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Efficacy and Safety of a Tubeless AID System Compared With Pump Therapy With CGM in the Treatment of Type 1 Diabetes in Adults With Suboptimal Glycemia: A Randomized, Parallel-Group Clinical Trial

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AIM: Evaluate the efficacy and safety of AID versus pump therapy + CGM in adults with type 1 diabetes with suboptimal glycemic outcomes

PARTICIPANTS
194 adults aged 18–70 years with type 1 diabetes and HbA_{1c} 7-11% in France and the U.S.
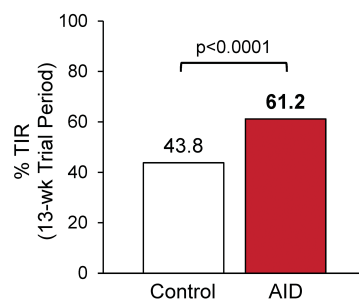
STUDY DESIGN
13-week RCT (2:1) of AID (Omnipod 5 System, n=132) versus pump therapy + CGM (Control, n=62) following a 2-week standard therapy period

PRIMARY OUTCOME
Treatment group comparison of time in range (70-180mg/dL) during the trial period

RESULTS

% TIR (13-wk Trial Period) — Control 43.8, AID 61.2, p<0.0001

AID versus Control
- ↑ Higher TIR +17.5% (+4.2 h/day)
- ↓ Greater reduction in HbA_{1c} -0.6%
- ↓ Less time spent >180mg/dL and <70mg/dL
- Clinically meaningful improvements in person-reported outcomes
- **All primary and secondary outcomes met after 13 weeks**

Results of this study demonstrate improved glycemic outcomes with a tubeless AID system compared with pump therapy with CGM among adults with type 1 diabetes, underscoring the clinical benefit of AID and bolstering recommendations to establish AID systems as preferred therapy for this population.

AID, automated insulin delivery; CGM, continuous glucose monitoring; RCT, randomized controlled trial; TIR, time in range.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  The tubeless Omnipod 5 automated insulin delivery (AID) system was shown to be safe and effective in several single-arm clinical trials, but a randomized study in adults with type 1 diabetes not achieving glycemic targets was needed.

- **What is the specific question we wanted to answer?**
  How does the efficacy and safety of tubeless AID compare with pump therapy with continuous glucose monitoring during a randomized study?

- **What did we find?**
  Use of the tubeless AID system resulted in a greater percentage of time in range (70–180 mg/dL) compared with pump therapy with continuous glucose monitoring.

- **What are the implications of our findings?**
  These findings highlight the clinical benefit of AID and support the adoption of AID systems as the preferred therapy for people with type 1 diabetes.

Efficacy and Safety of a Tubeless AID System Compared With Pump Therapy With CGM in the Treatment of Type 1 Diabetes in Adults With Suboptimal Glycemia: A Randomized, Parallel-Group Clinical Trial

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OBJECTIVE

To examine the efficacy and safety of the tubeless Omnipod 5 automated insulin delivery (AID) system compared with pump therapy with a continuous glucose monitor (CGM) in adults with type 1 diabetes with suboptimal glycemic outcomes.

RESEARCH DESIGN AND METHODS

In this 13-week multicenter, parallel-group, randomized controlled trial performed in the U.S. and France, adults aged 18–70 years with type 1 diabetes and HbA_{1c} 7–11% (53–97 mmol/mol) were randomly assigned (2:1) to intervention (tubeless AID) or control (pump therapy with CGM) following a 2-week standard therapy period. The primary outcome was a treatment group comparison of time in range (TIR) (70–180 mg/dL) during the trial period.

RESULTS

A total of 194 participants were randomized, with 132 assigned to the intervention and 62 to the control. TIR during the trial was 4.2h/day higher in the intervention compared with the control group (mean difference 17.5% [95% CI 14.0%, 21.1%]; $P < 0.0001$). The intervention group had a greater reduction in HbA_{1c} from baseline compared with the control group (mean ± SD −1.24 ± 0.75% [−13.6 ± 8.2 mmol/mol] vs. −0.68 ± 0.93% [−7.4 ± 10.2 mmol/mol], respectively; $P < 0.0001$), accompanied by a significantly lower time <70 mg/dL (1.18 ± 0.86% vs. 1.75 ± 1.68%; $P = 0.005$) and >180 mg/dL (37.6 ± 11.4% vs. 54.5 ± 15.4%; $P < 0.0001$). All primary and secondary outcomes were met. No instances of diabetes-related ketoacidosis or severe hypoglycemia occurred in the intervention group.

CONCLUSIONS

Use of the tubeless AID system led to improved glycemic outcomes compared with pump therapy with CGM among adults with type 1 diabetes, underscoring the clinical benefit of AID and bolstering recommendations to establish AID systems as preferred therapy for this population.

Despite advances in diabetes technology, people with type 1 diabetes often struggle to maintain optimal glycemic outcomes, with observational studies reporting that most are not meeting the recommended clinical target of HbA_{1c} <7% (53 mmol/mol) (1).

ORIGINAL ARTICLE

Consequently, individuals with type 1 diabetes are at increased risk for long-term complications, a reduced quality of life, financial burden, and a decreased life span (2). With its prevalence increasing globally (3), there is an urgent need to develop and implement in clinical practice innovative insulin delivery modalities that can improve glycemic outcomes and ultimately reduce the complications associated with type 1 diabetes.

Automated insulin delivery (AID) systems represent the latest advancement in technology to optimize glucose management in people with type 1 diabetes (4). By combining insulin delivery pumps, continuous glucose monitoring (CGM), and closed-loop control algorithms, AID systems aim to more closely emulate the physiological functions of a healthy pancreas by automatically adjusting insulin delivery to minimize time spent in hypoglycemia and hyperglycemia (4). AID systems have demonstrated efficacy in improving glycemic outcomes for people with type 1 diabetes across a range of ages and demographic populations, while reducing the burden of decision-making and enhancing quality of life (5).

With such promising results across systems (5), consensus guidelines are being updated to proactively offer AID systems for people with type 1 diabetes, with an emphasis on providing access to these devices early in the disease (4). However, the uptake of this technology has been limited by a myriad of factors (health care professional, patient, cost, payer, and health care system–related and device-specific factors, including tubing, ease of use, discreetness, etc.), hindering the full potential of AID systems to improve health outcomes (6). Broad uptake requires that these systems be simple, minimally invasive, and easy to use and wear for people with type 1 diabetes.

The Omnipod 5 AID system (Insulet Corporation, Acton, MA) is a tubeless, wearable device cleared by the U.S. Food and Drug Administration and Conformité Européenne and marked for use in people with type 1 diabetes aged ≥2 years, and it has been recently cleared by the U.S. Food and Drug Administration for use in people with type 2 diabetes aged ≥18 years. The safety and effectiveness of the system has been demonstrated in people with type 1 diabetes in two single-arm pivotal and extension trials (7–10). However, it has yet to be demonstrated whether similar benefits would be present in a randomized controlled trial (RCT) of individuals not meeting glycemic targets. The current study supports ongoing efforts to demonstrate the superiority of AID by examining the efficacy and safety of the tubeless AID system compared with pump therapy with CGM in an RCT of adults with type 1 diabetes not meeting the recommended glycemic targets in the U.S. and France.

RESEARCH DESIGN AND METHODS

Trial Conduct and Oversight
This parallel-group RCT was conducted at 10 sites in the U.S. and 4 sites in France. Central and local institutional review boards and ethics committees approved the protocol. Written informed consent was obtained from all participants. A medical monitor provided trial oversight. The trial was registered at ClinicalTrials.gov (NCT05409131).

Trial Design and Participants
Eligible participants were aged 18–70 years and had type 1 diabetes for ≥1 year with HbA_{1c} 7.0–11.0% (53–97 mmol/mol). The study included a requirement for at least 80% of participants to have a screening HbA_{1c} ≥8.0% (64 mmol/mol). Participants were recruited only if they were on pump therapy for at least 3 months, with a requirement that at least 50% were using an Omnipod pump (Omnipod or Omnipod DASH Insulin Management System) at the time of enrollment (complete eligibility criteria provided in Supplementary Table 1). Participants using AID devices, including predictive low-glucose suspend, in the 3 months prior to screening were excluded. There were no inclusion or exclusion criteria based on CGM use.

After screening, participants were provided an unmasked study CGM (Dexcom G6; Dexcom Inc., San Diego, CA) to use with their current baseline pump therapy for 2 weeks to collect glucose sensor data on their usual regimen (standard therapy phase). Standard therapy data could be retrospectively collected for U.S. participants who used a Dexcom G6 CGM as part of their usual therapy and had sufficient data available (i.e., >80% CGM use during any consecutive 14 days in the past 30 days, with ≥2,016 CGM readings during the 14 days).

Following the standard therapy phase, participants were randomly assigned 2:1 to the intervention group or control group for 13 weeks. In the intervention group, participants were trained on and used the Omnipod 5 AID System. The system comprises an insulin-filled tubeless on-body pump (Pod) with an embedded AID algorithm and the Omnipod 5 application, which controls the Pod via Bluetooth wireless technology, on a provided locked-down Android phone (Controller), used by participants in this study, or a compatible personal smartphone. An interoperable CGM is required to use AID: the Dexcom G6 CGM was used in this study (11). Participants in the intervention group used the system in Automated Mode, in which insulin delivery is modulated every 5 min based on CGM glucose values to bring glucose toward the selected target, which is customizable from 110 to 150 mg/dL in increments of 10 mg/dL. There were no prespecified recommendations for target selection, with the initial glucose target left to the discretion of the investigator. In Manual Mode, the system functions as a traditional insulin pump (11). Additional details on the system have been previously published (11). In the control group, each participant continued using their usual insulin pump with a Dexcom G6 CGM provided by the trial investigators.

During the 13-week trial (trial period), there were six follow-up visits either in person or by telephone (Supplementary Table 2). At each visit, participants were asked about medications, adverse events, and device issues; vital signs were assessed; and the study team reviewed system data history and adjusted system settings as needed. HbA_{1c} was assessed by a central laboratory (LabCorp) at screening and at the end of the study or upon early withdrawal. Questionnaires on quality of life and treatment satisfaction were conducted at baseline and at the end of the study or upon early withdrawal, including the Type 1 Diabetes Distress Scale (T1-DDS) (12), Hypoglycemia Confidence Scale (HCS) (13), and Diabetes Quality of Life-Brief (DQOL-Brief) (14). Reportable adverse events included severe hypoglycemia, diabetes-related ketoacidosis (DKA), hyperglycemia involving ketosis, adverse device events, any severe adverse events, and any adverse events that affected the participant's ability to adhere to study procedures or for which a visit to the hospital emergency department was made.

Outcomes

The primary outcome was the percentage of time in the glucose target range (time in range [TIR]) (70–180 mg/dL) during the 13-week trial period as measured with the study CGM. The secondary glycemic outcomes, which were tested in a hierarchical order to maintain the type I error rate at 5.0%, were percentage of time <54 mg/dL (noninferiority with a 1.0% margin), percentage of time >180 mg/dL, mean glucose, change from baseline in HbA_{1c}, and percentage of time <70 mg/dL during the 13-week trial period (Supplementary Table 3).

Other secondary outcomes also included in the hierarchy were person-reported outcome measures, including change from baseline in the T1-DDS, HCS, and DQOL-Brief total scores, as well as the proportion of participants who experienced a clinically meaningful change for each measure (i.e., responders) at the end of the study. The prespecified minimum clinically important difference for the T1-DDS was an improvement in total score ≥0.19 as defined in the literature (15). For the DQOL-Brief, as no minimum clinically important difference was available in the literature, a distribution-based method was selected to prespecify the clinically meaningful difference as ≥0.5 × SD of change from baseline in the total score as observed in the study. For the HCS, the prespecified clinically meaningful result was to have a total score ≥3 at the end of the study, indicating relatively high confidence in managing hypoglycemia as reported in the literature (13).

Exploratory outcomes included the proportion of participants with HbA_{1c} <7.0% (53 mmol/mol) and <8.0% (64 mmol/mol) at the end of the study, the proportion with ≥1% (10.9 mmol/mol) improvement or ≥10% relative improvement in HbA_{1c} from baseline, and the change in BMI and total daily insulin use from baseline. Additional exploratory outcomes included the percentage of time >250 mg/dL, percentage of time in tight range (70–140 mg/dL), glycemia risk index (16), coefficient of variation, and the percentage of TIR, time <54 mg/dL, and time <70 mg/dL during the day and night during the 13-week trial period.

Statistical Analysis

A sample of 131 participants (87 intervention, 44 control) was required to provide 90% power to detect a difference of 10% in TIR, assuming an SD of 16.5% in each group with a 2:1 intervention:control randomization (7). Up to 200 participants were recruited to allow for pre- and postrandomization attrition (assumed to be 15% and 22.9%, respectively).

A modified intention-to-treat analysis was conducted that included all participants randomized, unless otherwise noted. Strict control of type I error was maintained at a 5.0% level with a hierarchical testing procedure. For exploratory outcomes, there was no formal hypothesis testing, with no adjustments for multiplicity.

The continuous outcomes were analyzed using repeated-measures linear mixed-effects models, unless otherwise noted. Residual values were examined to confirm an approximate normal distribution. If values were highly skewed, then robust regression using M-estimation was used instead. Logistic mixed-effects models were used to examine proportion-based outcomes. Two-sided Fisher's exact test was used to examine the percentage of participants meeting CGM-based clinical targets (17). All models and reported treatment group differences included adjustment for the baseline level of the dependent variable, age, sex, and duration of diagnosis as fixed effects, with country and site as random effects. Sensitivity analyses were conducted based on various subsets (per protocol, complete case) or using imputation techniques (multiple imputation, worst case). Subgroup analyses by country, sex, race and ethnicity, age, BMI, baseline glycemic measures, and prior CGM use were conducted. Analyses were performed using SAS 9.4 statistical software.

RESULTS

Participants and Follow-up

A total of 234 individuals consented to participate: 196 were enrolled, 194 were randomized, and 192 completed the study (Supplementary Fig. 1). The 194 participants (60% female, mean ± SD age 36 ± 14 years) were randomly assigned to either the intervention group (n = 132) or the control group (n = 62) (Table 1). U.S. participants accounted for 61% of those randomized. Of the 194 participants randomized, 87% were Omnipod pump users, and 94% had previous or current CGM use. Baseline point-of-care HbA_{1c} was mean ± SD (range) 8.5 ± 0.8% (7.0–10.5%) [69 ± 8.7 (53–91) mmol/mol] in the intervention group and 8.6 ± 0.9% (7.0–10.9%) [70 ± 9.8 (53–96) mmol/mol] in the control group. At screening, the point-of-care HbA_{1c} measurement was ≥8.0% (64 mmol/mol) for 80% and 82% of participants in the intervention and control groups, respectively. Additional baseline characteristics of participants are presented in Table 1.

Efficacy Outcomes

The primary outcome of percentage of TIR increased from 43.9 ± 14.0% with standard therapy to 61.2 ± 11.2% during the 13-week trial period in the intervention group and from 41.3 ± 14.6% to 43.8 ± 14.5% in the control group, with an adjusted mean difference (intervention − control) of 17.5% (95% CI 14.0%, 21.1%; $P < 0.0001$), corresponding to an additional 4.2 h/day (Table 2 and Fig. 1A and B). The difference remained significant in sensitivity analyses (per protocol, complete case, multiple imputation, and worst case; all $P < 0.0001$) (Supplementary Table 4). For the primary outcome of TIR, interactions by country, sex, race and ethnicity, age, BMI, and baseline TIR were all nonsignificant ($P > 0.05$) (Supplementary Table 5). Supplementary Table 6 presents the change in TIR stratified by subgroup.

All secondary outcomes evaluated in the hierarchical testing procedure revealed statistically significant between-group differences (or noninferiority) according to the analysis plan, favoring the intervention (Table 2). The mean difference between treatment groups during the 13-week trial period in percentage of time <54 mg/dL was −0.05% (95% CI −0.11%, 0.00%; $P > 0.05$). Although there was no significant difference between the two groups, the noninferiority limit of 1.0% was met, as the upper limit of the 95% CI of the adjusted difference was <1.0%. The mean difference between treatment groups in the percentage of time >180 mg/dL was −16.8% (95% CI −20.8%, −12.8%; $P < 0.0001$), corresponding to 4.0 fewer hours per day. The mean difference between treatment groups in mean glucose was −26 mg/dL (95% CI −34, −18 mg/dL; $P < 0.0001$) (Fig. 1C). At the end of the study, HbA_{1c} was 7.25 ± 0.76% (56 ± 8.3 mmol/mol) in the intervention group and 7.84 ± 0.83% (62 ± 9.1 mmol/mol) in the control group. The mean difference between treatment groups in change in HbA_{1c} at 13 weeks was −0.58% (6.3 mmol/mol) (95% CI

Table 1—Characteristics of participants at baseline (modified intention-to-treat data set)

Characteristic	All randomized (n = 194)	Intervention group (n = 132)	Control group (n = 62)
Age (years)			
Mean ± SD	36 ± 14	36 ± 14	36 ± 13
Range	18–69	18–69	18–66
Duration of diabetes (years)			
Mean ± SD	19.5 ± 11.1	19.2 ± 11.0	20.2 ± 11.4
Range	1.8–54.0	1.8–54.0	2.2–50.5
Country, n (%)			
U.S.	118 (60.8)	80 (60.6)	38 (61.3)
France	76 (39.2)	52 (39.4)	24 (38.7)
BMI (kg/m^2), mean ± SD	26.2 ± 4.6	26.6 ± 4.8	25.4 ± 4.1
Female sex, n (%)	116 (59.8)	78 (59.1)	38 (61.3)
Race and ethnicity, n (%)†			
White	99 (83.9)	70 (87.5)	29 (76.3)
Hispanic or Latino	9 (7.6)	7 (8.8)	2 (5.3)
Not Hispanic or Latino	90 (76.3)	63 (78.8)	27 (71.1)
Black or African American	7 (5.9)	4 (5.0)	3 (7.9)
Hispanic or Latino	1 (0.8)	1 (1.3)	0 (0.0)
Not Hispanic or Latino	6 (5.1)	3 (3.8)	3 (7.9)
Asian	3 (2.5)	1 (1.3)	2 (5.3)
American Indian or Alaska Native	1 (0.8)	0 (0.0)	1 (2.6)
Other race	2 (1.7)	2 (2.5)	0 (0.0)
Hispanic or Latino	1 (0.8)	1 (1.3)	0 (0.0)
Not Hispanic or Latino	1 (0.8)	1 (1.3)	0 (0.0)
Multiple races	4 (3.4)	2 (2.5)	2 (5.3)
Not disclosed	2 (1.7)	1 (1.3)	1 (2.6)
Hispanic or Latino	2 (1.7)	1 (1.3)	1 (2.6)
Not Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)
HbA$_{1c}$ at screening (% [mmol/mol])			
Mean ± SD	8.5 ± 0.8 [69.0 ± 8.7]	8.5 ± 0.8 [69.0 ± 8.7]	8.6 ± 0.9 [70.0 ± 9.8]
Range	7.0–10.9 [53.0–96.0]	7.0–10.5 [53.0–91.0]	7.0–10.9 [53.0–96.0]
HbA$_{1c}$ ≥8% (64 mmol/mol) at screening, n (%)	157 (80.9)	106 (80.3)	51 (82.3)
Daily insulin dose (units/kg)‡			
Mean ± SD	0.62 ± 0.19	0.63 ± 0.20	0.59 ± 0.17
Range	0.23–1.28	0.23–1.28	0.30–1.16
Previous or current CGM use, n (%)	183 (94.3)	124 (93.9)	59 (95.2)
Duration of insulin pump use (years)			
Mean ± SD	9.6 ± 7.2	9.5 ± 7.4	9.8 ± 6.8
Range	0.3–49.3	0.3–49.3	0.3–29.2

†Due to privacy laws, race and ethnicity were reported by participants in the U.S. only. ‡Baseline total daily insulin dose was determined from data collected during the standard therapy phase.

−0.79%, −0.37% [4.0, 8.6 mmol/mol]; $P < 0.0001$) (Supplementary Fig. 2). The mean difference between treatment groups in percentage of time <70 mg/dL was −0.36% (95% CI −0.61%, −0.11%; $P = 0.005$), corresponding to 5.2 fewer minutes per day (Fig. 1D). Supplementary Table 7 presents the change in percentage of time <70 mg/dL stratified by subgroup.

The mean differences between treatment groups in change in T1-DDS, HCS, and DQOL-Brief total scores were −0.18 (95% CI −0.32, −0.05; $P = 0.009$), 0.20 (95% CI 0.06, 0.34; $P = 0.005$), and 0.43

(95% CI 0.31, 0.55; $P < 0.0001$), respectively. The proportion of responders (participants who experienced the prespecified clinically meaningful result) was significantly greater in the intervention group than the control group at 13 weeks for each of the three person-reported measures (T1-DDS: mean difference of 24.3% [95% CI 6.0%, 44.1%; $P = 0.02$]; DQOL-Brief: mean difference of 52.7% [95% CI 36.2%, 67.9%; $P < 0.0001$]; HCS: mean difference of 18.9% [95% CI 4.5%, 34.7%; $P = 0.008$]). Supplementary Figs. 3–5 show the cumulative distribution function of the percentage of participants

experiencing a given change in T1-DDS or DQOL-Brief score or final HCS score at 13 weeks, demonstrating a separation between the intervention and control groups across a wide range of potential responder definitions.

Exploratory Outcomes

Exploratory outcomes based on the HbA$_{1c}$ level were significant in favor of the intervention (Supplementary Table 8). The proportion of participants in the intervention and control groups with HbA$_{1c}$ <7.0% (53 mmol/mol) were 39.5% and 9.1% and

Table 2—Primary, secondary, and exploratory outcomes

Outcome	Baseline/standard therapy†		13-Week trial period		Treatment effect	
	Intervention group (n = 132‡)	Control group (n = 62‡)	Intervention group (n = 132‡)	Control group (n = 62‡)	Adjusted difference, intervention − control (95% CI)	P
Primary outcome: TIR 70–180 mg/dL, %§‖	43.9 ± 14.0, 44.2 [34.7–54.8] (n = 129)	41.3 ± 14.6, 41.2 [31.4–52.2] (n = 61)	61.2 ± 11.2, 62.3 [55.2–68.8] (n = 131)	43.8 ± 14.5, 45.1 [34.3–53.6] (n = 62)	17.5 (14.0, 21.1)	<0.0001
Secondary outcomes in prespecified hierarchical order‖						
Time below glucose range <54 mg/dL (noninferiority), %¶	0.32 ± 0.53, 0.13 [0.00–0.39] (n = 129)	0.42 ± 0.91, 0.10 [0.00–0.43] (n = 61)	0.23 ± 0.23, 0.17 [0.07–0.28] (n = 131)	0.37 ± 0.53, 0.16 [0.06–0.45] (n = 62)	−0.05 (−0.11, 0.00)	0.0501
Time above glucose range >180 mg/dL, %§	54.4 ± 14.7, 54.7 [42.7–64.4] (n = 129)	57.1 ± 15.5, 56.3 [46.1–67.3] (n = 61)	37.6 ± 11.4, 36.3 [29.8–43.9] (n = 131)	54.5 ± 15.4, 54.0 [42.3–64.4] (n = 62)	−16.8 (−20.8, −12.8)	<0.0001
Mean sensor glucose, mg/dL§	200 ± 30, 198 [177–220] (n = 129)	204 ± 31, 198 [181–225] (n = 61)	174 ± 20, 170 [161–183] (n = 131)	200 ± 30, 195 [175–217] (n = 62)	−26 (−34, −18)	<0.0001
Change in HbA$_{1c}$, %#	8.48 ± 0.79, 8.40 [7.95–8.95] (n = 132)	8.57 ± 0.95, 8.50 [8.00–9.10] (n = 62)	7.25 ± 0.76, 7.10 [6.80–7.70] (n = 119)	7.84 ± 0.83, 7.90 [7.30–8.30] (n = 55)	−0.58 (−0.79, −0.37)	<0.0001
Change in HbA$_{1c}$ mmol/mol#	69 ± 8.6, 68 [63–74] (n = 132)	70 ± 10.4, 69 [64–76] (n = 62)	56 ± 8.3, 54 [51–61] (n = 119)	62 ± 9.1, 63 [56–67] (n = 55)	−6.3 (−8.6, −4.0)	<0.0001
Time below glucose range <70 mg/dL, %¶	1.66 ± 1.79, 1.07 [0.52–2.22] (n = 129)	1.66 ± 2.25, 0.96 [0.23–2.07] (n = 61)	1.18 ± 0.86, 1.04 [0.57–1.59] (n = 131)	1.75 ± 1.68, 1.14 [0.58–2.60] (n = 62)	−0.36 (−0.61, −0.11)	0.0050
Change in T1-DDS total score#	2.01 ± 0.69, 1.93 [1.46–2.36] (n = 132)	2.27 ± 0.71, 2.21 [1.71–2.71] (n = 62)	1.72 ± 0.63, 1.54 [1.29–2.00] (n = 130)	2.08 ± 0.68, 1.91 [1.63–2.45] (n = 60)	−0.18 (−0.32, −0.05)	0.0094
Change in HCS total score#	3.24 ± 0.54, 3.24 [2.89–3.72] (n = 132)	3.13 ± 0.52, 3.11 [2.88–3.56] (n = 62)	3.40 ± 0.50, 3.56 [3.00–3.78] (n = 131)	3.14 ± 0.58, 3.12 [2.78–3.67] (n = 60)	0.20 (0.06, 0.34)	0.0048
Change in DQOL-Brief total score#	3.75 ± 0.47, 3.73 [3.43–4.07] (n = 132)	3.62 ± 0.49, 3.60 [3.33–3.93] (n = 62)	4.11 ± 0.47, 4.17 [3.87–4.47] (n = 130)	3.60 ± 0.47, 3.57 [3.24–4.00] (n = 60)	0.43 (0.31, 0.55)	<0.0001
T1-DDS–proportion of participants with a clinically meaningful change (≥0.19), %**	—	—	53.8 (45.3–62.4)	45.0 (32.4–57.6)	24.3 (6.0, 44.1)	0.0145
DQOL-Brief–proportion of participants with a clinically meaningful change (≥0.238), %**	—	—	59.2 (50.8–67.7)	21.7 (11.2–32.1)	52.7 (36.2, 67.9)	<0.0001
HCS–proportion of participants with a clinically meaningful result (final score ≥3), %**	—	—	81.7 (75.1–88.3)	61.7 (49.4–74.0)	18.9 (4.5, 34.7)	0.0076
Exploratory outcomes††						
Time above glucose range >250 mg/dL, %¶	25.4 ± 13.8, 24.1 [14.0–35.3] (n = 129)	27.6 ± 14.6, 24.4 [15.7–37.0] (n = 61)	13.5 ± 8.2, 11.6 [7.9–17.9] (n = 131)	25.7 ± 14.3, 23.4 [14.4–33.4] (n = 62)	−10.8 (−12.8, −8.9)	<0.0001
Time in tight glucose range 70–140 mg/dL, %§,‡‡	24.6 ± 9.8, 24.2 [17.7–31.3] (n = 129)	23.2 ± 10.4, 22.2 [16.6–30.6] (n = 61)	36.3 ± 10.3, 36.3 [29.5–43.9] (n = 131)	24.8 ± 10.5, 23.5 [16.4–33.1] (n = 62)	11.5 (8.4, 14.5)	<0.0001
Glycemia risk index§,‡‡	67 ± 20, 67 [52–83] (n = 129)	71 ± 20, 75 [54–85] (n = 61)	44 ± 15, 41 [33–52] (n = 131)	68 ± 20, 67 [54–83] (n = 62)	−24 (−29, −19)	<0.0001
Coefficient of variation of sensor glucose, %§	37.2 ± 5.3, 37.7 [33.5–40.6] (n = 129)	36.8 ± 5.9, 36.8 [32.6–39.7] (n = 61)	36.3 ± 4.1, 36.1 [33.5–39.1] (n = 131)	37.3 ± 5.2, 37.7 [33.9–40.6] (n = 62)	−1.1 (−2.6, 0.4)	0.1516

Table 2—Continued

Outcome	Baseline/standard therapy†		13-Week trial period		Treatment effect	
	Intervention group (n = 132‡)	Control group (n = 62‡)	Intervention group (n = 132‡)	Control group (n = 62‡)	Adjusted difference, intervention − control (95% CI)	P
TIR 70–180 mg/dL, daytime (0600–0000 h), %§	45.5 ± 14.8, 45.6 [35.5–57.4] (n = 129)	42.1 ± 15.3, 41.6 [30.9–53.0] (n = 61)	60.5 ± 11.9, 62.0 [53.8–67.8] (n = 131)	44.4 ± 15.2, 44.8 [34.4–56.2] (n = 62)	16.1 (12.3, 19.9)	<0.0001
TIR 70–180 mg/dL, nighttime (0000–0600 h), %§	39.2 ± 16.0, 41.4 [27.0, 50.9] (n = 129)	38.8 ± 17.4, 39.0 [26.2–49.1] (n = 61)	63.3 ± 13.4, 65.1 [54.4–72.9] (n = 131)	41.8 ± 14.7, 40.3 [31.2–53.7] (n = 62)	21.7 (17.8, 25.5)	<0.0001
BMI (kg/m²)¶	26.6 ± 4.8, 25.6 [23.2–29.3] (n = 132)	25.4 ± 4.1, 24.5 [22.2–28.1] (n = 62)	27.2 ± 5.2, 26.4 [23.5–30.2] (n = 126)	25.7 ± 3.9, 24.7 [22.8–27.7] (n = 56)	0.25 (−0.03, 0.52)	0.0782
Total daily insulin use (units/kg)#	0.63 ± 0.20, 0.61 [0.50–0.74] (n = 130)	0.59 ± 0.17, 0.54 [0.46–0.65] (n = 58)	0.58 ± 0.19, 0.56 [0.46–0.68] (n = 132)	0.57 ± 0.16, 0.56 [0.46–0.65] (n = 57)	−0.03 (−0.06, 0.00)	0.0789

Data are mean ± SD and median [interquartile range] unless otherwise indicated. To convert the values for glucose to mmol/L, multiply by 0.05551. Analyses conducted on a modified intention-to-treat data set. †Baseline and follow-up (end-of-trial) data were used for change in HbA$_{1c}$, T1-DDS score, HCS score, DQOL-Brief score, BMI, and total daily insulin. The remaining outcomes compared the standard therapy phase with the trial period. ‡Three participants were randomized to the intervention and one participant randomized to control prior to complete collection of standard therapy CGM data. §P value determined using repeated-measures linear mixed-effects model with treatment group, visit, treatment group-by-visit interaction, age, sex, and duration of diagnosis as fixed effects and country and site as random effects. ||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 ≥0.05 was observed, the outcomes below that finding on the list were not formally tested. ¶P value determined using robust regression model using M-estimation with Huber weight function with treatment group, age, sex, baseline value of the outcome, and duration of diagnosis as fixed effects. Missing data were handled using multiple imputation. #P value determined using a linear mixed-effects model with treatment group, age, sex, duration of diagnosis, and baseline value of the outcome as fixed effects and country and site as random effects. **P value determined using a logistic mixed-effects model with treatment group, age, sex, duration of diagnosis, and continuous baseline value of the outcome as fixed effects and country and site as random effects. ††There was no formal hypothesis testing for exploratory outcomes. ‡‡Post hoc analysis.

with HbA$_{1c}$ <8.0% (64 mmol/mol) and were 85.7% and 52.7%, respectively (all P ≤ 0.0002). An improvement of at least 1.0% (10.9 mmol/mol) in HbA$_{1c}$ from baseline was seen in 70.6% of the intervention group and 30.9% of the control group (P < 0.0001). At least a 10% relative improvement in HbA$_{1c}$ from baseline was seen in 77.3% and 34.5% of the intervention and control groups, respectively (P < 0.0001). Supplementary Table 9 shows the change in HbA$_{1c}$ stratified by subgroup.

Exploratory outcomes assessing further CGM-based measures (Table 2) showed that the intervention group had significantly less percentage of time >250 mg/dL than the control group, with a mean difference between treatment groups of −10.8% (95% CI −12.8%, −8.9%; P < 0.0001), corresponding to 2.6 fewer hours per day. The intervention group had a significantly greater percentage of time in tight range than the control group, with a mean difference between treatment groups of 11.5% (95% CI 8.4%, 14.5%; P < 0.0001), corresponding to an additional 2.8 h/day. The mean difference between treatment groups in glycemia risk index was −24 (95% CI −29, −19; P < 0.0001) (16). The coefficient of variation did not show a difference between groups (P > 0.05). The proportion of participants meeting consensus targets for sensor-based outcomes are listed in Supplementary Table 10. The proportion of participants in the intervention and control groups meeting the consensus target of TIR >70% were 20.6% and 3.2% (P = 0.001) and were 99.2% and 88.7% for the consensus target of <4% time <70 mg/dL (P = 0.002), respectively, during the 13-week trial period. Treatment comparisons stratified by daytime and nighttime for TIR and hypoglycemic metrics are shown in Table 2 and Supplementary Table 11, respectively.

There was no difference between the intervention and control groups in terms of change in BMI and total daily dose of insulin (Table 2). A summary of insulin requirements for both groups is presented in Supplementary Table 12.

Adverse Events
During the trial period, 13 adverse events among 12 participants were reported in the intervention group, and 10 adverse events among 9 participants were reported in the control group (number of events per 100 person-years, 40.4 and
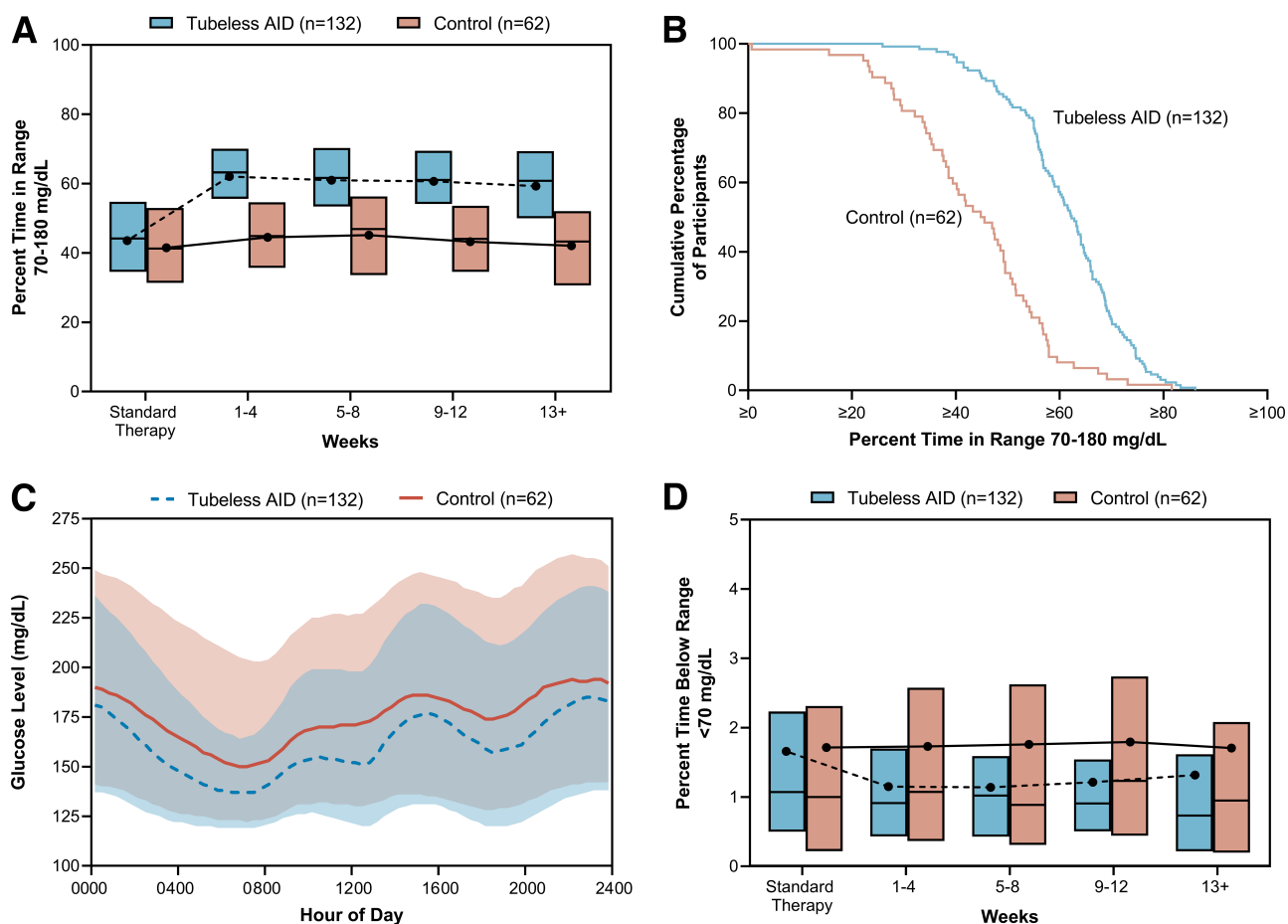
Figure 1—Glycemic outcomes during standard therapy and over the 13-week trial period for each treatment group. *A*: Box plot of the percentage of TIR (70–180 mg/dL) during standard therapy and over the 13-week trial period for each treatment group. *B*: Cumulative distribution plot of the cumulative percentage of participants compared with the percentage of TIR over the 13-week trial period for each treatment group. *C*: Envelope plot of the sensor glucose level over the 13-week trial period according to time of day. Lines denote the median values of the participants' glucose levels, and shaded regions indicate the interquartile range. *D*: Box plot of the percentage of time below range (<70 mg/dL) during standard therapy and over the 13-week trial period for each treatment group. To convert values for glucose to mmol/L, multiply by 0.05551.

68.3, respectively) (Table 3). One event in each group was considered a serious adverse event, including one case of severe hypoglycemia in the control group, and an unrelated tibia fracture in the intervention group. Hyperglycemia and/or prolonged hyperglycemia occurred in both groups, but no cases of DKA were reported.

System Use

Participants in the intervention group spent a median (interquartile range) 97.3% (92.7%–99.2%) of time in Automated Mode (mean ± SD 94.1 ± 8.7%) while wearing the system. In the intervention group, participants spent 59.3% of total cumulative study time at the 110 mg/dL target, 28.7% at the 120 mg/dL target, 5.8% at the 130 mg/dL target, 2.5% at the 140 mg/dL target, and 1.9% at the 150 mg/dL target

and 1.8% of time with the Activity feature enabled.

There were 54 device issues among 30 participants reported in the intervention group and 9 device issues among 6 participants reported in the control group. In the intervention group, device issues during the trial were related to the Pod (*n* = 32), CGM (*n* = 7), Controller (*n* = 12), and CGM transmitter (*n* = 3). In the control group, device issues were related to the Pod (*n* = 1), CGM (*n* = 6), and CGM receiver (*n* = 2). A summary of device issues is provided in Supplementary Table 13.

CONCLUSIONS

In this parallel-group RCT of adults with type 1 diabetes with suboptimal glycemic outcomes, use of the tubeless AID system was associated with an increase of 4.2 h/day (difference of 17.5%) in the

target glucose range compared with pump therapy with a CGM alone. This outcome was accomplished with a significantly lower percentage of time with sensor glucose in a hypoglycemic range (<70 mg/dL) and hyperglycemic range (>180 mg/dL), greater reduction in HbA_{1c} from baseline, no episodes of severe hypoglycemia or DKA, and a greater proportion of participants achieving clinically meaningful improvements in person-reported outcomes with AID use. Notably, these results were achieved in a study population comprising predominantly participants with an $HbA_{1c} \geq 8\%$ (64 mmol/mol), mirroring the real-world burden of type 1 diabetes where only a fraction of adults meet the target of <7% (53 mmol/mol) (1). Collectively, these results highlight the meaningful clinical and psychosocial impact of AID and its potential to ultimately reduce diabetes-related complications and

Table 3—Adverse events

Event	Intervention group (n = 132)	Control group (n = 62)
Any adverse event		
Events, n	13	10
Participants with an event, n (%)	12 (9.1)	9 (14.5)
Events per 100 person-years, n	40.4	68.3
Specific events, no. of events/no. of participants (% of participants) [no. events per 100 person-years]		
Severe hypoglycemia*	0/0 (0.0) [0.0]	1/1 (1.6) [6.8]
DKA†	0/0 (0.0) [0.0]	0/0 (0.0) [0.0]
Hypoglycemia‡	0/0 (0.0) [0.0]	0/0 (0.0) [0.0]
Hyperglycemia§	2/2 (1.5) [6.2]	0/0 (0.0) [0.0]
Prolonged hyperglycemia‖	4/4 (3.0) [12.4]	5/4 (6.5) [34.1]
Other adverse events¶	7/6 (4.5) [21.7]	4/4 (6.5) [27.3]

*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. One case of severe hypoglycemia in the control group was considered a serious adverse event. †Hyperglycemia with the presence of polyuria; polydipsia; nausea or vomiting; serum ketones >1.5 mmol/L or large/moderate urine ketones; either arterial blood pH <7.30, venous pH <7.24, or serum bicarbonate <15; and treatment provided in a health care facility. ‡Hypoglycemia resulting in an adverse event but otherwise not meeting the definition of severe hypoglycemia. §Hyperglycemia requiring evaluation, treatment, or guidance from intervention site or resulting in an adverse event but otherwise not meeting the definition of DKA or prolonged hyperglycemia. ‖Meter blood glucose measuring ≥300 mg/dL for >1 h and ketones >1.0 mmol/L. ¶Other related, but nonglycemic adverse events included one case of a skin reaction. Other nonrelated events included concussion, lumbosciatica, pneumonia, shoulder pain, angina, laryngitis, fibula fracture, foot fracture, and sciatica. One case of a tibia fracture in the intervention group was considered a serious adverse event.

mortality risk while reducing self-care burden in people with type 1 diabetes.

This trial highlights the undeniable advantage that an AID system can have in improving clinical outcomes beyond that of a nonautomated insulin pump with a CGM. Indeed, despite the addition or continuation of a study CGM with their usual pump therapy in the control group, all primary and secondary outcomes were met in the intervention group, emphasizing that AID use, rather than addition of a CGM, substantially improves glycemic and psychosocial outcomes. Notably, the majority (87%) of participants were already users of the non-AID Omnipod insulin pumps, with 97% of these participants currently or previously using a CGM for their diabetes management. Despite this, switching to an AID system of the same form factor (e.g., tubeless, on-body) was still associated with improved outcomes. Similarly, improvements in TIR were recently reported in prior Omnipod DASH (non-AID) users switching to the Omnipod 5 AID System in a real-world setting (18).

The treatment effects in the current trial reaffirm findings seen among adolescents and adults (aged 14–70 years) in single-arm pivotal and extension trials of tubeless AID use (7,9), as well as several other reports demonstrating similar improvements in glycemic outcomes with the tubeless AID system, despite differences in study design and baseline characteristics of study samples (18–20). While the increase in TIR (9.3%) observed in the pivotal trial was less pronounced than the current study, participants had a more favorable baseline TIR with standard therapy (64.7% vs. 43.9% [intervention group] for the pivotal vs. current trial, respectively) (7). This pattern aligns with research indicating that a lower initial TIR is associated with greater improvements in TIR when using AID systems (21). As such, when examining a subgroup of the pivotal trial adult participants with a baseline HbA1c ≥8% (64 mmol/mol) (mean 8.6% [70 mmol/mol]), TIR was comparable to the current work, starting at 42.6% and increasing to 58.2% with tubeless AID use (7,22). Furthermore, the mean baseline HbA1c level in the current study of 8.5% (69 mmol/mol) is more representative of a real-world population compared with previous studies, given that the U.S. Type 1 Diabetes Exchange Quality Improvement Collaborative recently reported a mean HbA1c of 8.4% (68 mmol/mol) in people with type 1 diabetes across all ages (1). Notably, while the greatest improvements in both TIR and HbA1c in the current work occurred in participants with HbA1c ≥8% (64 mmol/mol) at baseline, those with baseline HbA1c <8% (64 mmol/mol) still experienced a marked improvement with use of the tubeless AID system, emphasizing the glycemic benefits of AID for adults with type 1 diabetes across a broad range of baseline HbA1c levels above the recommended clinical target (1).

Other research has also demonstrated the glycemic benefits of AID systems compared with other insulin therapies (e.g., multiple daily injections, sensor-augmented pump therapy) for both open-source and commercially available systems (23–29). The current study results compare favorably with other commercially available systems demonstrating TIR values of ~60% for people starting with higher HbA1c levels (29–32). For example, participants using other AID systems with an HbA1c ≥8% (64 mmol/mol) or ≥8.5% (69 mmol/mol) achieved a TIR between 60.9% and 64.0% across studies (29–32). Collectively, while most of these and the current study results fall below the recommended target of >70% TIR (17), they all represent marked improvements from baseline, with 20.6% of participants in the current study meeting the recommended target for this metric with AID use (an increase from 1.6% with standard therapy). However, direct comparisons across studies should be considered with caution due to differences in study design and study samples.

Notably, while ~10% of participants in the present study were using a pump with AID capabilities prior to the study, the systems were not used with automation enabled. While the reasons for this are unknown, our study findings highlight that enabling automation would provide a significant benefit in glycemia. Furthermore, results of the current study demonstrated benefits of AID not only for glycemic outcomes but also for person-reported outcomes of diabetes distress, quality of life, and hypoglycemia confidence, increasing the likelihood that a user would continue using the system and thus receive the persistent glycemic benefits to improve their short- and

long-term health outcomes (33). Although beyond the scope of this study, the long-term impact of AID cannot be realized unless systems reduce burden and can be worn consistently, positively impacting quality of life as well as glycemia.

This study has several strengths, including its RCT design that addresses limitations of the previous single-arm pivotal and extension trials of this system by allowing consideration of study-related interactions (7–10). Additionally, the study sample with higher baseline HbA$_{1c}$ levels is more reflective of the real-world burden of type 1 diabetes. Furthermore, our examination of outcomes stratified by subgroup, though not statistically compared, indicated favorable results across various factors, including country, sex, race and ethnicity, age, BMI, baseline glycemic measures, and prior CGM use for those using the tubeless AID system, supporting the generalizability of the findings. Still, the homogeneity of the study population with respect to race and ethnicity and prior device use (97% were current or previous CGM users and 87% were using an earlier Omnipod System as their insulin pump therapy) is a limitation of the current work. Additionally, for participants whose CGM-based measures were collected prospectively during the standard therapy phase, the study effect could have affected the ability to assess their true prestudy glycemia levels. However, the intervention group still experienced a greater TIR during the 13-week trial period compared with the control group.

In conclusion, this tubeless AID system has demonstrated significant improvements in glycemic measures in adults with type 1 diabetes compared with those using standard pump therapy with CGM, as well as improvements in person-reported outcomes. The findings underscore the advantages of AID to improve clinical outcomes and to potentially reduce the short- and long-term complications and increased mortality risk associated with suboptimal glycemic outcomes. These findings support the efficacy of AID systems and further reinforce propositions to establish these systems as the preferred therapy for people with type 1 diabetes (4).

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