogenous insulin for a duration of two years following their most recent infusion. *Note that the patient may continue immunosuppressive therapy if they have attained the target HbA1c without recurring severe hypoglycemia, while exhibiting clinically relevant C-peptide levels, suggesting the potential benefits of immunosuppression outweigh the risks*.

11.0 DRUG-DRUG INTERACTIONS

According to the FDA review memorandum, there are no known drug interactions with donislecel, including with concomitant immunosuppressive therapy.[14] Prescribing information for donislecel does not provide any information on potential interactions.[10]

12.0 UTAH MEDICAID UTILIZATION DATA

There are not yet any pharmacy or medical claims, including inpatient claims, for donislecel among the Utah Medicaid Fee-for-Service population from June 2023 (month of FDA approval) through November

2023 (personal communication [email] with Jacob Crook, MS, Data Manager/Analyst, December 13, 2023).

13.0 CONSIDERATIONS FOR PRIOR AUTHORIZATION (PA) CRITERIA

The Drug Utilization Review (DUR) board may consider implementing the following prior authorization (PA) criteria for donislecel-jujn (Lantidra) to guide appropriate prescribing:

Considerations regarding patient eligibility for donislecel therapy:

- Patient should meet the FDA indication for donislecel based on provider attestation or clinical documentation:
    - Patient is an adult (≥18 years of age)
        - Donislecel is FDA-approved for adults.[10] Use in adults (≥18 years of age) is congruent with the youngest age enrolled in the 2 donislecel trials, UIH-001 and UIH-002.[13,14] The safety and effectiveness of donislecel has not yet been determined for pediatric patients <18 years of age.[10]
    - Patient has T1D and is unable to achieve their target glycemic goal (as measured by HbA1c) despite intensive diabetes management (eg, MDI or insulin pump therapy + glycemic monitoring with a CGM) and education.[10]
        - Note that "intensive diabetes management" is not explicitly defined in donislecel prescribing information, nor in FDA review documents regarding the donislecel clinical trials (UIH-001 and UIH-002).[10,13,14] Prescribing information hints that intensive diabetes management should include insulin, devices, and education.[10]
    - Patient has a history of, or currently experiences, severe recurrent hypoglycemic episodes.[10] For example, severe hypoglycemic episodes may be defined as an episode showing consistent symptoms of hypoglycemia, necessitating aid from another person, and either a blood glucose value <50 mg/dL or rapid resolution following the administration of glucose, carbohydrates, or glucagon.[14,38]
        - No evidence of benefit from donislecel in patients with well-controlled diabetes on insulin treatment, or those with hypoglycemia unawareness capable of preventing repeated severe hypoglycemic episodes (neuroglycopenia that requires outside intervention) while using intensive management.[10]
- May consider requiring patients to try (or be inappropriate for) automated insulin delivery (AID) systems (ie, insulin pump with automated insulin dosing and integrated CGM), or other CSII pump with CGM integration and advanced technology (eg, low-glucose suspend) if the patient is not a candidate for or unwilling to use an AID system.
    - In general, we infer that patients should explore a comprehensive array of insulin management therapies, including education and other advanced technologies for managing hypoglycemia (eg, insulin pump + CGM), prior to considering donislecel, especially given the potential risks of life-long immunosuppression. According to the 2020 ABCD position statement, it is ideal for patients to have previously trialed an insulin pump and CGM before determining suitability for islet cell transplantation, but this is not required.[29]

- Consider requiring provider attestation that the patient does not have a concomitant condition, including pregnancy, that is contraindicated to immunosuppressive therapy or the infusion procedure. Specifically for pregnancy, may consider requiring provider attestation that the patient is not pregnant (confirmed by a negative pregnancy test) prior to each infusion of donislecel, and that the patient intends to use effective contraception after receiving donislecel therapy.
    - Donislecel product labeling recommends that patients who may become pregnant should have a negative pregnancy test before starting donislecel due to the potential risk of fetal malformations that can result from immunosuppressants, and should use effective contraception before starting donislecel and chronically thereafter, provided the patient continues to be of reproductive potential.[10]

Considerations related to provider eligibility to prescribe:

- Consider requiring donislecel be prescribed by, or in consultation with, a provider specialized in islet cell transplantation, such as an endocrinologist, surgeon, or interventional radiologist.[10]

Considerations related to donislecel dosage and concomitant medications:

- In accordance with the FDA-approved labeling, require the first donislecel infusion be at least 5,000 equivalent islet number (EIN)/kg, and subsequent infusions (second and third) be at least 4,500 EIN/kg.[10]
    - The maximum dose should not exceed 1 x 10^6 EIN.[10]
- Consider requiring provider attestation that the patient will receive concomitant immunosuppressive therapy consisting of a steroid-sparing regimen (see **Table C1** for pre- and post-infusion immunosuppressive regimens recommended in the donislecel labeling), and prophylaxis for PCP and CMV after the donislecel infusion.

Considerations for subsequent donislecel infusions (up to 2 additional infusions):

- If the patient does not achieve adequate glycemic control while taking the prescribed immunosuppressive therapy, a second or third infusion of donislecel can be considered.[10] Donislecel prescribing information recommends a second or third infusion for patients a) who still require exogenous insulin within 1 year of a previous infusion, or b) within 1 year after losing exogenous insulin independence (regardless of duration from the prior infusion).[10]
    - UIH-001 and UIH-002 permitted a maximum of 3 infusions to be administered; there is a paucity of information about the effectiveness and safety beyond 3 infusions.[10,14]
    - Repeat infusions are not recommended for people with a history of portal thrombosis (unless the thrombosis only affected the second- or third-order portal vein branches).[10]

Additional considerations:

- Consider requiring provider attestation that the patient has received all necessary vaccinations (including live vaccinations), according to the most up-to-date guideline recommendations, before starting donislecel.[10]
- Consider requiring provider attestation that the provider has discussed with the patient, and appropriately weighted the risks and benefits, that donislecel may potentially increase panel reactive antibodies (PRAs), and thus may negatively impact future renal transplant eligibility.[10]

- To minimize the risk of islet graft rejection, may consider requiring that patients have a negative T- and B-cell crossmatch between the donor lymphocytes and recipient serum.[10]
- May consider requiring provider attestation that the patient does not have one or more of the following before each infusion[14]:
    - An active infection (eg, hepatitis B or C, tuberculosis)
    - Malignancy (*except basal or squamous cell carcinoma that is appropriately treated*)
    - A high-risk of bleeding (eg, hemoglobin value <12 g/dL for women and <13 g/dL for men, antiplatelet or anticoagulant use, history of Factor V deficiency)[14]
    - Liver disease
        - Although not a contraindication, it is important to consider that patients with liver disease may not be suitable candidates for donislecel because it is infused directly into the hepatic portal vein, which can potentially result in liver laceration or other procedural-related risks (eg, portal vein thrombosis, portal hypertension, life-threatening bleeding).[10]
        - In UIH-001 and UIH-002, participants were excluded if they had elevated liver function tests (>1.5 times the upper limit of normal).[14] Additionally, according to prescribing information, there is insufficient evidence to support the use of donislecel in patients with liver disease.[10]

14.0 SUMMARY

Type 1 diabetes mellitus (T1D) is characterized by destruction (usually autoimmune-mediated) of insulin-producing pancreatic β-cells, ultimately leading to a complete deficiency of endogenous insulin.[1-6] Without chronic exogenous insulin therapy, delivered either by multiple daily injections (MDI) or an insulin pump,[7] T1D is life-threatening.[1,7] Despite adherence to insulin treatment, some individuals with T1D (eg, those with severe recurrent hypoglycemia) may struggle to attain the necessary glycemic targets required to prevent diabetes-related complications.[8,9]

Donislecel-jujn (Lantidra), a single company's (CellTrans, Chicago, Illinois) preparation of an allogeneic (deceased donor-derived) islet cellular transplant product,[12] can potentially restore endogenous insulin secretion and physiologic glycemic control by delivering functional donor β-cells to the recipient, thereby potentially eliminating the need for exogenous insulin delivery.[10] Donislecel was approved by the United States (US) Food and Drug Administration (FDA) in June 2023 for *adults* with T1D who fail to achieve glycated hemoglobin (HbA1c) goals due to recurrent severe hypoglycemic episodes, despite the use of intensive diabetes management and education.[9,10] Prior to donislecel's approval, islet cell transplantation was considered an investigational procedure in the US, only to be conducted for research purposes in clinical trials, and therefore usually non-reimbursable by health insurance payors.[15,16,21]

Donislecel is administered through a *single* infusion into the hepatic portal vein, *with the option for up 2 additional infusions* for patients a) who still require exogenous insulin within 1 year of a previous infusion, or b) within 1 year after losing exogenous insulin independence (regardless of duration from the prior infusion).[10] It must be administered by a healthcare provider specialized in islet cell transplantation, within a controlled aseptic environment (eg, radiology suite, operating suite). Treated

patients should continue exogenous insulin until reaching insulin independence; the duration for achieving insulin independence is highly variable among patients, ranging from weeks to potentially never occurring, or not being sustained long-term.[10] Similar to other transplantation procedures (eg, pancreas transplantation), donislecel-treated patients require *life-long* immunosuppression to mitigate the risk of allogeneic graft rejection and/or the resurgence of immune-mediated destruction of islet cells[***].[1,7,10]

Recent clinical practice guidelines and consensus/position statements predate FDA approval of donislecel, and therefore do not specifically address its use; however, given that donislecel is a islet cell transplant, guidance regarding islet cell transplantation is applicable.[1,7,29,31] In general, islet cell transplantation is reserved for patients with T1D who have severe metabolic complications (eg, severe recurrent hypoglycemia, hypoglycemia unawareness) or severe glycemic lability despite optimal T1D management, or who may be ineligible for a pancreas transplant (eg, older adults).[1,7,29,31,34]

Two non-randomized, single-arm studies (UIH-001 and UIH-002) evaluated the use of donislecel, administered as 1 infusion up to a maximum of 3 infusions, among adults (≥18 years of age) with long-standing T1D (at least 5 years) and hypoglycemia unawareness and/or metabolic instability (eg, severe hypoglycemia) [10,13,14] The phase I/II study (UIH-001) was started in 2004 and the phase III study (UIH-002) in 2007; both trials were conducted at a single center (University of Illinois Hospital & Health Science System).[13,14]

Each study included a minimum **follow-up duration of 1 year after the previous infusion, with the option for additional follow-up at 5 and 10 years**.[13,14] Based on a pooled analysis across both trials (combined total of 30 participants), 25 participants (83%) achieved *any duration* of insulin independence (ie, achievement of glycemic control without exogenous insulin administration) after receiving 1 to 3 infusions of donislecel.[10,14] Of these, 4 participants sustained insulin independence for <1 year, 12 participants for 1 to 5 years, and 9 participants for >5 years.[10] Of the latter 9 participants, 4 have maintained insulin independence (as of April 2023), with the duration ranging from 11.0 to 17.6 years from their first infusion.[14]

Treatment with donislecel was associated with serious adverse reactions, typically due to the infusion procedure (liver laceration, hematoma, intra-abdominal bleeding, hemorrhage, and increased portal pressure) or immunosuppression (infections or malignancy).[10] Anemia was also a commonly reported reaction, usually caused by immunosuppression or procedural-related bleeding complications.[10]

Based on the donislecel prescribing information and the 2 clinical trials used in the FDA-approval for donislecel (UIH-001 and UIH-002), considerations for donislecel prior authorization (PA) criteria were developed to ensure appropriate use within the Utah Medicaid population. These criteria include recommendations regarding patient eligibility based on meeting the FDA-approved indication (ie, adults with T1D who fail to achieve HbA1c goals due to recurrent severe hypoglycemic episodes, despite intensive diabetes management and education), safety considerations, required concomitant immunosuppressive therapy, provider eligibility, and consideration for up to 3 total donislecel infusions.

[***] Note that certain clinical scenarios warrant discontinuing immunosuppressive therapy (eg, pregnancy). Please refer to **Section 10.3** for a complete list of these considerations, according to donislecel prescribing information.

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APPENDIX A: LITERATURE SEARCH STRATEGIES

Embase Search, Conducted November 8, 2023 (*yielded 3 results; none were a systematic review or randomized controlled trial*):

'donislecel'/exp OR 'donislecel':ti,ab,kw OR 'lantidra':ti,ab,kw OR 'bb-11807':ti,ab,kw OR 'bb 11807':ti,ab,kw

Ovid-Medline Search, Conducted November 8, 2023

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to November 7, 2023>

#	Searches	Results
1	(donislecel or Lantidra).ti,ab,kw,kf	2
2	(BB-11807).ti,ab,kw,kf	0
3	1 or 2	2[a]

[a] *None of the results were a systematic review or randomized controlled trial*

ClinicalTrials.Gov Search, Conducted November 8, 2023 (*yielded 1 result; NCT03791567, an expanded access study of donislecel for a subset of patients with T1D, aimed at addressing the interim period between completed clinical trials and the approval of the biological license application*):

'donislecel\(allogeneic islets of Langerhans for transplant\), under Intervention/treatment

Ovid-Medline Islet Cell Transplantation Review Search, Conducted November 8, 2023

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to November 7, 2023>

#	Searches	Results
1	*Diabetes Mellitus, Type 1/	72,634
2	(diabet* or type 1 DM or T1DM or T1D).ti	417,250
3	1 or 2	428,608
4	*Islets of Langerhans Transplantation/	7,691
5	(islet adj2 transplant*).ti	2,511
6	4 or 5	8,013
7	3 and 6	2,820
8	Limit 7 to “review articles”	609
9	Limit 8 to yr=“2020–Current”	84

APPENDIX B: DIAGNOSIS OF TYPE 1 DIABETES MELLITUS (T1D)

The general diagnosis of diabetes mellitus relies on clinical symptoms, in addition to laboratory criteria, establishing overt hyperglycemia. Meeting any of the following laboratory criteria is diagnostic for diabetes, according to the American Diabetes Association (ADA) and American Association of Clinical Endocrinology (AACE)[4,30]:

- Fasting plasma glucose (FPG) ≥126 mg/dL
- 2-hour plasma glucose ≥200 mg/dL after a 75-gram oral glucose tolerance test (OGTT)
- A1C ≥6.5%
- Random plasma glucose of ≥200 mg/dL if the patient is symptomatic

While the presence of hyperglycemic symptoms or hyperglycemic crisis and a random plasma glucose level ≥200 mg/dL confirms a diabetes diagnosis, repeat testing (ie, at least 2 abnormal results) is required for asymptomatic individuals.[4,29,30]

Screening for the presence of immunologic markers, such as islet autoantibodies, can help differentiate type 1 diabetes mellitus (T1D) from type 2 diabetes mellitus (T2D).[1,4,29,30] The 2021 consensus statement by the ADA and the European Association for the Study of Diabetes (EASD) mentions that the initial antibody to be assessed should be glutamic acid decarboxylase (GAD or GAD65); if the GAD test returns negative, islet tyrosine phosphatase 2 (IA-2) and/or zinc transporter 8 (ZnT8) should also be tested, if available.[1] The presence of positive islet autoantibodies (one or more) in an individual with clinical characteristics of T1D serves as a strong predictor of rapid progression and significant insulin deficiency.[1] Therefore, a patient in this clinical scenario is considered to have T1D even if they do not require insulin treatment at diagnosis.[1,29] Notably, a lack of autoantibodies or a negative result does not definitively exclude a diagnosis of T1D, and would require additional evaluation; approximately 5% to 10% of adult-onset T1D cases test negative for islet autoantibodies.[1,29] **Table B1** highlights the clinical sensitivity and specificity of 4 islet autoantibody tests approved by the United States (US) Food and Drug Administration (FDA).[42-45]

Table B1. Sensitivity and Specificity of Islet Autoantibody Assays, per Manufacturer[46-50]

Islet autoantibody	Test description	Clinical sensitivity	Clinical specificity
GAD	Semi-quantitative ELISA kit for use in human serum	83.0%	99.0%
IA-2[a]	Quantitative ELISA kit for use in human serum	58.2%	97.0%
ZnT8[a]	Semi-quantitative ELISA kit for use in human serum	68.0%	98.0%
Insulin	Semi-quantitative RIA kit for use in human serum	50.0%	99.0%

[a] *According to the manufacturer, this test should not be used alone to determine the diagnosis of T1D, but rather, should be used with other results.*

Abbreviations: ELISA, enzyme-linked immunosorbent assay; GAD, glutamic acid decarboxylase; IA-2, islet antigen-2; RIA, radioimmunoassay; T1D, type 1 diabetes mellitus; ZnT8, zinc transporter 8

Low or absent insulin secretion, as measured by the marker C-peptide, can be used to further support the diagnosis of T1D in those where a definitive diabetes type is uncertain at least 3 years after the general diabetes diagnosis, or for those who test negative for islet autoantibodies.[1,4,29] Although a low (<200 pmol/L) or absent C-peptide level may occur in other types of diabetes, this result, in the absence of hypoglycemia, indicates severe insulin deficiency and can be used to confirm T1D.[1,29] Nonetheless, neither the 2023 ADA guideline nor the 2022 AACE guideline provide a formal recommendation on C-peptide to aid in the diagnosis of T1D. **Table B2** provides a summary of select guideline recommendations for diagnosing T1D.

Table B2. Selected Guideline and Consensus/Position Statement Recommendations on the Diagnosis of Type 1 Diabetes Mellitus

Professional organization and guideline; publication year	**Recommendations** (Evidence grade)
United States Guidelines/Consensus Statements	
American Diabetes Association (ADA) Classification and Diagnosis of Diabetes: Standards of Care in Diabetes Guideline; 2023[4] [a]	Target age group/population for recommendations: children and adults with diabetes[35] • Diagnostic laboratory criteria for diabetes mellitus includes the following (**Ungraded discussion point**): ○ FPG ≥126 mg/dL (7.0 mmol/L)[b] or ○ 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) after a 75-gram OGTT or ○ A1C ≥6.5% (48 mmol/mol) using a standardized and certified assay or ○ Random plasma glucose ≥200 mg/dL (11.1 mmol/L) if the patient has symptoms of hyperglycemic crisis or hyperglycemia (eg, polydipsia, polyuria) • If a clear clinical diagnosis is not evident (eg, patient is symptomatic and has a random plasma glucose ≥200 mg/dL), then confirmatory diagnostic testing is required from either the same sample or separate samples, showing 2 abnormal results (**Ungraded discussion point**) • The presence of multiple confirmed islet autoantibodies is a risk factor for the onset of clinical T1D (stage 3); assessing dysglycemia can enhance the ability to predict short-term risk. When multiple islet autoantibodies are detected, consider referring the patient to a specialized center and/or enrolling the patient in a clinical trial or using an approved treatment with the goal of delaying progression to clinical T1D. (**B**)
American Association of Clinical Endocrinology (AACE) Developing a Diabetes Mellitus Comprehensive Care Plan Guideline; 2022[30] [c]	Target age group/population for recommendations: children and adults with diabetes • Diagnostic laboratory criteria for diabetes mellitus includes the following (**Grade A; BEL 2 and expert opinion**): ○ FPG ≥126 mg/dL (7.0 mmol/L)[b] or ○ 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) after a 75-gram OGTT while fasting for at least 8 hours prior or ○ A1C ≥6.5% (48 mmol/mol) or ○ Random (non-fasting) plasma glucose ≥200 mg/dL (11.1 mmol/L) if the patient has hyperglycemic symptoms (eg, polydipsia, polyuria) • If a clear clinical diagnosis is not evident (ie, patient is symptomatic and has a random plasma glucose ≥200 mg/dL), then confirmatory diagnostic testing is required from either the same sample or separate samples, showing 2 abnormal results. (**Grade A; BEL 2 and expert opinion**) • T1D is characterized by significant insulin deficiency with concurrent hyperglycemia, and positive autoantibodies to GAD65, IA-2, ZnT8, and/or insulin. To establish an accurate diagnosis and differentiate between T1D and T2D in pediatric and adult populations, it is essential to consider immune markers (ie, autoantibodies) and the clinical presentation, which can guide appropriate treatment. (**Grade A; BEL 2**)

*[a] Evidence rating from 2023 American Diabetes Association (**ADA**) guideline[35]: A (highest level of evidence): based on well-designed randomized controlled trials or well-conducted meta-analysis of randomized controlled trials; B (moderate level of evidence): based on well-conducted observational studies (cohort or case-control), or meta-analysis of observational studies; C (low level of evidence): based on poorly controlled or uncontrolled studies, or conflicting evidence where most of the weight supports the recommendation; E (no clinical evidence): based on clinical experience or expert consensus*

[b] Fasting is considered not eating for at least 8 hours

*[c] Evidence rating from 2022 American Association of Clinical Endocrinology (**AACE**) guideline[30]: BEL and evidence grade: Recommendation achieved >66% consensus was assigned Grade A, B, C, or D based on the BEL and the presence or absence of predominant negative or positive subjective evidence factors and/or qualifiers; recommendation with ≤66% consensus was assigned Grade D, regardless of the BEL and presence/absence of negative or positive subjective evidence factors and/or qualifiers. Grade A represents a strong recommendation, Grade B represents an intermediate recommendation, Grade C represents a weak recommendation, and Grade D is used for no clinical evidence and is based on expert opinion. Strong (level I) evidence: randomized controlled trials or meta-analysis of randomized controlled trials; intermediate (level II) evidence: observational studies; weak (level III) evidence: case series, case reports, economic studies, preclinical studies, research and explorative studies; no (level IV) evidence: based on opinion, theory, consensus, guideline, position, or other relevant research or significantly flawed study*

[d] Note that sentences in the ADA/EASD consensus report that used the wording "recommended" were assigned 'author consensus opinion', otherwise they were assigned 'ungraded discussion point'. While the recommendations were evidence-based when possible, the authors note that recommendations were based on their consensus opinion.

*[e] National Institute for Health and Care Excellence (**NICE**) recommendation strength: Consider: generally indicates a weak recommendation for the intervention, implying that the intervention should be used for certain patients if the benefits outweigh the risks; Should not: generally indicates a strong recommendation against the intervention.[36]*

Abbreviations: A1C, glycosylated hemoglobin or hemoglobin A1c; AACE, American Association of Clinical Endocrinology; ABCD, Association of British Clinical Diabetologists; ADA, American Diabetes Association; BEL, best evidence level; dL, deciliter; EASD, European Association for the Study of Diabetes; FPG, fasting plasma glucose; GAD(65), glutamic acid decarboxylase; IA-2, islet tyrosine phosphatase 2; L, liter; mg, milligram; mmol, millimole; mol, mole; NICE, National Institute for Health and Care Excellence; nmol, nanomole; OGTT, oral glucose tolerance test; pmol, picomole; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; ZnT8, zinc transporter 8

Table B2. Selected Guideline and Consensus/Position Statement Recommendations on the Diagnosis of Type 1 Diabetes Mellitus

Professional organization and guideline; publication year	**Recommendations** (Evidence grade)

American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)
 	
The Management of Type 1 Diabetes in Adults: A Consensus Report; 2021[1 d]
	Target age group/population for recommendations: adults with T1D
	• It is recommended to evaluate the presence of autoantibodies as the primary diagnostic step in adults suspected of having T1D (**Author consensus opinion**)
	  ○ The initial antibody measured should be GAD; if negative, IA-2 and/or ZnT8 should also be tested, depending on availability. (**Ungraded discussion point**)
	• Measurement of islet cell antibodies are no longer recommended due to its inherent biological assay imprecision, as more precise methods involving the direct measurement of individual antibodies have superseded it. (**Ungraded discussion point**)
	• In cases of diagnostic uncertainty, a random (non-fasting) C-peptide measurement, along with concurrent glucose assessment, within 5 hours of a meal, is recommended for individuals who are more than 3 years post-diagnosis. Note that C-peptide testing may also be used at initial presentation to differentiate T1D from monogenic diabetes in adults <35 years of age. (**Author consensus opinion**)
	  ○ For those who are taking insulin, the C-peptide measurement should be performed before insulin discontinuation (**Ungraded discussion point**)
	  ○ When possible, it is recommended to use plasma C-peptide testing, which exhibits slightly superior performance compared to urine measurements that may be affected by renal function. If decided to use the urinary C-peptide: creatinine ratio, a value <0.2 nmol/mol can serve as the threshold for severe insulin deficiency. (**Author consensus opinion**)

United Kingdom Guidelines/Position Statements	
National Institute for Health and Care Excellence (NICE) Type 1 Diabetes in Adults: Diagnosis and Management; 2022[31 e]	Target age group/population for recommendations: adults (≥18 years) with T1D • Adults suspected of having T1D should be tested for islet autoantibodies, taking into consideration that a false negative rate is lowest closer to the time of diagnosis, and the false rate can be minimized by testing for 2 different autoantibodies (with at least 1 positive). (**Ungraded recommendation**) • For cases of diagnostic uncertainty regarding diabetes type in islet autoantibody-negative patients, a random (non-fasting) plasma C-peptide measurement, with a concurrent glucose assessment, should be considered. • During follow-up clinical assessments, consider measuring plasma C-peptide to reevaluate the diagnosis of diabetes type if uncertainty exists regarding the accuracy of the T1D diagnosis. • Routine measurement of C-peptide should not be used to confirm T1D

[a] *Evidence rating from 2023 American Diabetes Association (**ADA**) guideline[35]: A (highest level of evidence): based on well-designed randomized controlled trials or well-conducted meta-analysis of randomized controlled trials; B (moderate level of evidence): based on well-conducted observational studies (cohort or case-control), or meta-analysis of observational studies; C (low level of evidence): based on poorly controlled or uncontrolled studies, or conflicting evidence where most of the weight supports the recommendation; E (no clinical evidence): based on clinical experience or expert consensus*

[b] *Fasting is considered not eating for at least 8 hours*

[c] *Evidence rating from 2022 American Association of Clinical Endocrinology (**AACE**) guideline[30]: BEL and evidence grade: Recommendation achieved >66% consensus was assigned Grade A, B, C, or D based on the BEL and the presence or absence of predominant negative or positive subjective evidence factors and/or qualifiers; recommendation with ≤66% consensus was assigned Grade D, regardless of the BEL and presence/absence of negative or positive subjective evidence factors and/or qualifiers. Grade A represents a strong recommendation, Grade B represents an intermediate recommendation, Grade C represents a weak recommendation, and Grade D is used for no clinical evidence and is based on expert opinion. Strong (level I) evidence: randomized controlled trials or meta-analysis of randomized controlled trials; intermediate (level II) evidence: observational studies; weak (level III) evidence: case series, case reports, economic studies, preclinical studies, research and explorative studies; no (level IV) evidence: based on opinion, theory, consensus, guideline, position, or other relevant research or significantly flawed study*

[d] *Note that sentences in the ADA/EASD consensus report that used the wording "recommended" were assigned 'author consensus opinion', otherwise they were assigned 'ungraded discussion point'. While the recommendations were evidence-based when possible, the authors note that recommendations were based on their consensus opinion.*

[e] *National Institute for Health and Care Excellence (**NICE**) recommendation strength: Consider: generally indicates a weak recommendation for the intervention, implying that the intervention should be used for certain patients if the benefits outweigh the risks; Should not: generally indicates a strong recommendation against the intervention.[36]*

Abbreviations: A1C, glycosylated hemoglobin or hemoglobin A1c; AACE, American Association of Clinical Endocrinology; ABCD, Association of British Clinical Diabetologists; ADA, American Diabetes Association; BEL, best evidence level; dL, deciliter; EASD, European Association for the Study of Diabetes; FPG, fasting plasma glucose; GAD(65), glutamic acid decarboxylase; IA-2, islet tyrosine phosphatase 2; L, liter; mg, milligram; mmol, millimole; mol, mole; NICE, National Institute for Health and Care Excellence; nmol, nanomole; OGTT, oral glucose tolerance test; pmol, picomole; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; ZnT8, zinc transporter 8

Table B2. Selected Guideline and Consensus/Position Statement Recommendations on the Diagnosis of Type 1 Diabetes Mellitus

Professional organization and guideline; publication year	**Recommendations** (Evidence grade)

Association of British Clinical Diabetologists (ABCD)
 	
Standards of Care for Management of Adults with Type 1 Diabetes Position Statement; 2020[29]
	Target age group/population for recommendations: adults with T1D
	• Diagnostic laboratory criteria for diabetes mellitus includes the following (**Ungraded discussion point**):
	  ○ Confirmed by a single random plasma glucose ≥200 mg/dL (11.1 mmol/L) if the patient has hyperglycemic symptoms (eg, polydipsia, polyuria)
	  ○ Asymptomatic patients require two separate abnormal laboratory results of either a FPG ≥126 mg/dL (7.0 mmol/L) and/or a 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) after a 75-gram OGTT
	• Islet autoantibody testing is recommended for patients who have a clinical presentation consistent with T1D (**Ungraded discussion point**)
	• In adult onset cases where diagnostic uncertainty exists regarding diabetes type, evaluating islet autoantibody seropositivity for GAD, IA-2, and/or ZnT8 around the time of diabetes diagnosis (<3 years) can assist in determining the diabetes type (**Ungraded discussion point**)
	• Measurement of islet cell antibodies is not recommended because most of the available assays have low sensitivity (use non-human pancreas) (**Ungraded discussion point**)
	• C-peptide testing is recommended in all adults with T1D after at least 3 years from diagnosis, or in adults suspected of having T1D who test negative for islet autoantibodies (**Ungraded discussion point**)
	  ○ Random (non-fasting) plasma C-peptide result of <200 pmol/L or a urine C-peptide: creatinine ratio of <0.2 nmol/mol, without hypoglycemia, indicates severe insulin deficiency and may confirm T1D. (**Ungraded discussion point**)

[a] *Evidence rating from 2023 American Diabetes Association (**ADA**) guideline[35]: A (highest level of evidence): based on well-designed randomized controlled trials or well-conducted meta-analysis of randomized controlled trials; B (moderate level of evidence): based on well-conducted observational studies (cohort or case-control), or meta-analysis of observational studies; C (low level of evidence): based on poorly controlled or uncontrolled studies, or conflicting evidence where most of the weight supports the recommendation; E (no clinical evidence): based on clinical experience or expert consensus*

[b] *Fasting is considered not eating for at least 8 hours*

[c] *Evidence rating from 2022 American Association of Clinical Endocrinology (**AACE**) guideline[30]: BEL and evidence grade: Recommendation achieved >66% consensus was assigned Grade A, B, C, or D based on the BEL and the presence or absence of predominant negative or positive subjective evidence factors and/or qualifiers; recommendation with ≤66% consensus was assigned Grade D, regardless of the BEL and presence/absence of negative or positive subjective evidence factors and/or qualifiers. Grade A represents a strong recommendation, Grade B represents an intermediate recommendation, Grade C represents a weak recommendation, and Grade D is used for no clinical evidence and is based on expert opinion. Strong (level I) evidence: randomized controlled trials or meta-analysis of randomized controlled trials; intermediate (level II) evidence: observational studies; weak (level III) evidence: case series, case reports, economic studies, preclinical studies, research and explorative studies; no (level IV) evidence: based on opinion, theory, consensus, guideline, position, or other relevant research or significantly flawed study*

[d] *Note that sentences in the ADA/EASD consensus report that used the wording "recommended" were assigned 'author consensus opinion', otherwise they were assigned 'ungraded discussion point'. While the recommendations were evidence-based when possible, the authors note that recommendations were based on their consensus opinion.*

[e] *National Institute for Health and Care Excellence (**NICE**) recommendation strength: Consider: generally indicates a weak recommendation for the intervention, implying that the intervention should be used for certain patients if the benefits outweigh the risks; Should not: generally indicates a strong recommendation against the intervention.[36]*

Abbreviations: A1C, glycosylated hemoglobin or hemoglobin A1c; AACE, American Association of Clinical Endocrinology; ABCD, Association of British Clinical Diabetologists; ADA, American Diabetes Association; BEL, best evidence level; dL, deciliter; EASD, European Association for the Study of Diabetes; FPG, fasting plasma glucose; GAD(65), glutamic acid decarboxylase; IA-2, islet tyrosine phosphatase 2; L, liter; mg, milligram; mmol, millimole; mol, mole; NICE, National Institute for Health and Care Excellence; nmol, nanomole; OGTT, oral glucose tolerance test; pmol, picomole; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; ZnT8, zinc transporter 8

APPENDIX C: PRE- AND POST-INFUSION MEDICATION REGIMENS

Recommended pre- and post-infusion (donislecel) medication regimens are summarized below in **Table C1**, according to prescribing information.

Table C1. Recommended Pre-and Post-Infusion Medication Regimens for Donislecel Therapy[10]

Pre-infusion	Post-infusion

Immunosuppression:
• Start 30 to 360 minutes before the infusion
• The following agents should be used, as determined by the physician's judgment:
  ○ Non-depleting monoclonal anti-IL-2 receptor antibody[a] (start 120 minutes before the infusion)
  ○ Calcineurin inhibitor
  ○ mTOR inhibitor
  ○ TNF blocker
Prophylaxis:
• Antibiotic prophylaxis should be used during the periprocedural period
If deemed necessary:
• May give saline/glucose infusion and insulin (via an intravenous insulin pump) during the periprocedural period
	Immunosuppression:
	• Administer a non-depleting monoclonal anti-IL-2 receptor antibody[a] 2 weeks post-infusion, for 2 doses total
	• Administer a TNF blocker on days 3, 7, and 10 after the infusion
	• For life-long immunosuppression[b], a calcineurin inhibitor + mTOR inhibitor (or suitable alternatives) should be used, as determined by the physician's judgement; systemic steroids should not be used
	  ○ Dosage should be adjusted based on frequent monitoring of trough levels
	Prophylaxis:
	• Prophylaxis for PCP and CMV should be administered immediately after the infusion, and continued as directed

[a] *A polyclonal, T-cell-depleting antibody should be used in patients with a history of anaphylaxis to a non-depleting monoclonal anti-IL-2 receptor antibody.*

[b] *Note that there may be certain clinical scenarios that warrant discontinuing immunosuppression (eg, pregnancy; see **Section 10.3** for a complete list of possible scenarios, according to the donislecel prescribing information).*

Abbreviations: CMV, cytomegalovirus; IL, interleukin; mTOR, mammalian target of rapamycin; PCP, Pneumocystis jirovecii pneumonia; TNF, tumor necrosis factor

APPENDIX D: GLYCEMIC TARGETS BASED ON REVIEWED UNITED STATES GUIDELINES

Table D1. Glycemic Targets According to the American Diabetes Association (ADA) and American Association of Clinical Endocrinology (AACE)[51]

American Diabetes Association (ADA), Glycemic Targets, Older Adults, Children and Adolescents, and Pregnancy Guidelines; 2023[52-55]
Monitoring[53]**:**
• Evaluate glycemic status (eg, A1C, TIR) at least twice a year in patients meeting treatment goals or who have stable glycemic control. For patients with unmet glycemic targets and/or recent therapy changes, glycemic status should be evaluated at least quarterly and as needed. • A1C may be a less dependable marker of actual glycemic status in patients with conditions that impact red blood cell turnover (eg, recent blood transfusion, anemia hemoglobinopathies, pregnancy, end-stage kidney disease). • Hypoglycemia classification: ○ **Level 1:** <70 mg/dL and ≥54 mg/dL ○ **Level 2:** <54 mg/dL ○ **Level 3:** severe episode characterized by altered mental and/or physical status requiring treatment assistance from another person • At each visit, it is essential to assess and, when necessary, investigate the occurrence and risk of hypoglycemia, especially for older adults who are more prone to hypoglycemia. The assessment of hypoglycemia awareness should involve using validated tools (eg, Gold score, Clarke score). ○ Impaired hypoglycemia awareness or the occurrence of ≥1 level 3 hypoglycemic episodes should prompt the initiation of appropriate education and thorough review and modification of the treatment regimen to reduce the frequency of hypoglycemic events. ○ Patients receiving insulin therapy who exhibit hypoglycemia unawareness, one level 3 hypoglycemic event, or a recurrent, unexplained pattern of level 2 hypoglycemia should temporarily adjust their glycemic targets to proactively prevent hypoglycemic episodes for a period of at least several weeks to partially restore hypoglycemic awareness and minimize the risk of future occurrences.
Adults, non-pregnant[53]**:**
• A1C target is generally <7% (without significant hypoglycemia). ○ A lower A1C target (eg, A1C <6.5%) can be considered if it can be achieved safely without significant hypoglycemia or other adverse events. Patients for which this may be suitable include those with shorter duration of diabetes, long life expectancy, absence of other relevant comorbidities, and who are highly motivated with excellent self-care abilities. ○ A less stringent A1C target (eg, <8%) may be appropriate in individuals with reduced life expectancy or if harms of more intensive treatment outweigh the benefits (eg, significant risk of hypoglycemia). • Pre-prandial capillary PG target is generally 80 to 130 mg/dL; goal can be less or more stringent depending on the patient's needs. • Peak post-prandial capillary PG (1 to 2 hours after starting a meal) target is generally <180 mg/dL; goal can be less or more stringent depending on the patient's needs.
Older adults[52]**:**
• A1C target of <7% to 7.5% can be considered for older adults who are otherwise healthy (eg, few chronic comorbidities, non-altered cognitive function, non-impaired functional status). • A1C target of <8% can be considered for older adults with multiple chronic comorbidities, functional dependence, or cognitive impairment. • To reduce the risk of hypoglycemia, CGM should be used.
Children and adolescents[54]**:**
• A1C target of <7% is recommended for most children and adolescents; a more stringent A1C of <6.5% can be set if it can be achieved without significant hypoglycemia, undue burden of care, negatively impacting well-being, or those with nonglycemic factors that reduce A1C (eg, decreased erythrocyte lifespan). • A less stringent A1C target of <7.5% may be considered for patients with increased hypoglycemia risk (eg, unable to express hypoglycemia symptoms, hypoglycemia unawareness, unable to routinely check blood glucose), unable to access analog insulin therapy, advanced insulin delivery systems and/or CGM, or who have nonglycemic factors that increase A1C. • A1C target of <8% can be considered for patients with severe hypoglycemia, reduced life expectancy, or if harms outweigh benefits.
Pregnant patients[55]**:**
• A1C target of <6% is ideal during pregnancy if it can be achieved without significant hypoglycemia; a A1C target of <7% can be considered if necessary to reduce the risk of hypoglycemia. • A target FPG<95 mg/dL and 1-hour post-prandial glucose <140 mg/dL or 2-hour post-prandial glucose <120 mg/dL is recommended.

Abbreviations: A1C, glycosylated hemoglobin or hemoglobin A1c; AACE, American Association of Clinical Endocrinology; ADA, American Diabetes Association; CGM, continuous glucose monitor(ing); dL, deciliter; FPG, fasting plasma glucose; mg, milligram; PG, plasma glucose; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; TIR, time in range

Table D1. Glycemic Targets According to the American Diabetes Association (ADA) and American Association of Clinical Endocrinology (AACE)[51]

American Association of Clinical Endocrinology (AACE), Developing a Diabetes Mellitus Comprehensive Care Plan Guideline; 2022[30]
Adults, non-pregnant:
• A1C target is generally ≤6.5%, which may require a FPG <110 mg/dL and a 2-hour post-prandial glucose of <140 mg/dL. • A less stringent A1C target of 7% to 8% may be considered in patients with hypoglycemia unawareness, history of severe hypoglycemia, reduced life expectancy, long-standing diabetes, or other conditions (eg, severe renal disease, multiple comorbidities) in whom the lower target cannot be achieved despite intensive efforts, provided they do not experience hyperglycemia symptoms.
Pregnant patients:

• For patients with gestational diabetes, a target fasting and pre-prandial glucose of ≤95 mg/dL and a 1-hour post-prandial glucose ≤140 mg/dL or a 2-hour post-prandial glucose ≤120 mg/dL is recommended.
• The following target glucose goals are recommended in patients with pre-existing T1D or T2D, if they can safely be achieved:
  ○ Pre-prandial, bedtime, and overnight glucose of 60 to 95 mg/dL
  ○ 1-hour post-prandial glucose of 110 to 140 mg/dL
  ○ 2-hour post-prandial glucose of 100 to 120 mg/dL
  ○ Secondary target: A1C <6% if it can be achieved without significant hypoglycemia

Abbreviations: A1C, glycosylated hemoglobin or hemoglobin A1c; AACE, American Association of Clinical Endocrinology; ADA, American Diabetes Association; CGM, continuous glucose monitor(ing); dL, deciliter; FPG, fasting plasma glucose; mg, milligram; PG, plasma glucose; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; TIR, time in range

APPENDIX E: INCLUSION AND EXCLUSION CRITERIA IN DONISLECEL CLINICAL TRIALS (UIH-001 AND UIH-002)

Table E1. Inclusion and Exclusion Criteria from Clinical Trials for Donislecel (UIH-001 and UIH-002)[10,14,37,38]

Study identification number, trial name, study phase and design	Inclusion criteria	Exclusion criteria
UIH-001 (NCT00566813) *(currently, results are unpublished in peer-reviewed medical journals)* Islet transplantation in type 1 diabetic patients using the Edmonton Protocol of steroid free immunosuppression Phase I/II, prospective, non-randomized, single-arm, open-label study	• Aged 18 to 65 years (all sexes) • T1D duration of at least 5 years • Participant experienced **at least one of the following** despite optimal efforts to control glucose with "intensive insulin management"[a]: ○ Diminished recognition of hypoglycemia (hypoglycemia unawareness), defined as a self-reported lack of appropriate autonomic symptoms when blood glucose levels decrease below 54 mg/dL ○ Glycemic lability, marked by ≥2 documented episodes of severe hypoglycemia, or ≥2 DKA-related hospital visits within the previous year ○ Progressive diabetes-related microvascular complications: ▪ Retinopathy: defined by at least a three-step advancement (based on ETDRS grading), or a comparable result as determined by an ophthalmologist experienced in diabetic retinopathy ▪ Nephropathy: defined as an increase in microalbuminuria of ≥72 mg/24 hours (50 µg/min) over at least a 3-month period (starting at any point within the previous 2 years), despite ACE inhibitor therapy ▪ Neuropathy: defined as persistent or worsening autonomic neuropathy (eg, gastroparesis, postural hypotension), or severe peripheral neuropathic pain unresponsive to standard treatments (eg, gabapentin)	• Aged <18 or >65 years (all sexes) • Any C-peptide response ≥0.3 ng/mL or a C-peptide response to intravenous glucagon (1 mg) • Daily insulin needs of >0.7 IU/kg or a HbA1c >12% • BMI >26 kg/m^2 or weighing >70 kg at the screening visit • Received an antidiabetic medication, except for insulin, or the study drug within 4 weeks of enrollment • Within 2 months of enrollment, received live attenuated vaccine(s) • Macroalbuminuria, serum creatinine >1.5 mg/dL, or creatinine clearance <80 mL/min/1.73 m^2 • Untreated proliferative retinopathy • Positive pregnancy test, a desire for future conception, unwillingness to adhere to effective contraceptive strategies, or currently breastfeeding • PRA sensitization, as evidenced by positive anti-HLA antibodies on a "solid phase immunoassay with soluble HLA Class I molecules as a target, or a general PRA panel with reactivity >20%."[13] (page 15) ○ A negative donor crossmatch is required prior to transplantation for participants with a PRA panel reactivity >20% • Received a previous transplantation • Comorbid cardiac disease (ie, myocardial infarction within the previous 6 months, evidence of non-correctable coronary artery disease, evidence of ischemia, heart failure (>NYHA Class II) or history of stroke (within past 6 months) • Active substance abuse (including smoking) or alcohol use, or history of smoking (within previous 6 months) • Active infection (eg, hepatitis C or B, HIV) or prior or active tuberculosis, including those undergoing treatment for suspected tuberculosis • History of any malignancies (except squamous or basal cell carcinoma, but it should be removed prior to transplant) • Addison's disease • Elevated liver function tests (>1.5 times ULN or consistently elevated levels between normal and 1.5 with a re-test) • Current hyperlipidemia; symptomatic cholecystolithiasis or peptic ulcer disease; pancreatitis (acute or chronic); or persistent, intense diarrhea, vomiting, or other gastrointestinal conditions that potentially interfere with absorption of orally administered medications • Currently using chronic steroid therapy or anticoagulant therapy (except aspirin), those with a PT-INR > 1.5, history of Factor V deficiency, or low baseline hemoglobin levels (<12 g/dL for women or <13 g/dL for men) • History of medication non-adherence, allergic to radiographic contrast material, or unable to provide informed consent • Participant is an unsuitable transplant candidate based on an uncontrolled psychiatric condition (eg, bipolar disorder, schizophrenia) despite appropriate medication use

[a] *Although a detailed, explicit definition of "intensive insulin management" is not provided in the package insert or FDA review documents for donislecel, we infer this to mean multiple daily injections (MDI; basal-bolus) or continuous subcutaneous insulin infusion (CSII) via an insulin pump + glycemic monitoring with a continuous glucose monitor (CGM).*

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CGM, continuous glucose monitor; CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; dL, deciliter; ETDRS, Early Treatment Diabetic Retinopathy Study; g, gram; HbA1c, glycosylated hemoglobin or hemoglobin A1C; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; INR, international normalized ratio; IU, International Units; kg, kilogram; m, meter; MCT, medullary carcinoma of the thyroid; MDI, multiple daily injections; MEN2, multiple endocrine neoplasia type 2; mg, milligram; min, minute; mL, milliliter; ng, nanogram; NYHA, New York Heart Association; PRA, panel reactive antibody; PT, prothrombin time; T1D, type 1 diabetes mellitus; µg, microgram; UIC, University of Illinois at Chicago; UIH, University of Illinois Hospital and Health Sciences System or UI Health; ULN, upper limit of normal

Table E1. Inclusion and Exclusion Criteria from Clinical Trials for Donislecel (UIH-001 and UIH-002)[10,14,37,38]

Study identification number, trial name, study phase and design	Inclusion criteria	Exclusion criteria
UIH-002 (NCT00679042) *(currently, results are unpublished in peer-reviewed medical journals)* Islet transplantation in type 1 diabetic patients using the UIC protocol, Phase 3 Phase III, prospective, non-randomized, single-arm, open-label study	• Aged 18 to 75 years (all sexes) • T1D duration of at least 5 years • Participant experienced **both of the following** despite optimal efforts to control glucose with "intensive insulin management"[a]: ○ Diminished recognition of hypoglycemia (hypoglycemia unawareness), defined as a self-reported lack of appropriate autonomic symptoms when blood glucose levels decrease below 54 mg/dL ○ ≥1 severe hypoglycemic episode in the previous 3 years, defined as an episode showing consistent symptoms of hypoglycemia, necessitating aid from another person, and either a blood glucose value <50 mg/dL or rapid resolution following the administration of intravenous glucose, oral carbohydrates, or glucagon (unspecified route of administration).	• Aged <18 or >75 years (all sexes) • Any C-peptide response ≥0.3 ng/mL or a C-peptide response to intravenous glucagon (1 mg) • Daily insulin needs of >0.7 IU/kg or a HbA1c >12% • BMI >27 kg/m^2 • Received an antidiabetic medication, except for insulin, or the study drug within 4 weeks of enrollment • Within 2 months of enrollment, received live attenuated vaccine(s) • Macroalbuminuria, serum creatinine >1.5 mg/dL, or creatinine clearance <80 mL/min/1.73 m^2 • Untreated proliferative retinopathy • Positive pregnancy test, a desire for future conception, unwillingness to adhere to effective contraceptive strategies, or currently breastfeeding • PRA sensitization, as evidenced by positive anti-HLA antibodies on a "solid phase immunoassay with soluble HLA Class I molecules as a target, or a general PRA panel with reactivity >80%."[14] (page 41) ○ A negative donor crossmatch was required prior to transplantation for all participants • Received a previous transplantation, other than islet transplantation • Comorbid cardiac disease (ie, myocardial infarction within the previous 6 months, evidence of non-correctable coronary artery disease, evidence of ischemia, heart failure (>NYHA Class II) or history of stroke (within past 6 months) • Active substance abuse (including smoking) or alcohol use, or history of smoking (within previous 6 months) • Active infection (eg, hepatitis C or B, HIV) or prior or active tuberculosis, including those undergoing treatment for suspected tuberculosis • History of any malignancies (except squamous or basal cell carcinoma, but it was required to be removed prior to transplant), or known family history of MCT or MEN2 • Addison's disease • Elevated liver function tests (>1.5 times ULN or consistently elevated levels between normal and 1.5 with a re-test) • Current hyperlipidemia; symptomatic cholecystolithiasis or peptic ulcer disease; pancreatitis (acute or chronic); or persistent, intense diarrhea, vomiting, or other gastrointestinal conditions that potentially interfere with absorption of orally administered medications • Currently using chronic steroid therapy or anticoagulant/antiplatelet therapy (except low-dose aspirin after transplantation), those with a PT-INR > 1.5, history of Factor V deficiency, or low baseline hemoglobin levels (<12 g/dL for women or <13 g/dL for men) • History of medication non-adherence or unable to provide informed consent • Participant is an unsuitable transplant candidate based on an uncontrolled psychiatric condition (eg, bipolar disorder, schizophrenia) despite appropriate medication use • A condition that may interfere with the patient's safety based on the investigator's opinion

[a] *Although a detailed, explicit definition of "intensive insulin management" is not provided in the package insert or FDA review documents for donislecel, we infer this to mean multiple daily injections (MDI; basal-bolus) or continuous subcutaneous insulin infusion (CSII) via an insulin pump + glycemic monitoring with a continuous glucose monitor (CGM).*

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CGM, continuous glucose monitor; CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; dL, deciliter; ETDRS, Early Treatment Diabetic Retinopathy Study; g, gram; HbA1c, glycosylated hemoglobin or hemoglobin A1C; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; INR, international normalized ratio; IU, International Units; kg, kilogram; m, meter; MCT, medullary carcinoma of the thyroid; MDI, multiple daily injections; MEN2, multiple endocrine neoplasia type 2; mg, milligram; min, minute; mL, milliliter; ng, nanogram; NYHA, New York Heart Association; PRA, panel reactive antibody; PT, prothrombin time; T1D, type 1 diabetes mellitus; µg, microgram; UIC, University of Illinois at Chicago; UIH, University of Illinois Hospital and Health Sciences System or UI Health; ULN, upper limit of normal