ORIGINAL ARTICLE

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

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ABSTRACT

BACKGROUND

Zimislecel is an allogeneic stem cell–derived islet-cell therapy. Data on the safety and efficacy of zimislecel in persons with type 1 diabetes are needed.

METHODS

We conducted a phase 1–2 study of zimislecel in persons with type 1 diabetes. In part A, participants received a half dose of zimislecel (0.4×10^9 cells) as a single infusion into the portal vein, with an option for a second half dose within 2 years. In parts B and C, participants received a full dose of zimislecel (0.8×10^9 cells) as a single infusion. All the participants also received glucocorticoid-free immunosuppressive therapy. The primary end point in part A was safety. The primary end point in part C was freedom from severe hypoglycemic events during days 90 through 365, with a glycated hemoglobin level of less than 7% or a decrease of at least 1 percentage point from baseline in the glycated hemoglobin level at one or more time points between days 180 and 365. Secondary end points in part C included safety and insulin independence between days 180 and 365. Assessment of the primary and secondary end points in part C involved the participants who received the full dose of zimislecel as a single infusion in part B or C. Detection of serum C-peptide during a 4-hour mixed-meal tolerance test was used to assess engraftment and islet function. All the analyses were interim and not prespecified.

RESULTS

A total of 14 participants (2 in part A and 12 in parts B and C) completed at least 12 months of follow-up and were included in the analyses. C-peptide was undetectable at baseline in all 14 participants. After zimislecel infusion, all the participants had engraftment and islet function, as evidenced by the detection of C-peptide. Neutropenia was the most common serious adverse event, occurring in 3 participants. Two deaths occurred — one caused by cryptococcal meningitis and one by severe dementia with agitation owing to the progression of preexisting neurocognitive impairment. All 12 participants in parts B and C were free of severe hypoglycemic events and had a glycated hemoglobin level of less than 7%; these participants spent more than 70% of the time in the target glucose range (70 to 180 mg per deciliter). Ten of the 12 participants (83%) had insulin independence and were not using exogenous insulin at day 365.

CONCLUSIONS

The results of this small, short-term study involving persons with type 1 diabetes support the hypothesis that zimislecel can restore physiologic islet function, warranting further clinical investigation. (Funded by Vertex Pharmaceuticals; VX-880-101 FORWARD ClinicalTrials.gov number, NCT04786262.)

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More than 8 million people worldwide live with type 1 diabetes.[1] This chronic disease is caused by autoimmune-mediated destruction of insulin-producing beta cells in pancreatic islets that leads to dysglycemia and lifelong dependence on insulin therapy.[2-6] To prevent long-term microvascular and macrovascular complications of type 1 diabetes, the insulin dose is adjusted to reach glucose levels that result in a glycated hemoglobin level of less than 7% and a percentage of time spent in the target glucose range (70 to 180 mg per deciliter [3.9 to 10 mmol per liter]) of more than 70%, as recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[6-8]

The range of therapeutic levels of insulin is narrow, and dose adjustments increase the risk of hypoglycemia[7] and make it challenging to meet glycemic goals. Approximately 75% of persons with type 1 diabetes do not have a glycated hemoglobin level of less than 7%[9,10]; glycated hemoglobin levels of 7% or higher are associated with increased risks of retinopathy, neuropathy, nephropathy, cardiovascular disease, and early death.[11-13] Severe hypoglycemic events are medical emergencies that can result from too much insulin relative to the need and may lead to loss of consciousness, accidents (e.g., falls or motor vehicle collisions), seizures, coma, and death.[14] Despite therapeutic advances in type 1 diabetes, the available treatment options are burdensome and do not have the precision, accuracy, and reliability of physiologic glucose regulation resulting from the restoration of pancreatic islet function.[15] In a recent survey of patients who were using an automated insulin-delivery system, a technology that represents the most advanced approach for glycemic control, approximately 35% did not meet the target glycated hemoglobin level of less than 7% recommended by the ADA and EASD, and approximately 9% reported recurrent severe hypoglycemic events.[16]

Restoring the function of islets can lead to physiologic glycemic control without an increased risk of hypoglycemia.[6,17] Beta-cell replacement with the use of islet or pancreas transplantation reduces or eliminates the need for insulin therapy, which decreases the risk of severe hypoglycemia caused by insulin. However, beta-cell replacement is limited by organ availability and variable islet quality.[6,17,18] The need for multiple transplants from multiple donors in order to achieve acceptable clinical outcomes further limits the usefulness of islet transplantation.[19-21]

Pluripotent stem cells can be differentiated into therapeutic cells to replace damaged or destroyed cells during disease. Studies have shown that stem cells can be differentiated into insulin-expressing beta cells and glucagon-expressing alpha cells capable of reversing diabetes in preclinical models.[22,23] Using an approach based on this discovery, we developed zimislecel (VX-880), a treatment composed of allogeneic stem cell–derived, fully differentiated islets. We hypothesized that administering zimislecel by means of procedures used in the transplantation of islets from a deceased donor[24,25] would lead to regulated secretion of endogenous insulin, improved glycemic control, elimination of severe hypoglycemic events, and insulin independence in humans. We report interim data from a phase 1–2 study evaluating the effects of a single infusion of zimislecel in persons with type 1 diabetes who have recurrent severe hypoglycemic events and impaired awareness of hypoglycemia despite appropriate disease management.

METHODS

STUDY DESIGN AND PARTICIPANTS

We conducted the phase 1–2 VX-880-101 FORWARD study in North America and Europe. VX-880-101 FORWARD (currently in phase 3) is an ongoing, open-label, 5-year study that is assessing the safety and efficacy of zimislecel (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Part A was designed to assess the safety of zimislecel, part B to assess safety and islet function, and part C to further assess safety and efficacy in additional participants. Persons 18 to 65 years of age who had type 1 diabetes with impaired awareness of hypoglycemia (defined by a reduced ability to perceive the onset of hypoglycemia), at least two severe hypoglycemic events in the previous year, and insulin dependence for at least 5 years were eligible. A severe hypoglycemic event was defined by the presence of symptoms of hypoglycemia during which the participant needed assistance with treatment and by either a blood glucose level of less than 54 mg per deciliter (3.0 mmol per liter) or prompt recovery after the receipt of oral carbohydrate, intravenous glucose, or glucagon.

Additional details about hypoglycemic events are provided in the Supplementary Appendix.

All the participants had received appropriate diabetes care, defined as standard insulin therapy by means of multiple daily injections or an insulin pump, under the direction of an endocrinologist, diabetologist, or diabetes specialist (an internist, physician assistant, or nurse practitioner experienced in the management of diabetes); all the participants had undergone at least three clinical evaluations documented by a diabetes specialist during the 12 months before screening. A continuous glucose monitor had been used consistently by the participants for at least 3 months before screening.

We assessed zimislecel at a half dose of 0.4×10^9 cells in part A and at a full dose of 0.8×10^9 cells in parts B and C. Zimislecel was administered by means of a single gravity-assisted infusion through a catheter in the portal vein over a period of 30 to 60 minutes. Induction immunosuppressive treatment was given before the infusion, and maintenance immunosuppressive treatment was given after the infusion. In parts A and B, the administration of zimislecel was staggered as a safety measure; a participant needed to have completed a follow-up period of at least 29 days before a subsequent participant received zimislecel. In part C, zimislecel was administered concurrently to all the participants. Progression through the study was based on reviews conducted by an independent data monitoring committee. As prespecified in the protocol, participants in part A could receive a second half dose of zimislecel within 2 years after the first infusion, if needed. Additional details about the administration of zimislecel are provided in the Supplementary Appendix.

We completed the enrollment of participants and the administration of zimislecel in the phase 1–2 portion of the study. Here, we report results of an unplanned interim analysis of the participants who completed phases 1 and 2. After the completion of 5 years of follow-up, participants will undergo additional follow-up during a 5-year extension study.

STUDY OVERSIGHT

The study was designed by Vertex Pharmaceuticals (study sponsor) along with the study steering committee. Safety oversight was provided by an independent data monitoring committee. Severe hypoglycemic events that occurred during the year before screening (in parts B and C) and during the study were adjudicated by an independent committee. Participants provided written informed consent. Data collection and analyses were performed by the sponsor. Three of the authors (all employed by the sponsor) wrote the first draft of the manuscript with assistance from medical writers employed by the sponsor. The authors had access to the data and reviewed and approved the manuscript for submission. The investigators vouch for the accuracy and completeness of data generated at their respective sites; the authors and the sponsor vouch for the fidelity of the study to the protocol (available at NEJM.org). Confidentiality agreements were in place between the sponsor and the study sites.

END POINTS

The primary end point in part A was safety. The primary end point in part C was freedom from severe hypoglycemic events from day 90 through day 365 after zimislecel infusion, with a glycated hemoglobin level of less than 7% or a reduction of at least 1 percentage point from baseline in the glycated hemoglobin level at one or more visits between day 180 and day 365. The secondary end points in part C were insulin independence (defined in the Supplementary Appendix) at one or more visits between day 180 and day 365 after zimislecel infusion, a peak C-peptide level of at least 100 pmol per liter during a 4-hour mixed-meal tolerance test as assessed at each study visit, and safety. Assessment of the primary and secondary end points in part C involved the participants who received the full dose of zimislecel as a single infusion in part B or C. Efficacy was assessed on the basis of the serum C-peptide level and the glucose level (measured with the use of a 4-hour mixed-meal tolerance test), the glycated hemoglobin level, continuous glucose monitoring, and exogenous insulin needs.

STATISTICAL ANALYSIS

As prespecified in the statistical analysis plan, available with the protocol, safety data were summarized with the use of descriptive statistics for all the participants who received zimislecel. The primary and secondary efficacy end points were analyzed among the participants who received the full dose of zimislecel as a single infusion and completed at least 12 months of follow-up. Other

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Participants (N=12)
Mean age at screening (range) — yr	42.7 (24–60)
Female sex — no. (%)	4 (33)
White race — no. (%)†	12 (100)
Mean weight (range) — kg	74.1 (56.0–97.5)
Mean body-mass index (range)‡	25.0 (21.7–28.5)
Mean duration of type 1 diabetes (range) — yr	22.3 (7.8–47.4)
Mean glycated hemoglobin level (range) — %	7.8 (7.1–9.9)
Percentage of time in target glucose range (range)§	49.5 (19.0–66.2)
Mean fasting C-peptide level (range) — pmol/liter¶	Undetectable
Mean total daily insulin dose (range) — U	40.9 (19.8–52.0)
Mean daily insulin need (range) — U/kg	0.55 (0.35–0.64)
Mean no. of severe hypoglycemia events per year (range)	2.7 (2–4)
Use of insulin pump at prescreening or screening visit — no. (%)	8 (67)
Use of hybrid closed-loop system at prescreening or screening visit — no. (%)	6 (50)

* Data are for the 12 participants in parts B and C (4 in part B and 8 in part C) who received a full dose of zimislecel (0.8×10^9 cells) as a single infusion and completed at least 12 months of follow-up.
† Race was reported by the participant.
‡ Body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.
§ The target glucose range is 70 to 180 mg per deciliter (3.9 to 10 mmol per liter).
¶ The fasting C-peptide level was calculated as the mean of the level at 10 minutes before the mixed-meal tolerance test and the level at the start of the test.

Table 2. Adverse Events.*

Event	Participants (N=14)
	no. (%)
Diarrhea	11 (79)
Headache	10 (71)
Nausea	9 (64)
Covid-19	7 (50)
Mouth ulceration	7 (50)
Neutropenia	6 (43)
Rash	6 (43)

* Shown are adverse events that occurred in at least six participants who received a half dose of zimislecel (0.4×10^9 cells) as a single infusion or two half doses as a single infusion each (part A) or a full dose of zimislecel (0.8×10^9 cells) as a single infusion (parts B and C) and completed at least 12 months of follow-up. Adverse events are reported according to *Medical Dictionary for Regulatory Activities*, version 27.1, preferred terms. Data were collected through October 18, 2024. Covid-19 denotes coronavirus disease 2019.

efficacy end points were analyzed among the participants who received the full dose of zimislecel as a single infusion. Efficacy data were summarized with the use of descriptive statistics.

RESULTS

POPULATION

The flow of the enrolled participants through the trial at the time of the interim analysis (October 18, 2024) is shown in Figure S2. Fourteen participants who received zimislecel and completed at least 12 months of follow-up were included in the analyses. Two participants received a half dose of zimislecel (part A), and 12 participants received a full dose of zimislecel (4 participants in part B and 8 participants in part C). One participant in part A received a second half dose of zimislecel 9 months after the first half dose and withdrew consent (not because of an adverse event) approximately 3 months after the second half dose.

Demographic and clinical characteristics of the 12 participants in parts B and C are shown in Table 1, and those of the 14 participants in parts A, B, and C are shown in Table S1. The mean duration of diabetes was 22.8 years (range, 7.8 to 47.4), with a mean total daily insulin dose of 39.3 units (range, 19.8 to 52.0). Participants had had two to four severe hypoglycemic events during the year before screening. In all the participants, fasting C-peptide levels (calculated as the mean of the level at 10 minutes before the mixed-meal tolerance test and the level at the start of the test) were undetectable at screening and baseline glycated hemoglobin levels were greater than 7% (range, 7.1 to 9.9). The demographic characteristics of the participants were generally representative of the global population of patients with type 1 diabetes (Table S2).

SAFETY

Among the 14 participants who received zimislecel and completed at least 12 months of follow-up, most adverse events were mild or moderate in severity. The most common adverse events, defined as those occurring in at least 6 participants, were diarrhea, headache, nausea, coronavirus disease 2019, mouth ulceration, neutropenia, and

rash (Table 2). No adverse events led to study discontinuation. Serious adverse events of neutropenia leading to extended hospitalization for observation occurred in 3 participants, and serious adverse events of acute kidney injury occurred in 2 participants; all other serious adverse events occurred in 1 participant each (Table S6). No serious adverse events were considered by the investigator to be related or possibly related to zimislecel.

Two participants died (Table S5). One death occurred in part B approximately 19.5 months after zimislecel infusion and was due to serious cryptococcal meningitis caused by an extensive sinus surgery that was complicated by injury to the base of the skull (i.e., cribriform plate and lamellar bone). This participant had been taking high-dose systemic glucocorticoids (a medication prohibited by the protocol) for a prolonged period and was also receiving immunosuppressive therapy. Cryptococcal meningitis was considered by the investigator to be related to the use of immunosuppressive medication. The other death occurred in part A approximately 30 months after zimislecel infusion and was due to severe dementia with agitation owing to the progression of preexisting neurocognitive impairment. This participant had had a history of severe traumatic brain injury due to a motor vehicle accident before enrollment; the accident was caused by a severe hypoglycemic event.

Seven participants had nonserious adverse events that were considered by the investigator to be related (which includes possibly related) to zimislecel. All these adverse events were mild in severity and included transient increases in liver-function values that generally occurred within 6 days after zimislecel infusion and resolved within 30 days. Decreases in white blood cell counts and renal function were observed and were generally consistent with the use of immunosuppressive therapy. Additional safety data are included in Tables S7 through S9.

EFFICACY

Half Dose of Zimislecel

In part A of the study, two participants received a half dose of zimislecel. At day 90, both participants had a detectable fasting C-peptide level; during the 4-hour mixed-meal tolerance test, both participants had a detectable stimulated C-peptide level and less excursion (i.e., a smaller postprandial increase) in the glucose level than at baseline. Insulin independence occurred in one participant. The clinical course in both participants is shown in Figures S3 and S4.

Full Dose of Zimislecel

In parts B and C of the study, 12 participants received a full dose of zimislecel as a single infusion. No participants had a severe hypoglycemic event during the evaluation period (days 90 through 365). Freedom from severe hypoglycemic events with a glycated hemoglobin level of less than 7% occurred in all 12 participants who completed the day 365 visit.

At screening, fasting and mixed-meal–stimulated C-peptide levels were at or below the lower limit of detection (13 pmol per liter) in all 12 participants. At day 90, all the participants had a detectable fasting C-peptide level; during the 4-hour mixed-meal tolerance test, all had a detectable stimulated C-peptide level (mean level at 90 minutes, 424 pmol per liter) and less excursion in the glucose level than at baseline (Fig. 1A). Additional improvement in the mixed-meal–stimulated endogenous insulin level at 90 minutes was observed in all the participants at day 180 (mean C-peptide level at 90 minutes, 1036 pmol per liter); this improvement was sustained at later time points during the study (mean C-peptide level at 90 minutes, 1104 pmol per liter on day 270 and 1274 pmol per liter on day 365) (Fig. 1B). A peak C-peptide level of at least 100 pmol per liter (secondary end point) — the threshold for a functional islet graft[26] — was observed in all 12 participants at day 90 after infusion and at all subsequent time points (Table S3), a finding that indicates the durability of zimislecel islet survival and function.

At baseline, no participants had a glycated hemoglobin level at or below the target of 7% recommended by the ADA and EASD (mean level, 7.8%; range, 7.1 to 9.9). At day 120, all the participants had a glycated hemoglobin level of less than 7% (range, 5.7 to 6.7). The glycated hemoglobin level in all the participants remained less than 7% during subsequent follow-up (Fig. 2A). At day 365, the mean reduction from baseline in the glycated hemoglobin level was 1.81 percentage points.

Continuous glucose monitoring was used to assess the time spent in the recommended target glucose range of 70 to 180 mg per deciliter. At

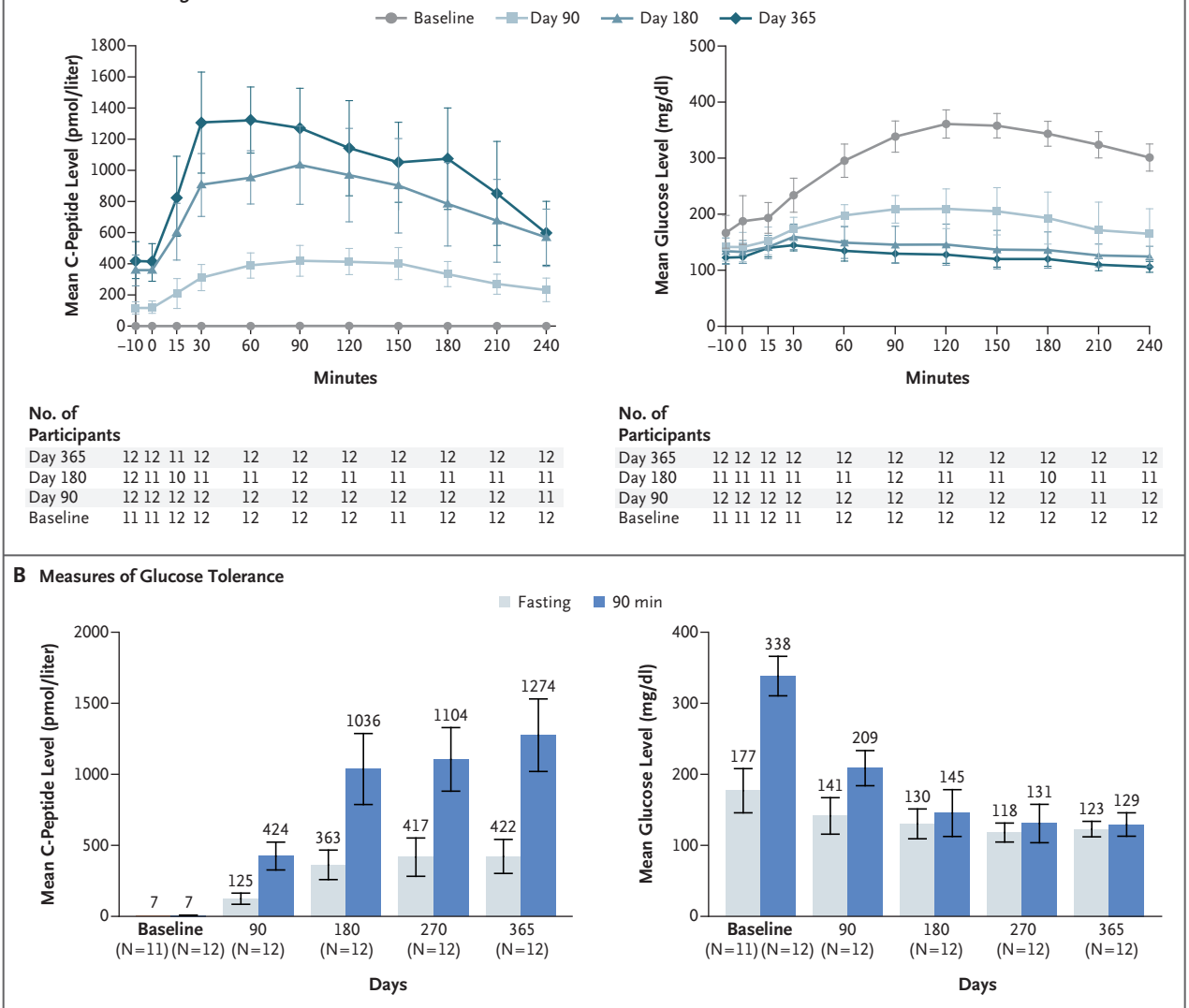

Figure 1. Endogenous Insulin Production and Glucose Tolerance.

Panel A shows the mean C-peptide levels (lower limit of detection, 13 pmol per liter) (left) and mean glucose levels (right) over time during a 4-hour mixed-meal tolerance test at baseline and at day 90 and day 180 after zimislecel infusion. Panel B shows the mean fasting C-peptide level and mean mixed-meal–stimulated C-peptide level at 90 minutes (left) and the mean fasting glucose level and mean mixed-meal–stimulated glucose level at 90 minutes (right) at baseline and at day 90, day 180, day 270, and day 365 after zimislecel infusion. Data are shown for the 12 participants who received the full dose of zimislecel (0.8×10^9 cells) as a single infusion and completed at least 12 months of follow-up. Fasting C-peptide and glucose levels were calculated as the mean of the level at 10 minutes before the mixed-meal tolerance test and the level at the start of the test. I bars indicate 95% confidence intervals.

baseline, no participant spent more than 70% of time in the target range; the mean time in range was 49.5% (range, 19.0 to 66.2). All the participants were spending more than 70% of time in the target range by day 150, and this level of glucose control was present in all the participants during subsequent follow-up (Fig. 3A). The mean time in the target glucose range improved to 93.3% (range, 79.5 to 96.9) at day 365 (Fig. 3B and Table S4). The mean variability in the glucose level, expressed as the mean glucose coefficient of variation, decreased from 36.3% at baseline to 21.2% at day 180 and 20.0% at day 365.

The use of exogenous insulin decreased or stopped in all 12 participants during follow-up (Fig. 2B). The mean insulin dose decreased by 92%

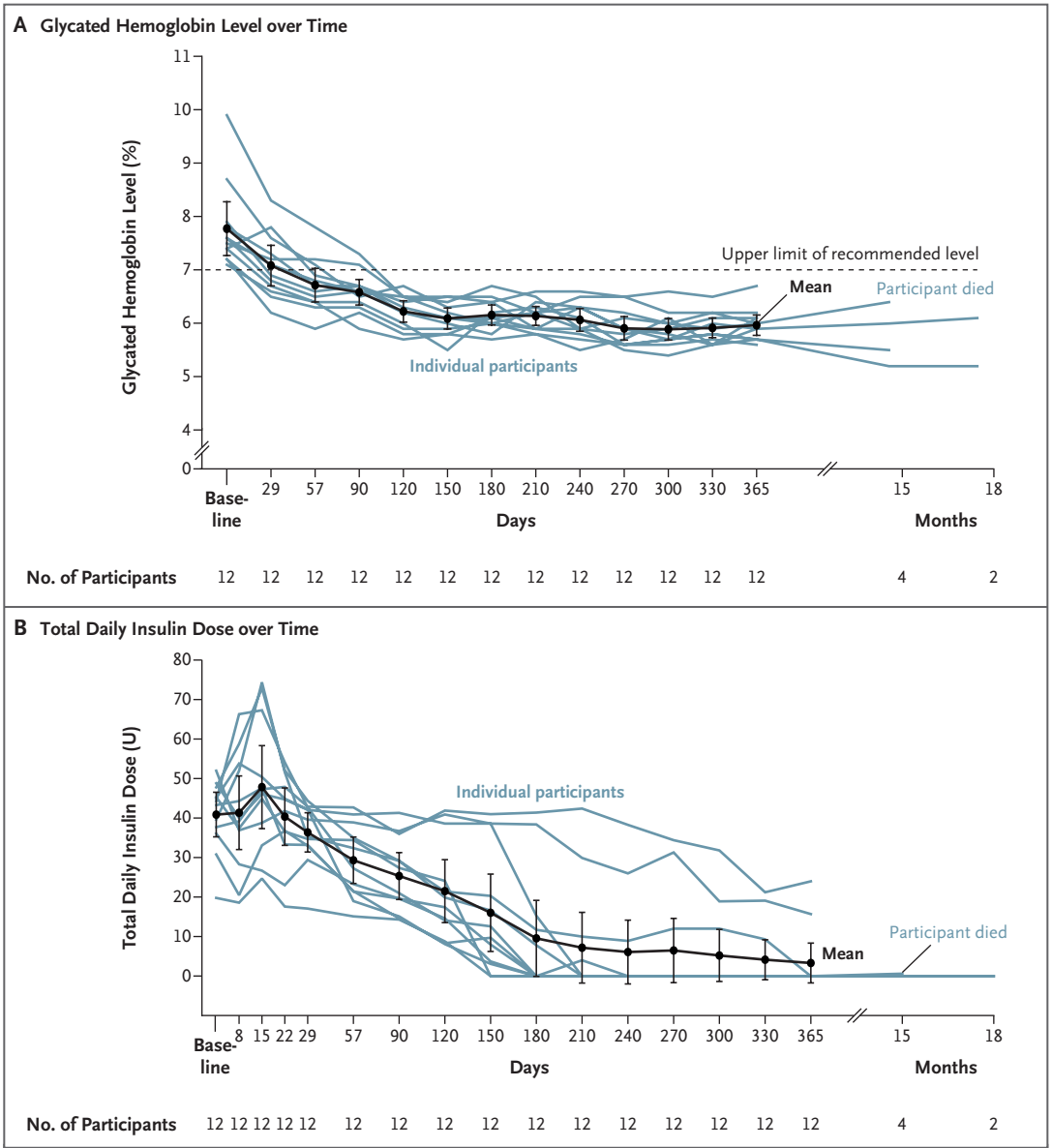

Figure 2. Glycated Hemoglobin Level and Total Daily Insulin Dose.

Panel A shows the glycated hemoglobin level over time. Blue lines indicate the glycated hemoglobin level in individual participants, the solid black line indicates the mean glycated hemoglobin during visits with data obtained from at least 5 participants, and the dashed line indicates the upper limit of the glycated hemoglobin level recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD). Panel B shows total daily insulin dose over time. Blue lines indicate the total daily insulin dose in individual participants, and the solid black line indicates the mean total daily insulin dose during visits with data obtained from at least 5 participants. Data are shown for the 12 participants who received the full dose of zimislecel as a single infusion and completed at least 12 months of follow-up. I bars indicate 95% confidence intervals.

between baseline and day 365. Insulin independence (secondary end point) occurred in 10 participants, among whom insulin therapy ended as early as day 150 and did not resume through day 365. Two participants continued receiving exogenous insulin; the insulin dose decreased by 70% and 36% between baseline and day 365, with improvements in the glycated hemoglobin level and the time in the target glucose range. Both participants had received high-dose glucocorti-

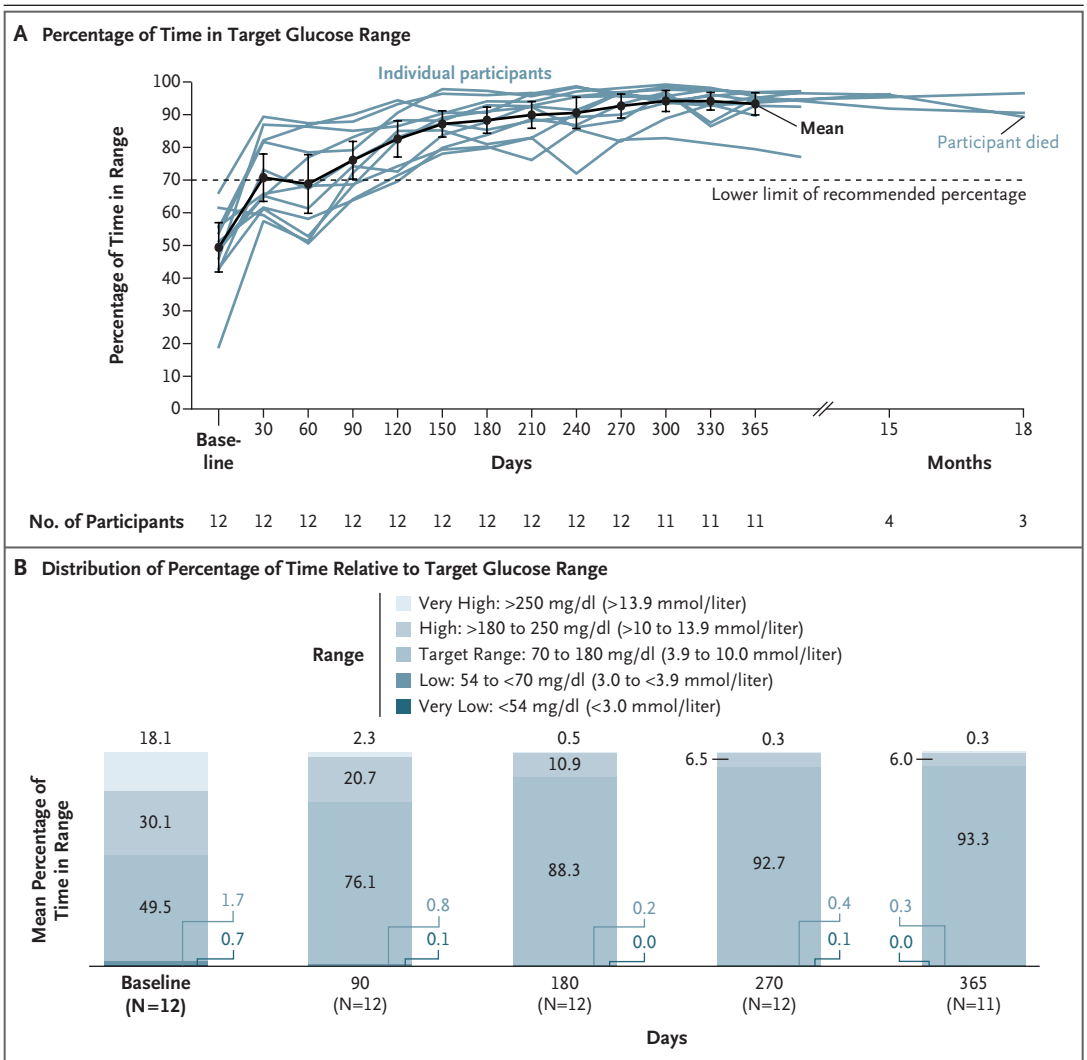

Figure 3. Time Spent in the Target Glucose Range.

Panel A shows the percentage of time in which the glucose level was in the target range of 70 to 180 mg per deciliter (3.9 to 10 mmol per liter) recommended by the ADA and EASD during the follow-up period. Blue lines indicate the percentage of time that individual participants spent in the target glucose range, the solid black line indicates the mean time in the target range during visits with data obtained from at least 5 participants, and the dashed line indicates the lower limit of the percentage of time in the target range recommended by the ADA and EASD for persons with type 1 diabetes. Panel B shows the mean distribution of the percentage of time spent below, within, and above the target glucose range. Percentages may not sum to 100 because of rounding. Data are shown for the 12 participants who received the full dose of zimislecel as a single infusion and completed at least 12 months of follow-up. I bars indicate 95% confidence intervals.

coid therapy (prohibited by the protocol) within 1 day after zimislecel infusion. High-dose glucocorticoid use during the periinfusion period, along with resulting glucotoxicity (impaired beta-cell function during periods of high glucose levels), may have adversely affected islet engraftment, islet survival, or both in these two participants. Glucotoxicity due to glucocorticoid-induced hyperglycemia has been associated with increased beta-cell apoptosis during islet engraftment.[27]

DISCUSSION

We report on the use of zimislecel, a fully differentiated, allogeneic pluripotent stem cell–derived islet-cell therapy for type 1 diabetes. Directed dif-

ferentiation of pluripotent stem cells into specialized cell types can potentially provide an inexhaustible supply of replacement tissues for serious diseases. Our study showed that stem cell–derived islets engrafted, produced endogenous insulin, and restored the physiologic function of islets, leading to improved glycemic control, elimination of severe hypoglycemic events, and insulin independence in persons with type 1 diabetes.

The study participants were generally representative of patients with type 1 diabetes. All the participants in our study were using continuous glucose monitoring and were receiving appropriate medical care before enrollment; 50% of the participants were using an automated insulin-delivery system. A glycated hemoglobin level of more than 7% and a time in the target glucose range of less than 70% are associated with an increased risk of microvascular and macrovascular complications of type 1 diabetes. However, as in many persons living with type 1 diabetes,[9,10] these targets could not be safely reached in the study participants before enrollment. Although the insulin dose can be increased in order to treat hyperglycemia, intensification of insulin therapy is associated with a heightened risk of hypoglycemia, including life-threatening severe hypoglycemic events. Participants in our study were not candidates for intensification of insulin therapy because their awareness of hypoglycemia was impaired; the risk of severe hypoglycemic events among patients with impaired awareness is up to 6 times as high as that among those with normal awareness.[6,28]

Basal and mixed-meal–stimulated insulin production were restored in the participants after a single infusion of zimislecel, with simultaneous and appropriate improvements in glucose regulation. These findings showed that zimislecel islet cells were functional and self-regulated appropriately. A full dose of zimislecel administered as a single infusion led to the restoration of islet function. In all 12 participants who received the full dose, this restoration resulted in clinically meaningful and marked improvements in glycemic control, including the occurrence of a glycated hemoglobin level of less than 7% and a time in range of more than 70% and the elimination of severe hypoglycemic events. In addition, the use of exogenous insulin was reduced or eliminated in all 12 participants, with 83% no longer needing insulin therapy at 12 months. Although elimination of the need for exogenous insulin is desired, the results of this study show clinical benefits from the restoration of islet function, even in the absence of complete elimination of insulin therapy. These results are consistent with observations from the Diabetes Control and Complications Trial, which showed that residual beta-cell function is associated with a reduced risk of severe hypoglycemia, improved glycemic control, and a decreased risk of microvascular complications.[7] Freedom from severe hypoglycemic events with a glycated hemoglobin level of less than 7% occurred in all 12 participants who received the full dose of zimislecel as a single infusion and completed at least 12 months of follow-up, and insulin independence (secondary end point) occurred in 10 (83%) of these participants.

Most adverse events were mild or moderate in severity, and most of the adverse events with a causal relationship to a drug taken during the study were attributed to immunosuppressive therapy. Transient elevations in liver aminotransferase levels, decreased white-cell counts, and decreased renal function were observed; these findings have been previously associated with the infusion procedure and immunosuppressive regimens used in studies of islet transplantation.[25,29,30] There were two deaths — one caused by cryptococcal meningitis and one by severe dementia with agitation owing to progression of preexisting neurocognitive impairment.

The results of this unplanned interim analysis of our single-group, phase 1–2 study support further investigation of zimislecel in larger, longer studies involving diverse populations. These results also support our hypothesis that zimislecel can restore physiologic islet function, improve glycemic control, and eliminate the shortcomings of insulin-replacement therapy, including treatment-related adverse events and the burden of managing the insulin dose. More generally, these findings provide evidence that pancreatic islets can be effectively produced from pluripotent stem cells and used to treat type 1 diabetes.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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