ZIMISLECEL (VX-880) for Type 1 Diabetes ADA Update

June 20, 2025

Presentation intended for the investment community

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Agenda

Welcome

Susie Lisa, CFA, Senior Vice President, Investor Relations, Vertex

Introduction to Vertex's T1D cell therapy programs

Felicia Pagliuca, Ph.D., Senior Vice President, Cell and Genetic Therapy Research and Site Head, Vertex

Zimislecel ADA presentation

Michael Rickels, M.D., Professor of Medicine at University of Pennsylvania, Director of Penn Diabetes Research Center

Real-world perspectives on caring for patients with T1D & potential role of zimislecel

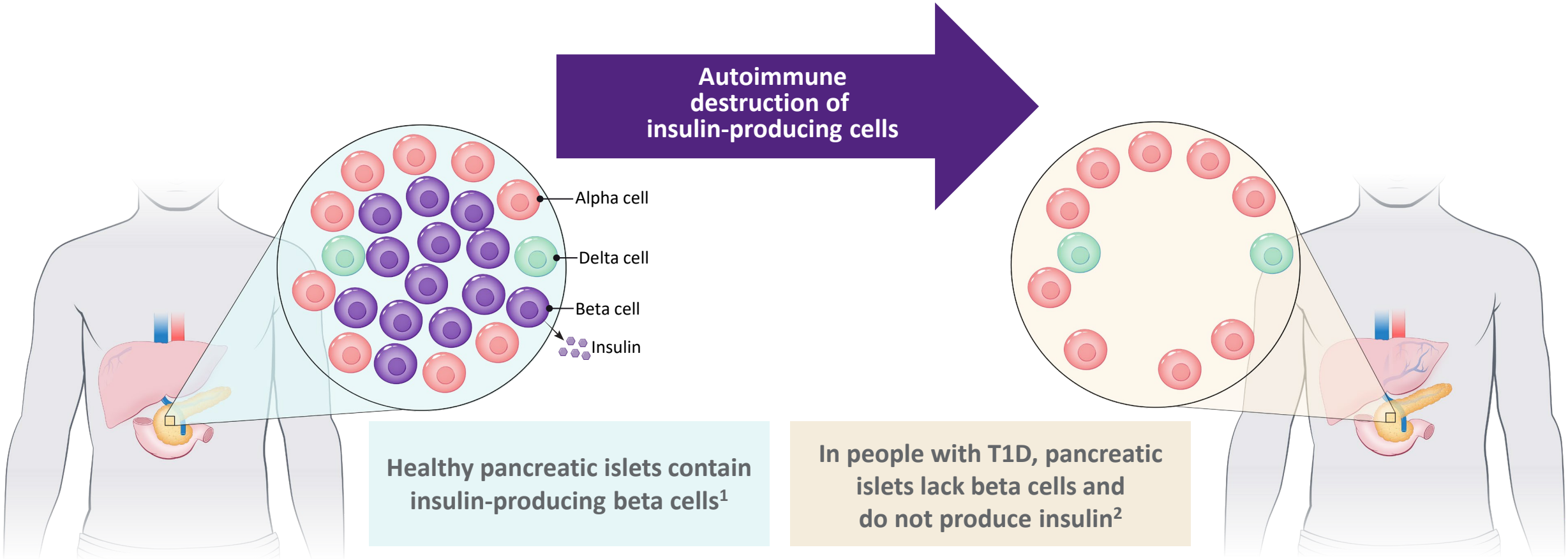
James F. Markmann, M.D., Ph.D., Professor of Surgery at the Perelman School of Medicine, University of Pennsylvania

Questions & Answers

Dr. Rickels, Dr. Markmann, Felicia Pagliuca

Felicia Pagliuca, Ph.D.
Senior Vice President,
Cell and Genetic Therapy Research,
Vertex Pharmaceuticals

Type 1 Diabetes is caused by autoimmune destruction of insulin-secreting pancreatic islet beta cells



Healthy pancreatic islets contain insulin-producing beta cells[1]

In people with T1D, pancreatic islets lack beta cells and do not produce insulin[2]

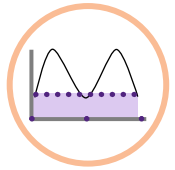
T1D, type 1 diabetes.

1. Rorsman P, et al. *Physiol Rev.* 2018;98:117-214. 2. Holt RIG, et al. *Diabetes Care.* 2021;44(11):2589-2625

Despite optimal medical care, T1D requires intensive, lifelong management and has high unmet need

~3.8M diagnosed patients in the US and Europe

- Expect to serve ~60K patients with the initial zimislecel filing



These 60K patients have the highest unmet need and experience **severe hypoglycemic events (SHEs)**, a serious and potentially life-threatening complication of insulin therapy

Despite optimal medical care, T1D is associated with **substantial morbidity**, including microvascular and macrovascular complications and **reduced life expectancy**

Current disease management is **highly burdensome**, requiring frequent or continuous administration of exogenous insulin and blood glucose monitoring, every day

BURDEN OF T1D

SHEs can result in seizures, cardiac arrythmia, coma, and even death

Amiel S. 2021. Diabetologia. **64**, 963-970

Recurrent SHEs can increase mortality rate up to ~5x of those who do not have SHEs

Moser et al. 2023 Aug;25(8):2243-2254.

~9% experience recurrent SHEs despite best available therapies

Sherr, J. et al. 2024. Diabetes Care, 47, 941–947.

Zimislecel is an investigational islet cell therapy comprised of fully differentiated, glucose-responsive, insulin-producing, allogeneic, stem cell-derived islet cells that replace the islet cells destroyed in T1D

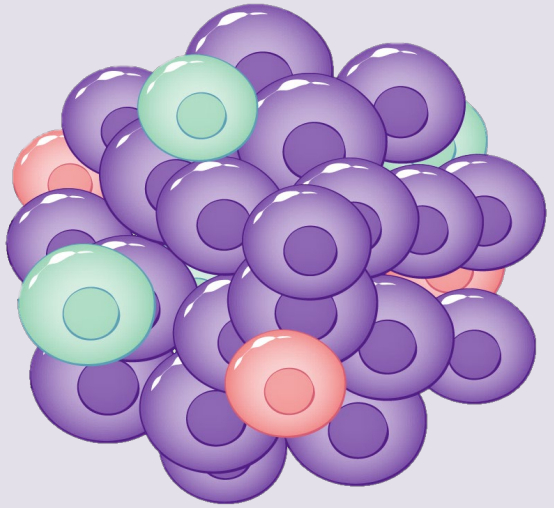


Illustration depicts islet cell composition

- Zimislecel is delivered by an **infusion into the hepatic portal vein**

- A standard, steroid-free induction (anti-thymocyte globulin) and maintenance (tacrolimus and sirolimus) **immunosuppressive regimen** protects the cells from the immune system.

- The cell infusion protocol and immunosuppressive regimen are **well-established**

Vertex continues to serially innovate: alternative immunosuppression, gene-edited hypoimmune and other approaches all in the research stage

Zimislecel pivotal trial progressing rapidly, setting up global regulatory submissions in 2026

- Phase 1/2/3 pivotal trial expected to enroll a total of 50 patients
- Expect to complete enrollment and dosing in the pivotal trial **this summer**

- **Multiple global regulatory designations secured:**
  - RMAT and Fast Track in the U.S.
  - PRIME in the EU
  - Innovation Passport under the Innovative Licensing and Access Pathway in the U.K.

- **Expect regulatory submissions in 2026**
- Actively preparing for launch
- Highly concentrated market can be served with a specialty commercial model

Michael R. Rickels, MD, MS

Willard and Rhoda Ware Professor in Diabetes and Metabolic Diseases
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Durable Glycemic Control and Elimination of Exogenous Insulin Use with VX-880 in Patients with Type 1 Diabetes (T1D): VX-880-101 (FORWARD)

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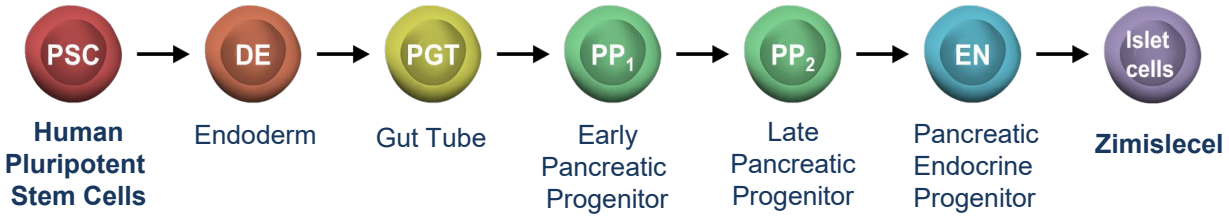
Disclosures

Company/Name	Funded Research/Grants	Consultant	Speaker's Bureau/ Honoraria	Advisory Board	Society/ Association	Other
Vertex Pharmaceuticals		X				Study Investigator
Novo Nordisk		X				
Sernova Corp				X		
Six Degrees Worldwide			X			
Bayer Healthcare Ltd.			X			
National Institutes of Health	X					
Helmsley Charitable Trust	X					
Dompe farmaceutici S.p.A.	X					
International Pancreas & Islet Transplant Association					Treasurer	

Zimislecel (VX-880) is an Islet Cell Therapy in Clinical Development for T1D Complicated by Recurrent Severe Hypoglycemia



Zimislecel is an investigational allogeneic stem cell-derived, fully differentiated, insulin-producing **islet cell therapy**

Zimislecel is delivered by **infusion** into the **hepatic portal vein**

A steroid free **immunosuppressive regimen** is used to protect the cells from the immune system:

- induction (anti-thymocyte globulin)
- maintenance (tacrolimus + sirolimus)

The cell infusion protocol and immunosuppressive regimen have been established with deceased donor islet cell transplants

T1D, Type 1 diabetes

FORWARD Study VX-880-101: Enrollment in the Phase 1/2 Portion is Complete and Enrollment in the Phase 3 Portion is Ongoing

Study Design for Phase 1/2 Portion:

Open-label, Single Arm with 3 Parts:

- Part A with sequential dosing (half dose)
- Part B with sequential dosing (full dose)
- Part C with concurrent dosing (full dose)

Key inclusion criteria:

- Diagnosis of T1D and 18 to 65 years of age
- Impaired hypoglycemic awareness
- ≥2 SHEs in year before screening

Primary efficacy endpoint: Proportion of participants free from SHEs from Day 90 through Month 12 with HbA1c <7% or ≥1% reduction in HbA1c from baseline between Day 180 and Day 365

- Following successful meetings with global regulatory agencies, the **Phase 1/2 study was transitioned to** a **Phase 1/2/3 pivotal study**
- **Data are presented** as of October 2024, from the **Phase 1/2 portion** of the study, prior to the conversion to the Phase 1/2/3 pivotal study:
  - **Efficacy** data on participants who received **the full dose** of zimislecel as a **single infusion** and have **at least 1 year of follow-up (N=12)**
  - **Safety** data on participants who received **either the half dose or full dose** of zimislecel and have **at least 1 year of follow-up (N=14)**

HbA1c, hemoglobin A1c; **SHE,** severe hypoglycemic event

Baseline Demographics: Participants With T1D Have Recurrent SHEs Despite Intensive Diabetes Management

Category, mean (min, max)	N=14
Age (years)	43.6 (24, 64)
Sex (F/M)	5/9
BMI (kg/m^2)	24.5 (21.3, 28.5)
Duration of diabetes (years)	22.8 (7.8, 47.4)
HbA1c (%)	7.8 (7.1, 9.9)
Fasting C-peptide (pmol/L)	Undetectable
Total daily insulin (unit/day)	39.3 (19.8, 52.0)
Total daily insulin (units/kg/day)	0.54 (0.35, 0.64)
Use of CGM, n (%)	14 (100.0)
Use of insulin pump, n (%)	9 (64.3)
Use of HCLS, n (%)	6 (42.9)
SHEs in year prior to screening	2.7 (2, 4)

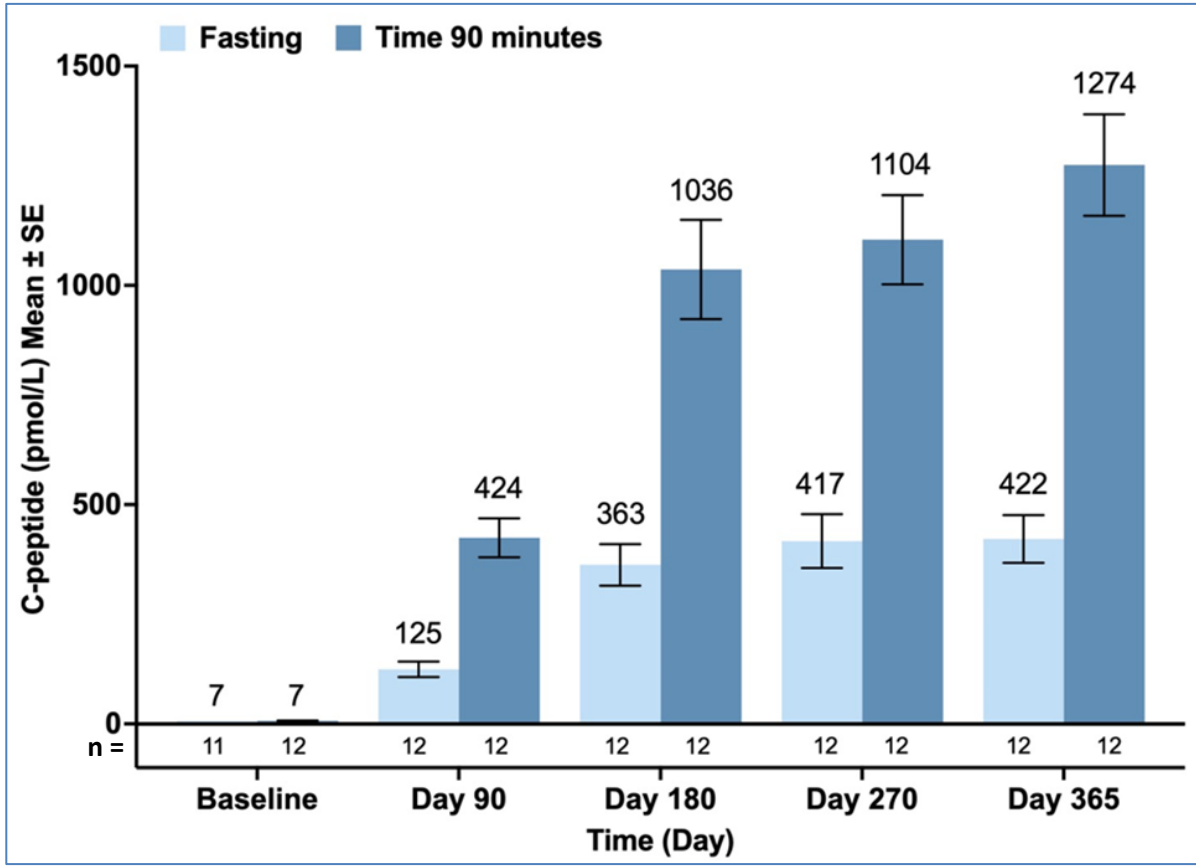
Baseline demographics for the 12 participants who received full dose in a single infusion with at least 1 year of follow-up are similar to the overall baseline demographics

Note: Data presented are from a data cut of October 2024.

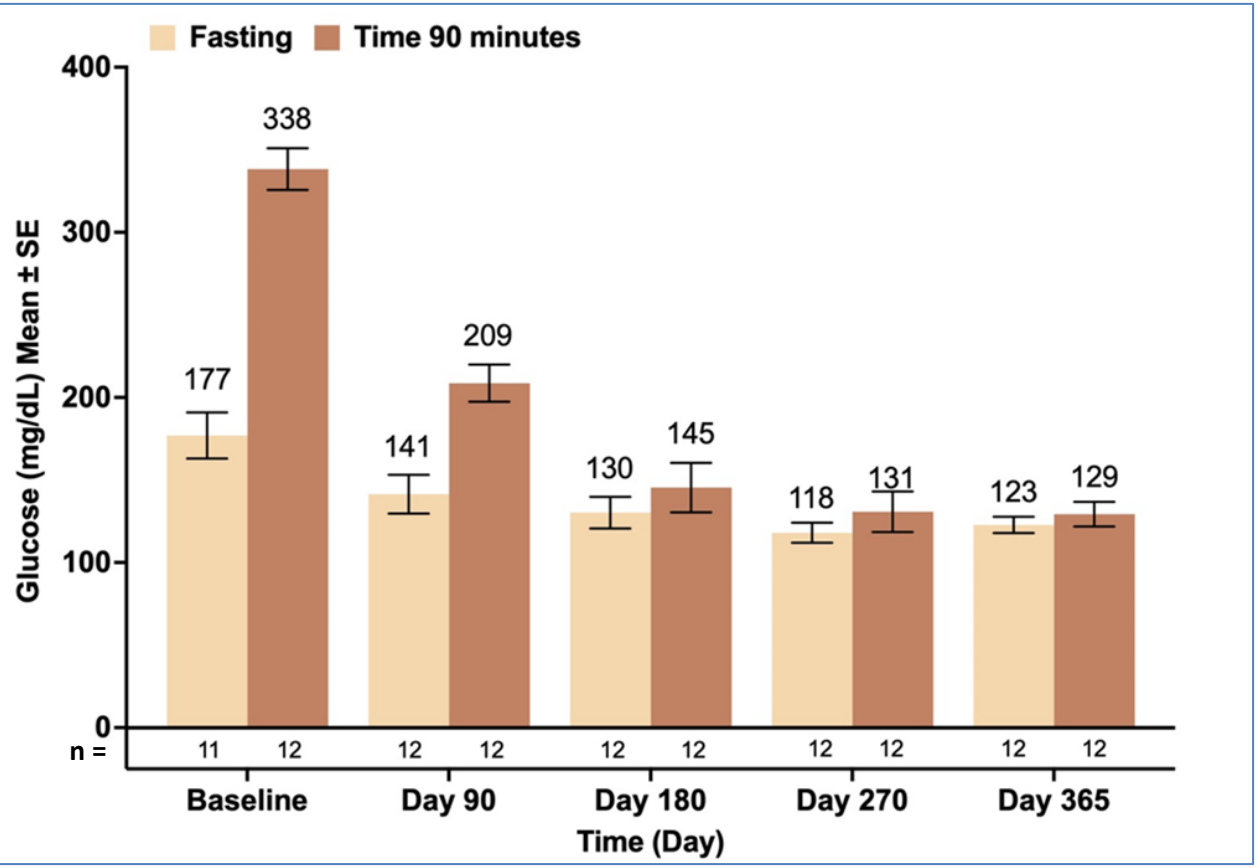
BMI, body mass index; **CGM**, continuous glucose monitor; **F,** female; **HbA1c,** hemoglobin A1c; **HCLS**, hybrid closed loop system; **M,** male; **SHEs,** severe hypoglycemic events; **T1D,** Type 1 diabetes

All 12 Participants Demonstrated Clinically Meaningful and Sustained Glucose Responsive Endogenous Insulin Production, and Improved Glucose Levels on MMTT through Day 365

C-peptide: Fasting and at 90 minutes during MMTT



Glucose: Fasting and at 90 minutes during MMTT

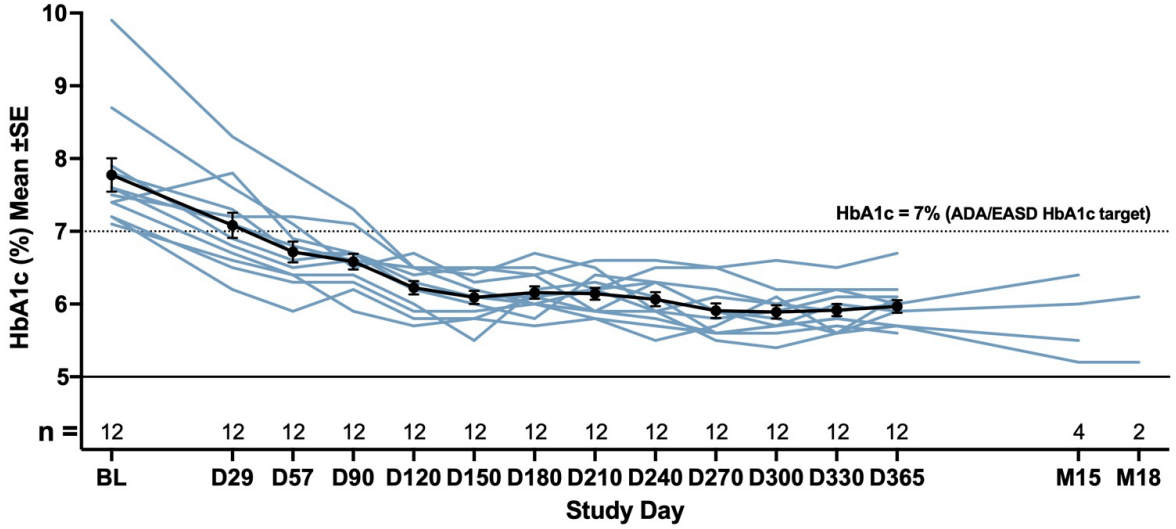


MMTT, mixed meal tolerance test

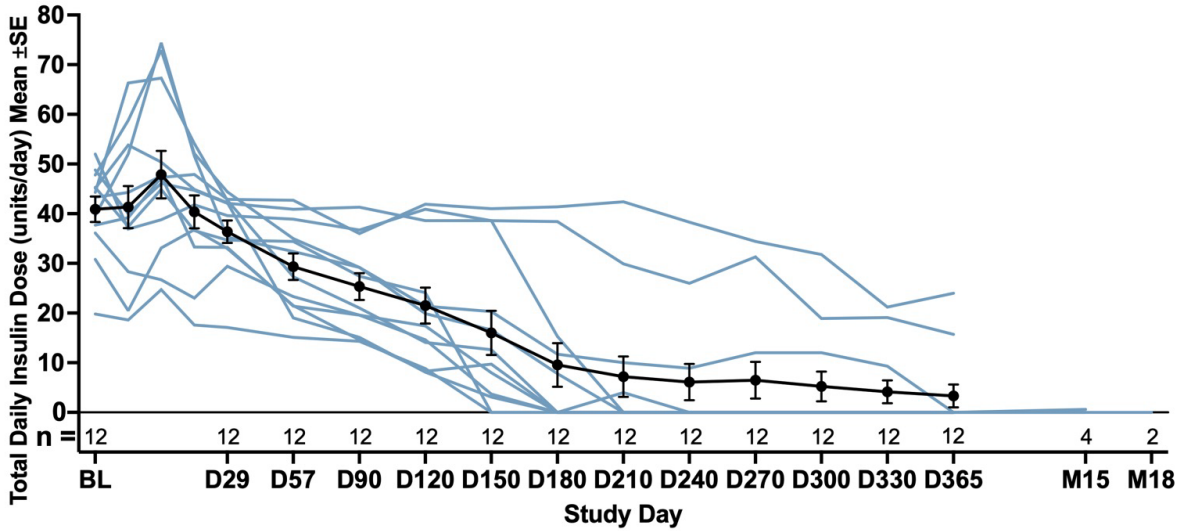
All 12 Participants had Improved HbA1c With Reduction or Elimination of Exogenous Insulin Use

- All 12 participants achieved a **reduction in HbA1c** to <7% (ADA/EASD HbA1c target)
- All 12 participants had **elimination of SHEs** during the evaluation period (Day 90 onward)
- All 12 participants had **reduction in exogenous insulin use**
- 10/12 (83%) **no longer required exogenous insulin** at Month 12 after a single dose of zimislecel
  - 1 had 70% reduction; received 1 dose of steroids (protocol prohibited) for a rash on the day of zimislecel infusion
  - 1 had 36% reduction; received 4 doses of steroids (protocol prohibited) in the peri-infusion period

HbA1c (%)

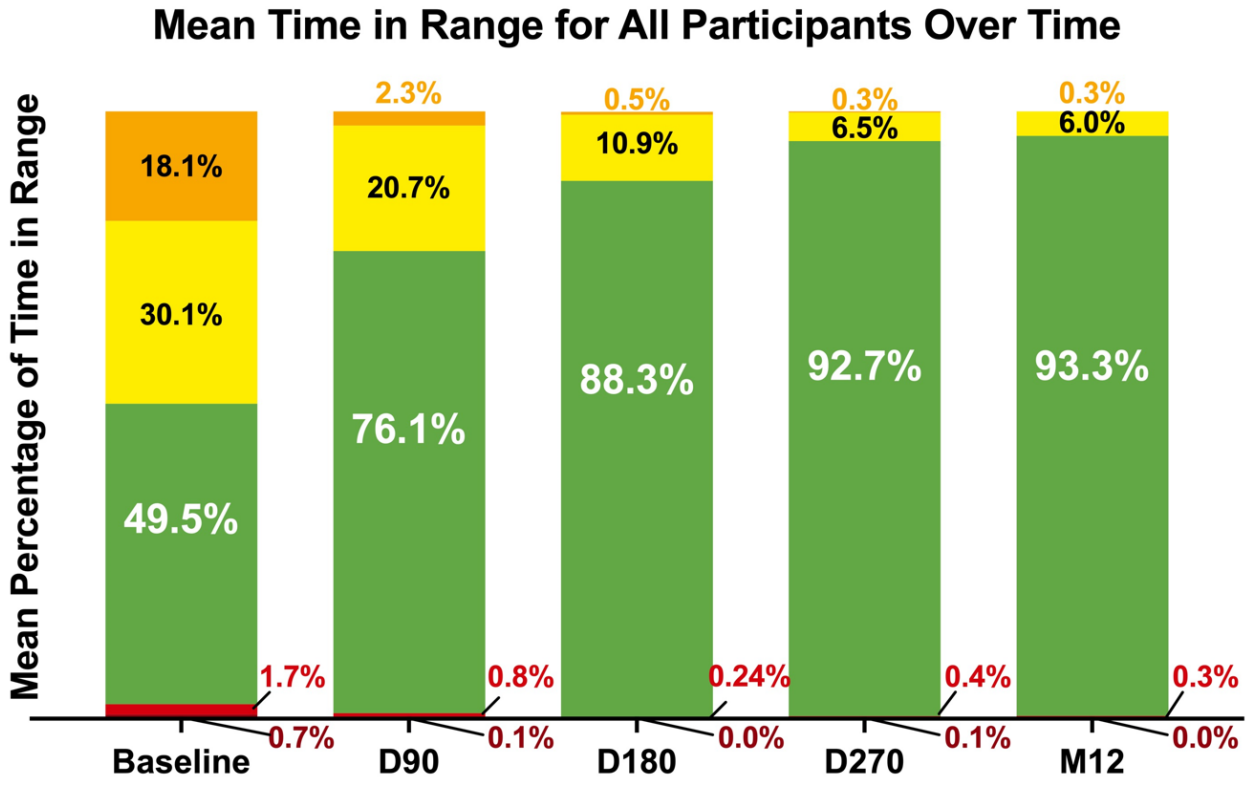


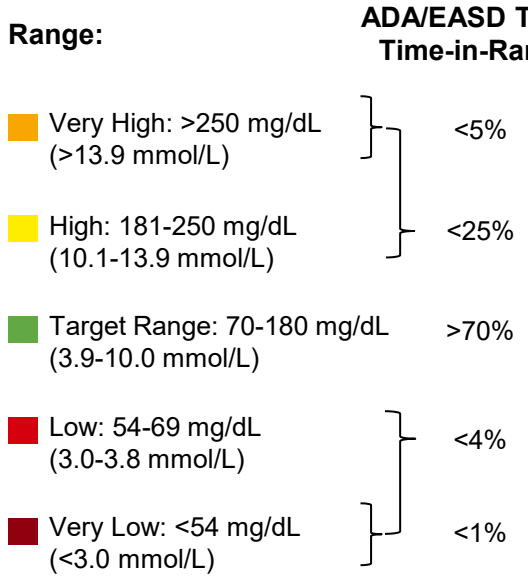
Total Daily Insulin Dose (units/day)



ADA, American Diabetes Association; **BL,** baseline; **D,** day; **HbA1c,** hemoglobin A1c; **M,** month; **SHEs,** severe hypoglycemic events

All 12 Participants Demonstrated Improvements in CGM Metrics and Achieved >70% Time in Range





n =	Baseline 12	D90 12	D180 12	D270 12	M12 12*
% no longer using exogenous insulin	0	0	58%	75%	83%
Total daily insulin dose (mean % CFB) (baseline, 40.9 unit/d)	NA	-37.8%	-78.3%	-84.9%	-92.2%
HbA1c (mean CFB) (baseline, 7.8%)	NA	-1.2%	-1.6%	-1.9%	-1.8%

*** n =11 at M12 Mean Time in Range**

ADA, American Diabetes Association; **CFB**, change from baseline; **CGM,** continuous glucose monitoring; **D,** day; **EASD,** European Association for the Study of Diabetes; **M,** month

All 12 Participants Achieved the Phase 1/2 Primary Endpoint

Study Endpoints	Evaluable Participants (Full Dose)*	Result n/N(%)
Primary Endpoint		
Proportion of participants **free of SHEs from Day 90 through Day 365** and with **HbA1c <7% or ≥1% reduction between Day 180 and Day 365**	12	12/12 (100%)

*Participants who received the full dose of zimislecel in a single infusion and have at least 1 year of follow-up.

HbA1c, hemoglobin A1c; **SHE,** severe hypoglycemic event

Safety Profile of Zimislecel is Consistent with Immunosuppressive Regimen and the Infusion Procedure

	Participants with AEs (N=14) n (%)
Any AEs	14 (100)
AEs by maximum severity	
Mild	1 (7.1)
Moderate	6 (42.9)
Severe	5 (35.7)
Life threatening	0
Death	2 (14.3)
AEs related to zimislecel	**7 (50.0)**
AEs related to immunosuppressive therapy	**14 (100.0)**
SAEs	**7 (50.0)**
SAEs related to zimislecel	**0**
AEs leading to study discontinuation	**0**

- Majority of **AEs** were of **mild or moderate severity**
- Of the **AEs with a causal relationship** to any study drug, **most were attributed** to **immunosuppressive therapy**
- **No SAEs** were considered **related to zimislecel**
- **2 deaths, previously reported*, occurred and were not considered related to zimislecel**

AE, adverse events; **SAEs,** serious adverse events; **SHE,** severe hypoglycemic event; **T1D,** Type 1 diabetes

* Previously reported deaths: 1. **Cryptococcal meningitis infection** due to complications from an elective sinus surgery (cribriform plate injury), high-dose steroids use (prohibited by protocol) in the weeks preceding and following the sinus surgery, and immunosuppressive medications 2. **Progression of pre-existing neurocognitive impairment** due to a severe traumatic brain-injury sustained in a motor vehicle accident caused by a SHE before study enrollment

Safety Profile of Zimislecel is Consistent with Immunosuppressive Regimen and the Infusion Procedure

Summary of Most Common Adverse Events (>40% Participants)	Participants with AEs (N=14) n (%)
Diarrhea	11 (78.6)
Headache	10 (71.4)
Nausea	9 (64.3)
COVID-19	7 (50.0)
Mouth ulceration	7 (50.0)
Neutropenia	6 (42.9)
Rash	6 (42.9)

- The most common AEs were diarrhea, headache, and nausea
- AEs were as expected based on the well-established safety profile of the immunosuppressive regimen and manageable
- Transient elevation of liver transaminases (ALT, AST), decreased white blood cell counts, and decreased renal function were observed
  - These findings are known to be associated with the infusion procedure and immunosuppressive regimens, as reported in islet transplantation studies

AE, adverse events; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase , **T1D**, **T**ype 1 diabetes

Updated Data from the Phase 1/2 Portion of the FORWARD Study Highlight the Curative Potential of Zimislecel in People Living with T1D

- **All 12 participants who received the full dose of zimislecel in a single infusion** demonstrated:
  - **engraftment** with glucose responsive **endogenous insulin production** (c-peptide),
  - **elimination of SHEs,**
  - **improvement in glycemic control** to ADA target levels (HbA1c <7% and TIR >70%), and
  - reduction in exogenous insulin use, with **10 of 12 participants eliminating insulin use.**
- All 12 participants with at least 1 year of follow-up **met the Phase 1/2 primary endpoint** of elimination of SHEs from Day 90 through Day 365 and with an HbA1c <7%.
- The safety profile is **consistent** with the **immunosuppressive regimen** and **infusion procedure**.
- Phase 3 is well underway and is expected to **complete enrollment and dosing (N=50) in mid-2025**.

Zimislecel has curative potential in people living with T1D

HbA1c, hemoglobin A1c; **SHEs,** severe hypoglycemic events; **T1D,** Type 1 diabetes; **TIR,** time in range

Thank you to the FORWARD PHASE 1/2/3 STUDY participants and their families, investigators, sites, and the STUDY team

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John Fung, University of Chicago

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Stem Cell–Derived, Fully Differentiated Islets for Type 1 Diabetes

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Real-world perspective on caring for patients with T1D & potential role of zimislecel

James F. Markmann, M.D., Ph.D.

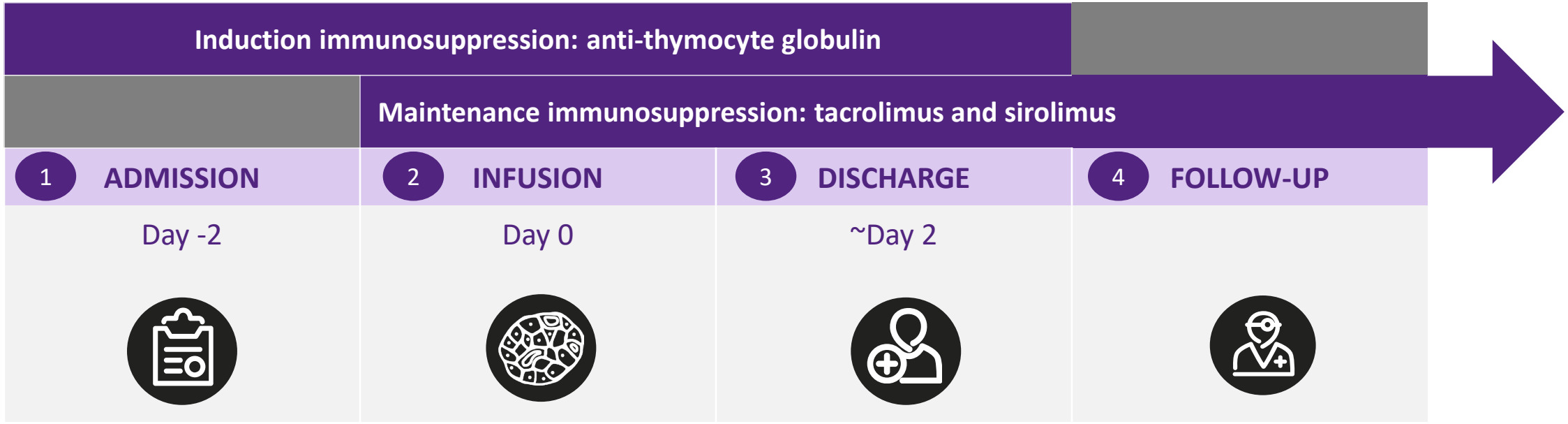
Professor in Surgery at the Perelman School of Medicine, University of Pennsylvania

Areas of Expertise: board certified general surgeon with extensive speciality training in islet transplantation and research in transplant immunology and ways to improve the efficiency of islet function for Type 1 diabetes

- Introduction
- Management of Type 1 diabetes and immunosuppression
- Potential role of zimislecel for patients with Type 1 diabetes

Disclosures: Dr. Markmann serves as a scientific advisory board member for iTolerance, eGenesis, Qihan Biotech. He is a consultant and principal investigator for the Vertex T1D clinical trial program.

Anticipated Islet Cell Therapy treatment journey is aligned to well-established protocols and standard immunosuppressive medications



1. **Patients admitted** & induction immunosuppression commences
2. **Islets infused** into the hepatic portal vein through a minimally invasive procedure (e.g., by interventional radiology)
3. **Induction immunosuppression completed** after zimislecel infusion; **maintenance immunosuppression initiated**
4. **Patients discharged** with ongoing follow-up for immunosuppression and insulin requirements

Treatment journey timing may vary by patient. Timing illustrated is based on clinical experience.

ZIMISLECEL (VX-880) for Type 1 Diabetes ADA Update

June 20, 2025

Zimislecel has shown transformative benefit for patients with T1D

Key ADA update takeaways:

- Type 1 diabetes is a **large patient population** (~3.8M in North America and Europe) with a **high unmet need; expect first submission will be for ~60K patients**
- Updated zimislecel data demonstrate a **durable therapy** with **curative potential** for people living with T1D
- With potential global regulatory filings in 2026, Vertex is expanding its manufacturing and commercial capabilities to ensure **launch readiness**
- **Serial innovation** is underway with additional T1D programs in preclinical stage