JAMA Network Open

Original Investigation | Diabetes and Endocrinology

Automated Insulin Delivery in Adults With Type 2 Diabetes
A Nonrandomized Clinical Trial

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Abstract

IMPORTANCE There is a need for additional treatment options for people with type 2 diabetes treated with insulin. Given the limited data on the use of automated insulin delivery (AID) systems in type 2 diabetes, studies evaluating their safety and efficacy are important.

OBJECTIVE To evaluate the association of AID with hemoglobin A_{1c} (HbA_{1c}) levels in a diverse cohort of adults with type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS This single-arm prospective trial was conducted at 21 clinical centers in the United States among individuals aged 18 to 75 years with type 2 diabetes who had been using insulin for at least 3 months prior to screening. Participants with AID system use were excluded. The study started with a 14-day standard therapy phase, followed by 13 weeks of treatment with the investigational device. The first participant was enrolled April 11, 2023, and the last participant follow-up visit was February 29, 2024.

INTERVENTION Participants used the Omnipod 5 AID System for 13 weeks following the 14-day standard therapy phase.

MAIN OUTCOMES AND MEASURES Primary outcome was change in HbA_{1c} level at 13 weeks, tested sequentially for noninferiority (0.3% margin) and superiority, compared with baseline.

RESULTS Among 305 participants (mean [SD] age, 57 [11] years; 175 [57%] female; 72 [24%] Black, 66 [22%] Hispanic or Latino, and 153 [50%] White), 289 (95%) completed the trial. At baseline, 223 (73%) were using multiple daily injections, 63 (21%) were using basal insulin without bolus, 17 (6%) were using an insulin pump, 188 (62%) were using continuous glucose monitoring, 168 (55%) were using glucagon-like peptide-1 receptor agonists (GLP-1RAs), and 134 (44%) were using sodium-glucose transport protein 2 inhibitors (SGLT-2is). Following AID use, HbA_{1c} levels decreased from a mean (SD) of 8.2% (1.3) at baseline to 7.4% (0.9) at 13 weeks (mean difference, −0.8 [95% CI, −1.0 to −0.7] percentage points; $P < .001$ for noninferiority and superiority). Improvement was seen across various subgroups (age, sex, race and ethnicity, insurance), and notably with or without use of GLP-1RAs or SGLT-2is and regardless of pretrial mealtime insulin regimen. Time in target glucose range (70-180 mg/dL) increased from a mean (SD) of 45% (25) to 66% (17) (mean difference, 20 [95% CI, 18 to 22] percentage points; $P < .001$). Percentage of time in hypoglycemic ranges of less than 54 mg/dL and less than 70 mg/dL was noninferior compared with standard therapy. There was 1 episode of severe hypoglycemia and none of diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome.

(continued)

Key Points

Question Is automated insulin delivery (AID) safe and effective for use in adults with type 2 diabetes who are being treated with insulin with or without other glucose-lowering medications?

Findings In this nonrandomized clinical trial including 305 adults with type 2 diabetes, there was a significant decrease in hemoglobin A_{1c} (HbA_{1c}) levels from 8.2% to 7.4% after 13 weeks of AID use, representing a 0.8–percentage point reduction.

Meaning In this study, a reduction in HbA_{1c} levels was observed in a socioeconomically, racially, and ethnically diverse cohort of adults with type 2 diabetes who were being treated with insulin with and without other glucose-lowering treatments following AID use.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE In this nonrandomized clinical trial, HbA_{1c} levels were lower in a diverse cohort of adults with type 2 diabetes following AID initiation, suggesting that AID may be a beneficial and safe option for people with type 2 diabetes using insulin.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05815342

JAMA Network Open. 2025;8(2):e2459348. doi:10.1001/jamanetworkopen.2024.59348

Introduction

Diabetes is a major public health concern, affecting more than 38 million Americans,[1] with high rates of morbidity and mortality.[2] Despite the growing use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose transport protein 2 inhibitors (SGLT-2is), many individuals with type 2 diabetes have hemoglobin A_{1c} (HbA_{1c}) levels greater than the target recommendations of the American Diabetes Association.[3] Automated insulin delivery (AID) systems have been demonstrated to improve glycemia in type 1 diabetes.[4-8] In type 2 diabetes, prior studies of AID have been limited to small (30 participants or less) feasibility trials.[9-13]

At the time of study start, the Omnipod 5 AID System (Insulet Corporation) was cleared by the US Food and Drug Administration (FDA) and Conformité Européenne–marked for individuals with type 1 diabetes aged 2 years and older. This wearable, tubeless pump communicates with an interoperable continuous glucose monitor (CGM) to adjust insulin delivery based on sensor glucose readings.[14] To determine the outcomes of AID in individuals with type 2 diabetes, this study evaluated the Omnipod 5 AID System in a multicenter, single-arm, pivotal trial enrolling a large and diverse population of adults with insulin-treated type 2 diabetes. Data from this study were used to obtain FDA clearance for individuals with type 2 diabetes aged 18 years and older.

Methods

Trial Conduct and Oversight

The trial protocol was approved by central and local institutional review boards with oversight from an independent medical monitor and an investigational device exemption from the FDA. Written informed consent was obtained from each participant. The protocol and statistical analysis plan are available in Supplement 1.

Trial Design and Participants

This 13-week single-arm, prospective trial evaluated the safety and efficacy of AID in adults diagnosed with type 2 diabetes in 21 centers in the United States. The single-arm noninferiority, followed by superiority, trial design was selected because it was appropriate for FDA clearance of a medical device and maximized intervention exposure across a large and heterogeneous group of people with type 2 diabetes. Participants were aged 18 to 75 years and treated with a stable insulin regimen for at least 3 months prior to screening. They could be additionally treated with other antihyperglycemic and weight loss medications without dose change for at least 4 weeks prior to the trial. All participants were required to have a baseline HbA_{1c} of less than 12% (to convert to proportion of total hemoglobin, multiply by 0.01), and for basal insulin–only users, there was a lower HbA_{1c} limit of 7%. Complete eligibility criteria in eTable 1 in Supplement 2. The study defined enrollment goals to recruit a diverse population (eTable 2 in Supplement 2).

CGM data were collected in a 14-day standard therapy phase using the Dexcom G6 CGM (Dexcom), masked for those not already using this CGM. During this period participants continued using their prestudy treatment.

Prior to initiating AID, investigators assessed insulin dosing at mealtimes and provided carbohydrate counting instructions or advised participants to use a simplified meal bolus technique (ie, small, medium, and large, fixed-dose, or correction-only). Participants then transitioned to the 13-week treatment phase using AID, during which those receiving stable doses of noninsulin antihyperglycemic medications continued use of these medications into the treatment phase. Initial pump settings were at the discretion of the investigator. The visit schedule and detailed methods are available in eTables 3 and 4 in Supplement 2.

Investigational Device

The investigational device includes a tubeless insulin pump (Pod) with embedded AID algorithm and an application on a provided locked-down Android phone or a personal Android smartphone with English or Spanish language options. The model predictive control algorithm used in the trial is the same AID algorithm cleared by FDA for use among patients with type 1 diabetes. When used in Automated Mode with an interoperable CGM (study CGM: Dexcom G6), the AID algorithm delivers dynamic microboluses of insulin every 5 minutes or pauses insulin based on glucose values to approach the user configurable target glucose value of 110 mg/dL to 150 mg/dL in 10mg/dL increments, adjustable by time of day (to convert glucose to micromoles per liter, multiply by 0.0555).[14]

Outcomes

The primary outcome was the change in HbA_{1c} at 13 weeks from baseline, tested sequentially for noninferiority (limit 0.3%) and superiority. Secondary glycemic outcomes, tested in a hierarchal fashion to preserve type I error (eTable 5 in Supplement 2), included change from baseline in mean sensor glucose; percentage of time with sensor glucose in ranges of interest (70-180 mg/dL [time in range, TIR], 70-140 mg/dL, ≥300 mg/dL, >250 mg/dL, >180 mg/dL, <70 mg/dL [noninferiority, 2.0% limit], and <54mg/dL [noninferiority, 0.5% limit]); Type 2 Diabetes Distress Assessment System (T2-DDAS),[15] Pittsburgh Sleep Quality Index (PSQI),[16] and Hypoglycemia Confidence Scale (HCS) total scores[17]; proportion with high distress (T2-DDAS ≥2.0), poor sleep quality (PSQI >5.0), and low hypoglycemia confidence (HCS <3.0); percentage of time with glucose less than 70 mg/dL (superiority); percentage of time with glucose less than 54 mg/dL (superiority); and coefficient of variation of sensor glucose. Reportable adverse events are listed in eTable 4 in Supplement 2, and additional outcomes not included in the hierarchy are listed in eTable 6 in Supplement 2.

Sample Size and Power Calculation

A sample of 300 participants initiating the treatment phase with the goal of 275 completers was planned to ensure sufficient exposure of system use by participants using multiple daily injections (MDI), basal without bolus insulin (referred to as basal insulin only), and other noninsulin glucose-lowering medications along with insulin. Based on prior studies,[13,18,19] an SD of 0.8 for the change in HbA_{1c} from baseline to 13 weeks was estimated. Assuming 275 completers, statistical power was calculated at greater than 99% for the primary outcome of change in HbA_{1c} levels from baseline to 13 weeks, tested for noninferiority with a limit of 0.3% (1-sided type I error rate of 2.5%; true mean difference of zero is assumed) and for superiority assuming a true mean difference of 0.4% (2-sided type I error rate of 5%).

Statistical Analysis

The primary analysis was conducted with complete cases. Sensitivity analyses were performed to handle missing HbA_{1c} values for both the noninferiority and superiority primary outcomes (statistical significance of $P < .025$ for 1-sided tests and $P < .05$ for 2-sided tests). A per-protocol analysis was performed including participants with sufficient system use as defined within eTable 4 in Supplement 2. The primary analysis and most secondary and exploratory analyses were analyzed using paired *t* tests. If not normally distributed, robust regression using M estimation with the Huber weight function or a nonparametric test was used.

Preplanned superiority analyses were conducted, stratified by insulin regimen at baseline (MDI [not including pump users] and basal without bolus insulin) using the method described for the primary analysis. For this and other planned secondary analyses outside the statistical hierarchy, the false discovery rate was controlled using the adaptive Benjamini-Hochberg procedure.[20] For preplanned assessments of differences across subgroups, linear or robust regression models were used to assess interaction between outcome and subgroup of interest adjusted for baseline outcome.

Additional details of the statistical testing methods are included in eTable 4 in Supplement 2. Data analyses were performed using SAS version 9.4 (SAS Institute).

Results

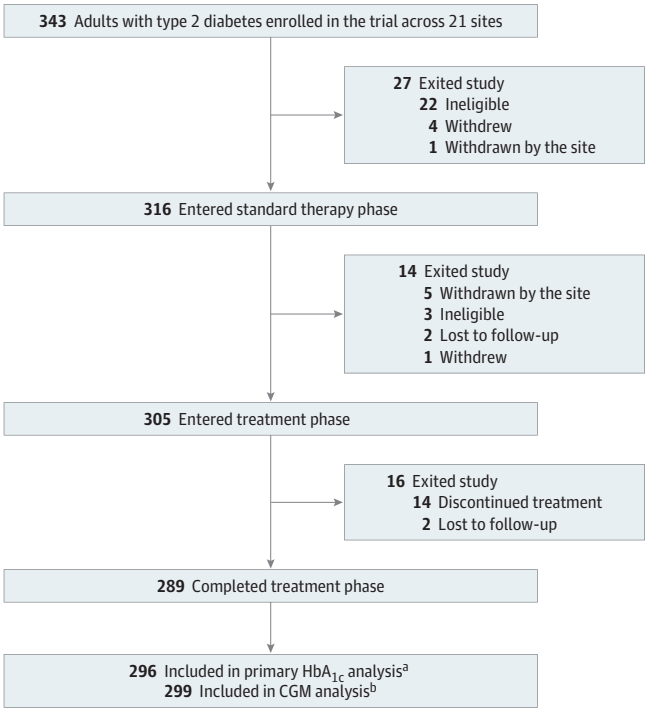
Participants

Between April 11, 2023, and November 14, 2023, 343 individuals were enrolled and 305 initiated AID, with 289 completing the 13-week follow-up period (**Figure 1**). Of the 305 initiating AID (175 [57%] female; mean [SD] age, 57 [11] years), 223 (73%) were using MDI at baseline; 17 (6%), an insulin pump without AID; and 63 (21%), basal insulin only; 188 (62%) were using CGM. One hundred sixty-eight (55%) were using a GLP-1RA, 135 (44%) an SGLT-2i, and 82 (27%) both. Other notable population characteristics included race (72 [24%] Black, not Hispanic or Latino; 153 [50%] White, not Hispanic or Latino), ethnicity (66 [22%] Hispanic or Latino), insurance (124 [41%] publicly funded or no health insurance). A full list of baseline characteristics is provided in **Table 1**. Baseline characteristics for the 16 noncompleters are summarized in eTable 7 in Supplement 2.

Primary Outcome

HbA_{1c} decreased by mean (SD) of 0.8 (1.0) percentage points (95% CI, −1.0 to −0.7 percentage points) from 8.2% (1.3) at baseline to 7.4% (0.9) at treatment phase end ($P < .001$ for noninferiority and superiority) (**Table 2**). Results were similar for the 247 participants included in the per-protocol analysis (eTable 8 in Supplement 2) and similar in analyses that excluded participants who were

Figure 1. Trial Flow Diagram



[a] Hemoglobin A_{1c} (HbA_{1c}) analyses included all participants who had values at both baseline and 13 weeks or early withdrawal if done 42 to 119 days from the initiation of automated insulin delivery system.

[b] Continuous glucose monitoring (CGM) analyses included all participants with at least 168 hours of CGM data during each of the standard therapy period and the 13-week treatment period.

Table 1. Baseline Characteristics of Trial Population

Characteristic	Participants, No. (%) (N = 305)
Age, mean (SD) [range], y	57 (11) [20-75]
Duration of type 2 diabetes, median (IQR), y	17 (11-24)
Sex	
Female	175 (57)
Male	130 (43)
Race and ethnicity[a]	
American Indian or Alaskan Native, not Hispanic or Latino	2 (<1)
Asian or Pacific Islander, not Hispanic or Latino	7 (2)
Black, not Hispanic or Latino	72 (24)
Hispanic or Latino	66 (22)
White, not Hispanic or Latino	153 (50)
≥1 Race, not Hispanic or Latino	3 (1)
HbA_{1c} level, mean (SD) [range], %	8.2 (1.3) [4.9-12.0]
HbA_{1c} category, %	
<7	45 (15)
7 to <8	107 (35)
8 to <9	82 (27)
9 to <10	32 (10)
≥10	39 (13)
Body mass index, mean (SD) [range][b]	35 (8) [22-70]
Standard period of insulin therapy	
Multiple daily injections	223 (73)
Basal insulin only injections	63 (21)
Insulin pump	17 (5.6)
Premix insulin injections	2 (<1)
Previous continuous glucose monitor use	
Never	75 (25)
In past, but not current	42 (14)
Current	188 (62)
Total daily dose of insulin, mean (SD) [range], U/kg	0.8 (0.5) [0.1-2.9]
Use of select noninsulin glucose-lowering medications	
GLP-1RA	168 (55)
SGLT-2i	135 (44)
DPP4i	8 (3)
GLP-1RA and/or SGLT-2i	221 (72)
GLP-1RA and SGLT-2i	82 (27)
Neither GLP-1RA nor SGLT-2i	84 (28)
Health insurance[c]	
Private	161 (53)
Medicaid	27 (9)
Medicare	52 (17)
Other government	27 (9)
No coverage	18 (6)
Education[d]	
High school diploma or less	99 (32)
Technical, vocational, or associate's degree	73 (24)
Bachelor degree	70 (23)
Advanced degree	40 (13)
Income, $[e]	
<50 000	84 (28)
50 000 to <100 000	75 (25)
≥100 000	67 (22)

(continued)

Table 1. Baseline Characteristics of Trial Population (continued)

Characteristic	Participants, No. (%) (N = 305)
Other key medical conditions	
Hypertension	223 (73)
Myocardial infarction	12 (4)
Stroke	5 (2)
Lipid abnormality	265 (87)
GAD antibody level, IU/mL[f]	
<5	284 (93)
5 to <250	7 (2)
≥250	13 (4)

Abbreviations: DPP4i, dipeptidyl peptidase 4 inhibitor; GAD, antiglutamic acid decarboxylase; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA_{1c}, hemoglobin A_{1c}; SGLT-2i, sodium-glucose cotransporter 2 inhibitor.

SI conversion factors: To convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01.

[a] Race and ethnicity were reported by the participants and are displayed exactly as reported. Race and ethnicity were unknown or not reported for 2 participants (<1%).

[b] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[c] Health insurance coverage was unknown or not reported for 20 participants (7%).

[d] Educational background was unknown or not reported by 23 participants (8%).

[e] Income was unknown or not reported for 79 participants (26%).

[f] GAD antibody level was unknown or not reported for 1 participant (<1%).

positive for glutamic acid decarboxylase (GAD) antibodies (eTable 9 in Supplement 2). HbA_{1c} reduction was observed in both prior MDI (−0.8 [95% CI, −0.9 to −0.7] percentage points; $P < .001$) and prior basal insulin only (−1.2 [95% CI, −1.5 to −0.9]; $P < .001$) users.

HbA_{1c} reduction was observed across a wide range of participant characteristics (**Figure 2**; eTable 10 in Supplement 2). A greater decrease in HbA_{1c} was associated with a higher baseline HbA_{1c} level (eFigure 1A in Supplement 2): those with baseline HbA_{1c} of 9.0% or greater had a decrease of −2.1 (95% CI, −2.3 to −1.9) percentage points, while those with baseline HbA_{1c} level of less than 7.0% saw no change (0.0 [95% CI, −0.3 to 0.2] percentage points) ($P < .001$). After adjustment for baseline HbA_{1c}, a similar change in HbA_{1c} level was observed among subgroups based on sex, age, socioeconomic status, pretrial mealtime insulin regimen, noninsulin glucose-lowering medication use, C-peptide level, and previous CGM use. There was an apparent interaction between change in HbA_{1c} and race and ethnicity, with non-Hispanic Black participants having a lower observed reduction following adjustment for baseline HbA_{1c}, although all racial and ethnic groups saw benefit (Figure 2; eTable 10 in Supplement 2). Further exploration into these data showed a difference in adoption of the 110 mg/dL glucose target setting between race and ethnicity groups (White [not Hispanic or Latino], Black [not Hispanic or Latino], and Hispanic or Latino used the 110 mg/dL target 56%, 37%, and 55% of cumulative total study time, respectively). A reduction in HbA_{1c} level was observed in both GLP-1RA users and nonusers: HbA_{1c} decreased from a mean (SD) of 8.1% (1.2) at baseline to 7.3% (0.8) at end of treatment in GLP-1RA users (adjusted difference, −0.9 [95% CI, −1.0 to −0.8] percentage points) and from a mean (SD) 8.4% (1.4) to 7.5% (1.0) for GLP-1RA nonusers (adjusted difference, −0.8 [95% CI, −0.9 to −0.6] percentage points). A similar pattern was observed for SGLT-2i users and nonusers. A similar decrease in HbA_{1c} was observed across varying baseline HbA_{1c} ranges in those who used or did not use GLP-1RA (eFigure 2A in Supplement 2). The proportion of participants achieving HbA_{1c} of less than 7% was 14% at baseline (42 of 296 participants) and 37% at treatment phase end (110 participants) (eTable 11 in Supplement 2).

Table 2. Primary and Secondary Outcomes

Outcome	Phase			
	Mean (SD)			
	Baseline or ST (2 weeks)[a,b]	End of treatment or treatment phase (13 weeks)[a,b]	Mean difference (95% CI)[b]	*P* value
Primary outcome				
HbA_{1c}, %				
Overall	8.2 (1.3)	7.4 (0.9)	−0.8 (−1.0 to −0.7)[c]	<.001[c,d]
Prior MDI users[e]	8.2 (1.4)	7.4 (0.9)	−0.8 (−0.9 to −0.7)	<.001[f]
Prior basal insulin only users	8.6 (1.2)	7.5 (0.8)	−1.2 (−1.5 to −0.9)	<.001[f]
Secondary outcomes in prespecified hierarchical order[g]				
Mean sensor glucose, mg/dL	202 (50)	170 (24)	−32 (−37 to −28)	<.001
Time in glucose range, %				
70-180 mg/dL	45 (25)	66 (17)	20 (18 to 22)	<.001
70-140 mg/dL	21 (18)	33 (17)	12 (10 to 13)	<.001
≥300 mg/dL[h]	8 (10)	2 (2)	−5 (−6 to −4)	<.001
>250 mg/dL[h]	20 (22)	7 (8)	−12 (−14 to −11)	<.001
>180 mg/dL	54 (25)	34 (17)	−20 (−22 to −18)	<.001
<70 mg/dL[i]	0.2 (0.3)	0.2 (0.2)	0.0 (−0.1 to 0.0)	<.001
<54 mg/dL[i]	0.01 (0.02)	0.04 (0.05)	0.01 (0.00 to 0.01)	<.001
T2-DDAS[j]				
Total intensity score	2.5 (1.0)	2.2 (0.9)	−0.3 (−0.4 to −0.2)	<.001
Score ≥2.0, No. (%)	201 (66)	167 (55)	NA	<.001
PSQI[j]				
Total score	7.3 (4.0)	7.0 (4.1)	−0.4 (−0.7 to 0.0)	.04
Score >5.0, No. (%)	190 (63)	174 (59)	NA	.10
HCS				
Total score	3.2 (0.6)	3.3 (0.6)	0.1 (0.0 to 0.1)	NA[k]
Score <3.0, No. (%)	98 (32)	75 (25)	NA	NA[k]
Coefficient of variation of sensor glucose, %	27.8 (6.3)	27.1 (5.1)	−0.7 (−1.4 to −0.1)	NA[k]

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; HCS, Hypoglycemia Confidence Scale; MDI, multiple daily injections; NA, not applicable; PSQI, Pittsburgh Sleep Quality Index; ST, standard therapy; T2-DDAS, Type 2 Diabetes Distress Assessment System.

SI conversion factors: To convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01; glucose to millimoles per liter, multiply by 0.0555.

[a] Baseline and follow-up (end of trial) data were used for change in HbA_{1c}, T2-DDAS, PSQI, and HCS total score. The remaining outcomes compared the ST phase with the treatment phase.

[b] The number of participants with available data ranged from 294 to 305 across outcomes.

[c] A sensitivity analysis was done using Rubin multiple imputation for the 9 participants who dropped out without a 13-week HbA_{1c} value. This gave the same point estimate, 95% CI, and *P* value as listed.

[d] *P* value is testing for superiority. Testing for noninferiority with a limit of 0.3% also gives $P < .001$.

[e] Does not include prior insulin pump users.

[f] This analysis was completed outside of the statistical hierarchy. The false discovery rate was controlled using the Benjamini-Hochberg procedure for HbA_{1c} level.

[g] A hierarchical approach was used to control the type I error. Hypothesis testing for secondary outcomes was performed sequentially in the order listed in the table. When a *P* value of .05 or higher was observed, the outcomes below that finding on the list were not formally tested.

[h] Robust mean.

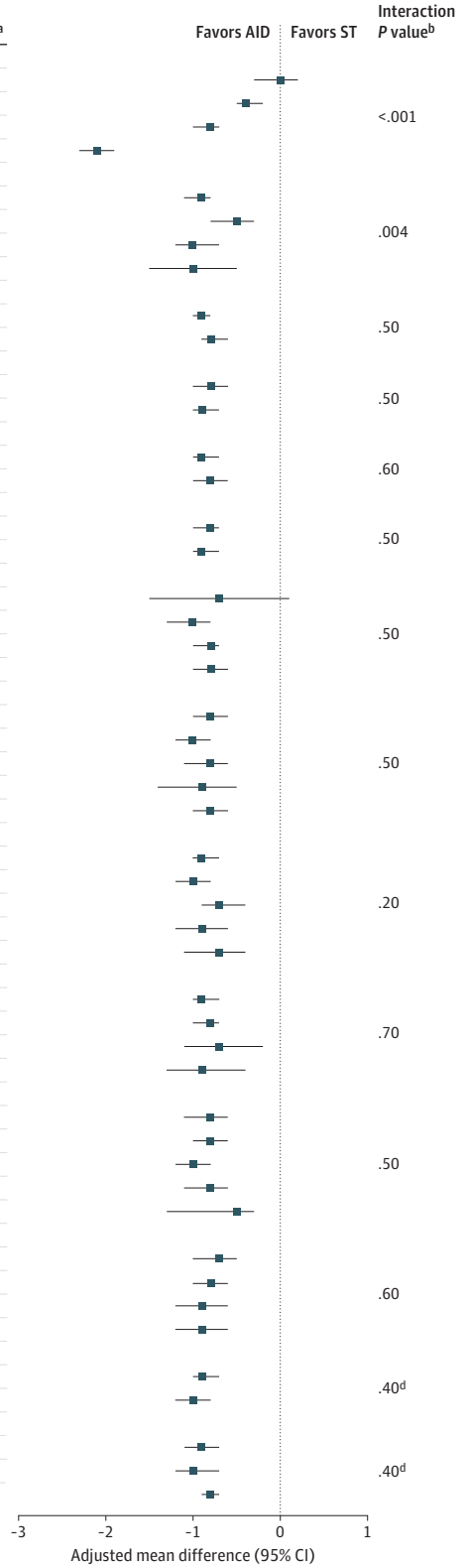
[i] Noninferiority margin of 2.0% for glucose less than 70 mg/dL or 0.5% for glucose less than 54 mg/dL.

[j] Lower scores indicate better outcomes (eg, less distress related to diabetes, better sleep quality).

[k] As part of the hierarchy testing and because of the *P* value for PSQI score greater than 5 was .10, the formal testing stopped, and *P* values were not given for any outcomes further down on the list, including superiority testing for percentage of time with glucose levels less than 70 mg/dL and less than 54 mg/dL, which would have been tested before coefficient of variation of sensor glucose.

Figure 2. Change in Hemoglobin A_{1c} (HbA_{1c}) Levels in Demographic and Clinical Subgroups

Source	Adjusted mean difference (95% CI)[a]	Interaction *P* value[b]
Baseline HbA_{1c}, %		
<7.0 (n = 42)	-0.0 (-0.3 to 0.2)	
7.0-7.9 (n = 104)	-0.4 (-0.5 to -0.2)	
8.0-8.9 (n = 82)	-0.8 (-1.0 to -0.7)	<.001
≥9.0 (n = 68)	-2.1 (-2.3 to -1.9)	
Race and ethnicity		
White, not Hispanic/Latino (n = 148)	-0.9 (-1.1 to -0.8)	
Black, not Hispanic/Latino (n = 69)	-0.5 (-0.8 to -0.3)	.004
Hispanic or Latino (n = 65)	-1.0 (-1.2 to -0.7)	
Other (n = 14)	-1.0 (-1.5 to -0.5)	
GLP-1RA Use		
Yes (n = 164)	-0.9 (-1.0 to -0.8)	.50
No (n = 132)	-0.8 (-0.9 to -0.6)	
SGLT-2i Use		
Yes (n = 130)	-0.8 (-1.0 to -0.6)	.50
No (n = 166)	-0.9 (-1.0 to -0.7)	
≥1 Agent		
Yes (n = 219)	-0.9 (-1.0 to -0.7)	.60
No (n = 77)	-0.8 (-1.0 to -0.6)	
Sex		
Female (n = 168)	-0.8 (-1.0 to -0.7)	.50
Male (n = 128)	-0.9 (-1.0 to -0.7)	
Age, y		
18 to <30 (n = 5)	-0.7 (-1.5 to 0.1)	
30 to <45 (n = 41)	-1.0 (-1.3 to -0.8)	.50
45 to <65 (n = 166)	-0.8 (-1.0 to -0.7)	
≥65 (n = 84)	-0.8 (-1.0 to -0.6)	
Annual income, $		
<50 000 (n = 81)	-0.8 (-1.0 to -0.6)	
50 000 to <100 000 (n = 72)	-1.0 (-1.2 to -0.8)	
100 000 to <200 000 (n = 51)	-0.8 (-1.1 to -0.6)	.50
≥200 000 (n = 16)	-0.9 (-1.4 to -0.5)	
Unknown (n = 76)	-0.8 (-1.0 to -0.6)	
Education		
High school, GED, or less (n = 95)	-0.9 (-1.0 to -0.7)	
Technical, vocational, or associates (n = 70)	-1.0 (-1.2 to -0.8)	
College degree (n = 70)	-0.7 (-0.9 to -0.4)	.20
Advanced degree (n = 40)	-0.9 (-1.2 to -0.6)	
Do not wish to provide (n = 21)	-0.7 (-1.1 to -0.4)	
Insurance		
Private (n = 159)	-0.9 (-1.0 to -0.7)	
Other (n = 101)	-0.8 (-1.0 to -0.7)	.70
No coverage (n = 18)	-0.7 (-1.1 to -0.2)	
No answer (n = 18)	-0.9 (-1.3 to -0.4)	
C-peptide, nmol/L		
<0.5 (n = 50)	-0.8 (-1.1 to -0.6)	
0.5 to <1.0 (n = 105)	-0.8 (-1.0 to -0.6)	
1.0 to <1.5 (n = 75)	-1.0 (-1.2 to -0.8)	.50
≥1.5 (n = 61)	-0.8 (-1.1 to -0.6)	
Missing (n = 5)	-0.5 (-1.3 to -0.3)	
Pretrial mealtime insulin regimen		
Carbohydrate counting (n = 49)	-0.7 (-1.0 to -0.5)	
Fixed dose (n = 108)	-0.8 (-1.0 to -0.6)	.60
Sliding scale (n = 46)	-0.9 (-1.2 to -0.6)	
Small/medium/large (n = 30)	-0.9 (-1.2 to -0.6)	
Insulin therapy[c]		
MDI (n = 216)	-0.9 (-1.0 to -0.7)	.40[d]
Basal-only injections (n = 62)	-1.0 (-1.2 to -0.8)	
CGM use[c]		
Never (n = 72)	-0.9 (-1.1 to -0.7)	
In the past (n = 41)	-1.0 (-1.2 to -0.7)	.40[d]
Current (n = 183)	-0.8 (-0.9 to -0.7)	



To convert C-peptide to nanograms per milliliter, divide by 0.331; HbA_{1c} to proportion of total hemoglobin, multiply by 0.01. AID indicates automated insulin delivery; CGM, continuous glucose monitoring; GED, General Educational Development; GLP-1RA, glucagon-like peptide-1 receptor agonist; MDI, multiple daily injections; SGLT-2i, sodium-glucose transport protein 2 inhibitor; ST, standard therapy.

[a] A total of 9 participants are missing a final HbA_{1c} result and are excluded from this analysis.

[b] Interaction *P* values were adjusted for false discovery rate and compare the change in outcome between the characteristic levels after adjusting for baseline HbA_{1c}, except for the stratification by baseline HbA_{1c} group.

[c] Prior insulin therapy and prior CGM use subgroups were added to the interaction testing post hoc.

[d] Post hoc interaction *P* values were adjusted for false discovery rate for prior insulin therapy and prior CGM use subgroups within their own category.

Secondary Outcomes

Glycemic Outcomes

TIR increased from a mean (SD) of 45% (25) at baseline to 66% (17) at 13 weeks (mean difference, 20 [95% CI, 18-22] percentage points; $P < .001$) or an additional 4.8 h/d in target range (Table 2; eFigure 2B in Supplement 2). The percentage of participants achieving TIR of greater than 70% of the time was 19% during standard therapy (57 of 299 participants) and 42% at end of treatment phase (127 participants) (eTable 11 in Supplement 2). A significant decrease occurred for percentage of time in hyperglycemia ranges, and the noninferiority outcomes were met for percentage of time with glucose less than 70 mg/dL and less than 54 mg/dL. Glycemic improvement was evident during both daytime and nighttime (eFigure 2C and eTable 12 in Supplement 2).

Patient-Reported Outcomes

The T2-DDAS total intensity score decreased by −0.3 points (95% CI, −0.4 to −0.2 points; $P < .001$). The percentage of participants with high distress (T2-DDAS ≥2.0) decreased from 66% at baseline (164 of 247 participants) to 55% at the end of treatment phase (133 participants) ($P < .001$). While the PSQI total score decreased by −0.4 points (95% CI, −0.7 to 0.0 points, $P = .04$), the percentage of participants with poor sleep quality (PSQI >5.0) did not change significantly (Table 2).

Additional Outcomes

Body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) changed from a mean (SD) of 34.9 (7.5) at baseline to 35.1 (7.6) at 13 weeks (change, 0.3 [95% CI, 0.1 to 0.4]; $P < .001$), corresponding to a body weight increase of 0.8 kg ($P < .001$). Total daily insulin requirements decreased from mean (SD) of 0.80 (0.46) U/kg/d at baseline to 0.57 (0.29) U/kg/d with AID (change, −0.23 U/kg/d [95% CI, −0.27 to −0.20 U/kg/d]; $P < .001$) (eTable 13 in Supplement 2). At baseline, 94 participants (31%) used 100 U/d of insulin or more, which decreased to 31 (10%) at 13 weeks.

System Use

In addition to the 2 participants who were lost to follow-up, 14 participants discontinued the AID system prior to 13 weeks. Participants spent a median (IQR) of 94% (87%-97%) of time in Automated Mode during trial participation (n = 305). The 110 mg/dL, 120 mg/dL, 130 mg/dL, 140 mg/dL, and 150 mg/dL targets were each used by 183, 133, 122, 80, and 89 participants, respectively, and were in use for 52%, 27%, 15%, 2%, and 4% of cumulative total study time.

Adverse Events and Device Issues

During the treatment period, 43 participants (14%) reported 53 nonserious adverse events (**Table 3**). There were no serious adverse device effects, and 19 nonserious adverse device effects reported in 17 participants (6%). There was 1 severe hypoglycemia event, deemed unrelated to malfunction of the trial device, and no cases of diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome. There were 13 nonglycemic serious adverse events, all unrelated to the trial device (eTable 14 in Supplement 2).

Overall, 73 device issues were reported during the treatment phase. A total of 58% of these were related to the Pod, 21% related to the controller or personal smartphone, 12% related to the CGM sensor, and 10% related to the CGM transmitter (eTable 15 in Supplement 3).

Acceptance of Treatment Technology Survey

At study end, participants completed a system opinion survey to assess their acceptance of the new treatment technology. The survey found that most participants strongly agreed or agreed that it was easy to use the bolus calculator (91%), they would recommend the AID system to family or friends (90%), the AID system was easy to wear (82%), they would continue using the AID system after

completion of the trial (78%), and they barely noticed wearing the AID System (72%) (eTable 16 in Supplement 2).

Discussion

In this multisite nonrandomized clinical trial of AID use in a heterogenous adult cohort with type 2 diabetes on insulin therapy, there was a substantial reduction in HbA_{1c}, with a particularly notable decrease of 2.1 percentage points in those with a high baseline HbA_{1c} (≥9.0%). Improvement in HbA_{1c} was observed in participants using MDI and in those using basal insulin only at baseline and across diverse racial, ethnic, and socioeconomic backgrounds; pretrial mealtime insulin regimen for those receiving meal time insulin; range of C-peptide levels; and noninsulin antihyperglycemic medication use, including GLP-1RAs and SGLT-2is.

Table 3. Adverse Events

Event type	Participants, No. (%) (n = 305)
Nonserious adverse event	
Participants with ≥1 event	43 (14)
Events, No.	53
Events per 100 person-years, No.	72
Adverse device effects, No.	19
Hyperglycemia[a]	12 (11)
Skin irritation or bleeding at insertion site	5 (4)
Hypoglycemia[b]	1 (1)
Other[c]	1 (1)
Serious adverse event	
Participants with ≥1 event	13 (4)
Events, No.[d]	13
Events per 100 person-years, No.	18
Adverse device effects, No.	0
Severe hypoglycemia[e]	1 (1)
Diabetic ketoacidosis[f]	0
Hyperosmolar hyperglycemic syndrome[g]	0

[a] Hyperglycemia requiring evaluation or treatment from a health care facility for an acute event involving hyperglycemia or the site was contacted to receive guidance on how to manage the hyperglycemia.

[b] Participant was experiencing hypoglycemia that required evaluation and treatment at the emergency department but did not meet the criteria for a severe hypoglycemic event.

[c] One participant administered an excessive bolus and was brought to the emergency department for monitoring but did not experience hypoglycemia.

[d] Detailed listing of the 13 serious adverse events are included in eTable 13 in Supplement 2.

[e] Severe hypoglycemia requiring the assistance of another person due to altered consciousness and requiring another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

[f] Hyperglycemia with the presence of polyuria, polydipsia, nausea or vomiting, serum ketones greater than 1.5 mmol/L or large to moderate urine ketones, either arterial blood pH less than 7.30, venous blood pH less than 7.24, or serum bicarbonate less than 15 mmol/L, and treatment provided in a health care facility.

[g] Hyperglycemia with the presence of polyuria, polydipsia, nausea, or vomiting, plasma glucose greater than 600 mg/dL, plasma effective osmolarity >320 mOsm/L, absence of significant ketones, and treatment provided in a health care facility.

Improvements also were observed in TIR, with an increase of 20 percentage points, amounting to an additional 4.8 h/d in target range. These glycemic improvements were achieved with no increase in hypoglycemia. Notably, a similar improvement in TIR was observed for both daytime and nighttime hours, which differs from what has been frequently observed in AID studies of individuals with type 1 diabetes, for whom a larger improvement in TIR is observed during nighttime, when meals are not being consumed, compared with the daytime.[4,19,21-23] The majority of participants (83%) did not experience a meaningful change in weight (within 5% of baseline); however, weight gain was observed primarily in those with highest baseline HbA_{1c} levels, indicative of a catabolic state in need of recovery.

A significant reduction in distress related to diabetes and improved quality of sleep also were observed. Of note, 94% of participants were pump naive at baseline and were able to initiate the study AID system without a run-in period of pump training prior to automation of insulin: whether this approach could be implemented across all available AID systems is unknown.

Although GLP-1RA and SGLT-2i therapy can produce substantial benefits in many people with type 2 diabetes,[24] most participants receiving stable doses in this trial were not achieving glycemic targets[3] at baseline; only 16% of GLP-1RA users and 15% of SGLT-2i users had baseline HbA_{1c} levels less than 7%, similar to the 13% frequency in participants not using GLP-1RAs or SGLT-2is. In this trial, similar improvements in glycemic outcomes with AID were observed in users and nonusers of GLP-1RA and SGLT-2i therapy, suggesting that adults with type 2 diabetes who are taking stable doses of GLP1-RA and SGLT-2i and require insulin therapy can benefit from AID.

There have been a small number of clinical trials assessing the feasibility of the more recently available hybrid and fully closed-loop AID systems in adults with type 2 diabetes.[9-13] The feasibility trial of the Omnipod 5 System used in this study showed similar glycemic improvements in 24 adults with type 2 diabetes.[13] Two trials of the t:slim X2 insulin pump with Control-IQ technology, a hybrid closed-loop AID system, each demonstrated improvements in glycemic outcomes in groups of 30 adults, with 1 being a 6-week single-arm trial[9] and the other being a 12-week randomized, parallel group trial.[10] Two randomized crossover trials evaluating the CamAPS HX fully closed-loop AID system over 20 days to 8 weeks of use also demonstrated improved glycemic outcomes in groups of 26 adults.[11,12] These small prior studies, while limited in their direct comparison to this present study due to differences in study type and hybrid vs fully closed-loop systems, further support the benefits of AID in adults with insulin-treated type 2 diabetes.

Limitations and Strengths

This study has limitations, including its single-arm design that did not include a concurrent control group. The amount of improvement that might be expected with CGM alone or attributed to a study effect can be estimated from a previous study evaluating CGM in type 2 diabetes. In a randomized clinical trial of CGM intervention in 158 people with type 2 diabetes using MDI,[25] the subgroups with baseline HbA_{1c} level of 8.5% or greater had a 1.1 percentage point improvement in HbA_{1c} with CGM vs a 0.7 percentage point improvement in the control group. The comparable sample of those with baseline HbA_{1c} level of 8.5% or greater in our study (113 participants) had an improvement of 1.7 percentage points for those not using CGM at baseline and 1.5 percentage points for those already using CGM. Looking within the groups of the previous CGM randomized clinical trial provides some perspective on how much improvement observed in this study might have been due to the addition of CGM or study effect alone.

Notable strengths of this trial include the large and diverse population recruited with varying racial and ethnic backgrounds, prior insulin regimen and medication use, representing the diverse general population with type 2 diabetes. This trial intentionally enrolled a higher proportion of Black and Hispanic participants to encompass communities disproportionately affected by adverse social determinants of health, who also have higher prevalence rates of diabetes[26] and have often been underrepresented in clinical trials.[27] Compared with the general US population,[28] this study sample

was similar in terms of education level, insurance, and skewed slightly more to the lower household income range, likely due to higher mean age.

Conclusions

During a single-arm nonrandomized trial in adults with type 2 diabetes, glycemia improved over 13 weeks of AID use with no increase in hypoglycemia. Improvement in HbA_{1c} levels was observed in participants using MDI and in those using basal insulin only at baseline, across diverse racial, ethnic, and socioeconomic backgrounds, and among individuals using noninsulin glucose-lowering medications, including GLP-1RAs and SGLT-2is.

ARTICLE INFORMATION

Accepted for Publication: November 26, 2024.

Published: February 14, 2025. doi:10.1001/jamanetworkopen.2024.59348

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Author Contributions: Drs Ly and Kollman had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: Pasquel, Davis, Huffman, Peters, Parker, Laffel, Romeo, Mathew, Castorino, Dungan, Kipnes, Jauch, Oser, Shah, Horowitz, Carlson, Warren, Deeb, Buse, Reed, Berner, Blevins, Bajaj, Kollman, Raghinaru, Ly.

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Administrative, technical, or material support: Huffman, Mathew, Oser, Carlson.

Supervision: Pasquel, Parker, Romeo, Castorino, Oser, Horowitz, Deeb, Buse, Berner, Bajaj.

Conflict of Interest Disclosures: Dr Pasquel reported receiving grants through the institution from Insulet, Tandem Diabetes Care, Ideal Medical Technologies, Novo Nordisk, and Dexcom; receiving consulting fees from Dexcom; receiving consulting fees to the institution from Insulet; and serving as associate editor for *JAMA Network Open* outside the submitted work. Dr Davis reported receiving grants from Insulet during the conduct of the study as well as consulting for Medscape and receiving grants from Insulet outside the submitted work. Dr Huffman

reported receiving speaker fees from Novo Nordisk and receiving research funding from Novo Nordisk, Arrowhead, Eli Lilly and Co, Biomea, CeCur, 89Bio, Gann & Lee, AstraZeneca, Kowa, Boehringer Ingelheim, and Fortrea outside the submitted work. Dr Peters reported receiving grants from Insulet during the conduct of the study; receiving research support from Abbott Diabetes Care; serving on advisory boards for Vertex and Medscape; and owning stock option in Omada Health outside the submitted work. Dr Parker reported receiving personal fees from Insulet during the conduct of the study; receiving research support from Corcept; receiving consulting fees and serving on the advisory board of Corcept; and receiving speaker fees from Novo Nordisk outside the submitted work. Dr Laffel reported receiving grants from Insulet during the conduct of the study; receiving consulting fees from Insulet, Novo Nordisk, Eli Lilly and Co, Roche, Janssen Pharmaceuticals, Dexcom, Boehringer Ingelheim, Medtronic, Vertex, and Provention Bio; receiving grants from Tandem Diabetes, Medtronic, and Dexcom; and receiving personal fees for serving on the advisory boards of Sequel Med Tech, Vertex, Tandem Diabetes, and Medtronic outside the submitted work. Dr Castorino reported receiving research support to the institution from Insulet, Dexcom, Medtronic, Abbott Diabetes, and MannKind; and receiving speaker, consulting, and other personal fees from Dexcom; and serving as a consultant and on the advisory board for MannKind outside the submitted work. Ms Kruger reported receiving grants from Tandem, Abbott, Insulet, Novo Nordisk, BetaBionics, and Embecta; receiving advisory and speaker fees from Abbott, Novo Nordisk, Eli Lilly and Co, and CeQur; receiving speaker fees from Dexcom; and receiving advisory fees from MannKind, Medtronic, Structure, Embecta, Insulet, and Pendulum outside the submitted work. Dr Dungan reported receiving grants paid to the employer from Insulet during the conduct of the study as well as receiving consulting fees from Eli Lilly and Co, Dexcom, Medscape, Oppenheimer, UpToDate, Elsevier, Med Learning Group, Impact Education, and Insulet and grants paid to the employer from Dexcom, Abbott, and Sanofi outside the submitted work. Dr Kipnes reported receiving research support from 89bio, Medtronic, Abbott, Akero Therapeutics, AstraZeneca, BioMea, Carmot, Dexcom, Fusion, Abbvie, Amgen, Biolinq, Diamyd, Endogenex, Fractyl, Gilead, Insulet, IONIS Pharmaceuticals, Kowa, MannKind, Novo Nordisk, Pfizer, Reata, Sinocare, Tandem, Trial Net, vTv Therapeutics, Zucara Therapeutics, Zydus, Boehringer Ingelheim, Corcept, and Eli Lilly and Co; receiving consulting fees from Corcept and Capillary Biomedical; serving on the advisory board of AP Stem and Corcept; and serving on the clinical events committee for the Jaeb Center for Health Research Foundation. Dr Jauch reported receiving grants from Insulet and Carmot Therapeutics during the conduct of the study. Dr Oser reported receiving a contract from Insulet study during the conduct of the study; consulting through the University of Colorado for Dexcom, Blue Circle Health, and MedScape; grants through the University of Colorado from the Helmsley Charitable Trust, the National Institute of Diabetes and Digestive and Kidney Diseases, Dexcom, and Abbott outside the submitted work. Dr Shah reported receiving grants and consulting from Insulet during the conduct of the study; grants from Dexcom and Enable Bioscience; and personal fees from Dexcom, Embecta, Ascensia Diabetes Care, Eli Lilly and Co, Sanofi, Novo Nordisk, Tandem Diabetes Care, Sequel Medtech, Genomelink, and Lumosfit outside the submitted work. Dr Horowitz reported receiving research support from Insulet and Bayer; receiving consulting fees from AbbVie; and serving on the speaker's bureau for Eli Lilly and Co and Novo Nordisk. Dr Carlson reported grants to the institution from Medtronic, Insulet, Tandem, Abbott, Dexcom, MannKind, Novo Nordisk, Eli Lilly and Co, and Sanofi; receiving personal fees paid to the institution from Insulet, Tandem, Abbott, and Novo Nordisk; serving on the advisory board for MannKind and Zealand; and being an employee of International Diabetes Center at Park Nicollet. Dr Warren reported receiving grants from Medtronic during the conduct of the study and receiving grants from Eli Lilly and Co, Novo Nordisk, AstraZeneca, Amgen, Insulet, Novartis, Diasome, and Sensionics; serving on the advisory board of Eli Lilly and Co; receiving consulting fees from Insulet, Medtronic, Eli Lilly and Co, Novo Nordisk, Boehringer Ingelheim, Amgen, AbbVie, Regeneron, Bayer, Biomea, and AstraZeneca; and receiving speaker honoraria from Eli Lilly and Co, Amgen, and Abbott outside the submitted work. Dr Buse reported receiving personal fees from Dexcom during the conduct of the study; receiving personal fees from Alkahest, Altimmune, Anji, Aqua Medical Inc, AstraZeneca, Boehringer Ingelheim, CeQur, Corcept Therapeutics, Eli Lilly, Embecta, GentiBio, Glyscend, Insulet, Mediflix, Medscape, Medtronic MiniMed, Mellitus Health, Metsera, Moderna, Novo Nordisk, Pendulum Therapeutics, Praetego, ReachMD, Stability Health, Tandem, Terns Inc, and Vertex; owning stock options in Glyscend, Mellitus Health, Pendulum Therapeutics, Praetego, and Stability Health; and receiving research support from Bayer, Boehringer-Ingelheim, Carmot, Corcept, Dexcom, Lilly, Insulet, MannKind, Novo Nordisk, and vTv Therapeutics outside the submitted work. Dr Blevins reported receiving research support from Boehringer Ingelheim, vTv Therapeutics, Tandem, Dexcom, MannKind, Eli Lilly and Co, Novo Nordisk, Insulet, Medtronic, and Abbott; serving on the speaker bureau for Dexcom, Eli Lilly and Co, and Novo Nordisk; and serving as an advisor to MannKind and Insulet during the conduct of the study. Dr Bajaj reported receiving personal fees from Insulet during the conduct of the study; receiving research support from Eli Lilly and Co and Novo Nordisk; receiving consulting fees from Dexcom and Eli Lilly and Co; and serving as an advisory board member for Eli Lilly and Co outside the submitted work. Dr Kollman reported receiving grants to the institution from Insulet during the conduct of the study and receiving grants to the institution from Tandem, Juvenile Diabetics Research Foundation, MannKind, BT1D, and Dexcom outside the submitted work. Dr Ly reported being employed by and owning stock in Insulet. Dr Beck reported receiving grants from Insulet during the conduct of the study; receiving grants, study

supplies, and consulting fees to the institution from Insulet, Tandem, and Beta Bionics; receiving grant funding and study supplies to the institution from Dexcom; grant funding to the institution from Bigfoot Biomedical, Embecta, Sequel Med Tech, and MannKind; receiving consulting fees and study supplies to the institution from Novo Nordisk; receiving consulting fees to the institution from Vertex, Hagar, Ypsomed, Sanofi, and Zucara; and receiving study supplies from Medtronic, Ascencia, Roche, and Eli Lilly and Co outside the submitted work. No other disclosures were reported.

Funding/Support: This trial was funded by Insulet Corporation.

Role of the Funder/Sponsor: Insulet was the study sponsor and investigational device exemption holder for the study. Representatives of Insulet participated in developing the design of the study but were not responsible for the conduct of the study other than contracting with participating sites and participating in site monitoring; were not responsible for the data collection, management, or analysis. Insulet worked in conjunction with Jaeb Center for Health Research on the preparation of the manuscript. An employee of the company (Dr Ly) was a member of the Steering Committee and coauthor and in this role, she was involved in the review of the manuscript and the interpretation of the data prior to submission for publication along with the other authors.

Group Information: The Omnipod 5 SECURE-T2D Consortium members appear in Supplement 3.

Disclaimer: Dr Pasquel is an associate editor of *JAMA Network Open* but was not involved in any of the decisions regarding review of the manuscript or its acceptance.

Meeting Presentation: The data were presented at the 84th Scientific Sessions of the American Diabetes Association; June 22, 2024; Orlando, Florida.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We extend our sincere thanks to the participants in this trial and their families. We thank the Jaeb Center for Health Research for their role in study coordination including Sarah Borgman, RN, Denise Martinez, MPH, Nnenna Mba-Oduwusi, MPH, Paige Miller, BS, Kaitlyn Garrett, MPH, Ashleigh Fults, MS, Elizabeth Dolzhenko, BS, Nicole Reese, BS, Rosa Pritchard, MBA, Zachary Thompson, MS, Lauren Kanapka, PhD, and Charles Spanbauer, PhD. We thank the Insulet clinical team, including Jack Peters, MPH, Amna Soomro, MBBS, Anna Busby, MS, Krista Kleve, MS, Anny Caruso, BS, Tanya Meletlides, Michaela Sorrell, BS, Becky Estabrook, BS, for their contributions to the conduct of the trial. We thank Ciana Thorne, BS, an employee of Insulet Corporation, for assisting with the preparation and revisions of the manuscript. None of the named individuals were compensated for their time outside of their usual salaries. We also thank the dedicated staff at each clinical site who made this trial possible.

Additional Information: Questionnaire copyright statement: Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research (Authors Daniel J. Buysse, Charles F. Reynolds III, Timothy H. Monk, Susan R. Berman, and David J Kupfer, 1989 and 2010, University of Pittsburgh). All rights reserved.

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SUPPLEMENT 1.
Trial Protocol and Statistical Analysis Plan

SUPPLEMENT 2.
eTable 1. Eligibility and Exclusion Criteria
eTable 2. Study Enrollment Goals
eTable 3. Schedule of Participant Visits and Procedures
eTable 4. Additional Research Design and Methods
eTable 5. Hierarchical Listing of Primary and Secondary Efficacy Outcomes
eTable 6. Listing of Additional Outcomes Included
eTable 7. Baseline Characteristics of the 16 Participants Who Did Not Complete the Trial
eTable 8. Per-Protocol Analyses
eTable 9. Analyses Excluding Participants Positive for GAD Antibodies
eTable 10. Subgroup Analysis for Primary Outcome
eTable 11. Percentage of Participants Achieving Targets
eTable 12. CGM Metrics by Time of Day Overall and by Prior Insulin Therapy Method
eTable 13. BMI, Weight, and Insulin Use
eTable 14. Summary of Serious Adverse Events
eTable 15. Summary of Device Issues
eTable 16. System Opinion Questionnaire
eFigure 1. Scatterplot of Change in HbA_{1c} Levels and Time With Glucose Between 70 and 180 mg/dL
eFigure 2. Glycemic Outcomes Stratified by Baseline HbA_{1c} and by Time of Day

SUPPLEMENT 3.
Nonauthor Collaborators

SUPPLEMENT 4.
Data Sharing Statement