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Twelve-month results of the ADAPT randomized controlled trial: Reproducibility and sustainability of advanced hybrid closed-loop therapy outcomes versus conventional therapy in adults with type 1 diabetes

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Abstract

Aims: To reassess the 6-month efficacy and to assess the 12-month sustained efficacy of the MiniMed™ 780G advanced hybrid closed-loop automated insulin delivery (AID) system compared to multiple daily injections plus intermittently scanned glucose monitoring (MDI+isCGM) in people with type 1 diabetes not meeting glucose targets.

Methods: The ADAPT study was a prospective, multicentre, open-label, randomized control trial in people with type 1 diabetes, with a glycated haemoglobin (HbA1c) concentration of at least 8.0% (64 mmol/mol), on MDI+isCGM therapy. After a 6-month study phase, participants randomized at baseline to MDI+isCGM switched to AID (SWITCH) while the others continued AID therapy (SUSTAIN) for an additional 6 months. The primary endpoint of this continuation phase was the within-group change in mean HbA1c between 6 and 12 months, with superiority in the SWITCH group and noninferiority in the SUSTAIN group ([ClinicalTrials.gov: NCT04235504](https://clinicaltrials.gov/ct2/show/study/NCT04235504)).

Results: A total of 39 SWITCH and 36 SUSTAIN participants entered the continuation phase. In the SWITCH group, HbA1c was significantly decreased by -1.4% (95% confidence interval [CI] -1.7% to -1.1% ; $P < 0.001$) from a mean \pm SD of $8.9\% \pm 0.8\%$ (73.9 ± 8.6 mmol/mol) at 6 months to $7.5\% \pm 0.6\%$ (58.5 ± 6.9 mmol/mol) at 12 months. Mean HbA1c increased by 0.1% (95% CI -0.05%

Shannon N. Edd and Javier Castañeda contributed equally to this work as first authors.

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to +0.25%), from $7.3\% \pm 0.6\%$ (56.5 ± 6.7 mmol/mol) to $7.4\% \pm 0.8\%$ (57.7 ± 9.1 mmol/mol) in the SUSTAIN group, meeting noninferiority criteria. Three severe hypoglycaemia events occurred in two SWITCH participants during the continuation phase.

Conclusion: ADAPT study phase glycaemic improvements were reproduced and sustained in the continuation phase, supporting the early adoption of AID therapy in people with type 1 diabetes not meeting glucose targets on MDI therapy.

KEYWORDS

insulin pump therapy, patient reported outcomes, randomized trial, subcutaneous injection, type 1 diabetes

1 | INTRODUCTION

In the management of type 1 diabetes, there is growing adoption of hybrid closed-loop systems, as they have been shown in clinical trials and real-world use to safely provide favourable glycaemic control compared to multiple daily injection (MDI) therapy and compared to sensor-augmented pump therapies.^{1–3} However, access to these technologies is often limited, as a stepwise approach to diabetes technologies is recommended. Hence, people with diabetes requiring intensive insulin therapy must start with MDI therapy and self-monitoring of blood glucose (SMBG) or intermittently scanned continuous glucose monitoring (isCGM) before progressing to MDI therapy with real-time continuous glucose monitoring (CGM), eventually moving on to automated insulin delivery (AID) system therapy if necessary.⁴ This can be a lengthy process, exposing people with diabetes to prolonged periods of suboptimal blood glucose levels. Following this stepwise approach, there is evidence demonstrating an improvement in glucose control with the MiniMed™ 780G Advanced Hybrid Closed-Loop AID system compared to its predecessors (MiniMed™ 670G system)⁵ and to sensor-augmented pumps with predictive low glucose management.⁶ However, to support a more direct approach to advanced diabetes management technology, it was of interest to compare the MiniMed™ 780G system to the most prevalent therapy, namely, MDI with isCGM.⁷

The Advanced Hybrid Closed Loop Study in Adult Population with Type 1 Diabetes (ADAPT) was the first randomized control trial assessing the efficacy and safety of the MiniMed™ 780G AID algorithm in comparison to MDI therapy with isCGM, in people with type 1 diabetes and suboptimal glucose control ($HbA_{1c} \geq 8.0\%$).⁸ The primary results of the ADAPT trial showed that the AID system safely provided a 1.4% reduction in HbA_{1c} and a 26.7% increase in time in range (TIR; 70–180 mg/dL) from baseline to the end of the 6-month study phase in participants randomized to AID treatment relative to those continuing with MDI and isCGM (MDI+isCGM) therapy.⁹ Participants randomized to AID treatment reached a mean HbA_{1c} of 7.3% at the end of the 6-month study period, whereas those randomized to continue MDI+isCGM therapy had a mean HbA_{1c} 8.9% at this timepoint.⁹ As such, these data suggest that the use of the AID system earlier in the type 1 diabetes treatment pathway would be

beneficial, thus supporting wider access to AID therapy in people with type 1 diabetes who do not meet glucose targets.

In addition to the main study phase, the ADAPT study design included a continuation phase of an additional 6 months, during which participants randomized to receive treatment with the AID system continued with AID therapy (SUSTAIN group) and participants randomized to MDI+isCGM switched to AID therapy for 6 months (SWITCH group). The aims of the continuation phase of the ADAPT study were twofold: (1) to test if improvements in glycaemic control observed in the main study phase were reproduced in the SWITCH group, and (2) to confirm long-term sustained glycaemic control benefits of AID therapy up to 12 months in the SUSTAIN group.

2 | METHODS

2.1 | Study design and participants

Details of the ADAPT parallel randomized controlled study design are available elsewhere.⁸ In summary, the ADAPT study recruited 84 participants with type 1 diabetes to a prospective, multinational, open-label randomized controlled trial. Eligible participants had an HbA_{1c} at baseline of at least 8.0% (64 mmol/mol) and were diagnosed with type 1 diabetes for at least 2 years, had been on MDI therapy for at least 2 years, and were using isCGM for at least 3 months prior to screening with an average of 5 or more isCGM scans per day and sensor readings at least 70% of the time during the month prior to screening. Exclusion criteria included the use of pramlintide, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 agonists/mimetics, metformin, SGLT2 inhibitors at screening, women who were pregnant at screening or planning to become pregnant during the study period, hearing or visual impairment that hindered the perception of glucose displays or alarms, or unresolved skin conditions near sensor placement areas. An exhaustive list of inclusion and exclusion criteria is available elsewhere.⁸ All participants gave their informed consent prior to inclusion in the study.

The study design consisted of a 2-week run-in phase followed by a 6-month study phase and a further 6-month continuation phase (Figure 1). During the 2-week run-in phase, baseline sensor glucose (SG) data were recorded using the Guardian Link 3 transmitter (data

recorder only) with the Guardian Sensor 3 (Medtronic), while participants continued with their MDI therapy. Participants who demonstrated tolerance to continuous wear of the CGM device and compliance with study procedures were 1:1 randomized (investigator-blinded, block randomization procedure, conducted electronically) either to continue with MDI+isCGM therapy (control arm) or to use the Medtronic MiniMed™ Advanced Hybrid Closed-Loop system (treatment arm), henceforth referred to as AID, for the 6-month study phase. The AID system consisted of the MiniMed™ 670G (version 4.0) insulin pump, which is equivalent to the commercialized MiniMed™ 780G pump except for the absence of Bluetooth connectivity and the 110 mg/dL (6.1 mmol/L) glucose target, along with the Guardian Link 3 transmitter and Guardian Sensor 3 (Medtronic). Participants used the Guardian 3 CGM system according to the instructions for use, which require a fingerstick blood glucose measurement at least every 12 hours after initial sensor warm-up. For the continuation phase, participants in the control arm switched from MDI+isCGM to the AID system (herein referred to as the SWITCH group), whereas the treatment arm continued with AID treatment (herein referred to as the SUSTAIN group) for an additional 6 months. The findings presented here pertain exclusively to the continuation phase.

Unless there was a hypoglycaemia concern, participants were encouraged to use the optimal AID pump settings, consisting of a 100 mg/dL (5.6 mmol/L) glucose target and an active insulin time of 2 hours. The study was conducted at multiple clinical sites with experience in treating people with type 1 diabetes on insulin pump therapy in France ($n = 6$ sites), Germany ($n = 4$ sites) and the United Kingdom ($n = 4$ sites). The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local legislation. Competent authority and ethics committee approvals were obtained for all study sites.

2.2 | Outcomes and statistical analyses

The primary endpoint for the continuation phase was the within-group change in mean HbA1c, measured in a central laboratory, between the end of the study phase (at 6 months) to the end of the continuation phase (at 12 months). The statistical analysis of the primary endpoint differed per treatment group: in the SWITCH group, change in HbA1c was tested for superiority, whereas in the SUSTAIN group, change in HbA1c was tested using a noninferiority test where

the upper limit of the confidence interval (CI) for the mean change was compared to the noninferiority margin of 0.3%, as a 0.3% change in HbA1c is considered to be non-clinically significant.¹⁰ Descriptive analysis of the within-group changes in HbA1c between baseline and end of the continuation phase (12 months) was conducted in both the SWITCH and SUSTAIN groups separately.

The secondary endpoints included CGM-based metrics of glycaemic control, system characteristics, metrics of insulin use, and patient-reported outcomes. A full overview of endpoints is listed in Table 2. In the SWITCH group, CGM metrics were compared between 2-week windows of CGM SG data at 3 and 6 months (study phase) and 2-week windows at 9 and 12 months (continuation phase), and in the SUSTAIN group, all available SG data over the entire 6 months of the study phase and 6 months of the continuation phase were compared. Patient-reported outcomes were assessed at baseline, 6 months and 12 months using the Diabetes Quality of Life Questionnaire (DQoL),^{11,12} the Diabetes Treatment Satisfaction Questionnaire (DTSQ),¹³ and the Hypoglycaemia Fear Survey.¹⁴ The statistical analyses of within-group changes in continuous endpoints used paired *t*-tests and 95% CI in cases where the normality assumption was met, otherwise endpoints were reported as median and 95% CI (estimated using the Hodges-Lehmann method) and compared using a Wilcoxon signed rank test. Noninferiority test margins were set at 6% for TIR (70-180 mg/dL [3.9-10.0 mmol/L]) and time above range (TAR; >180 mg/dL [10.0 mmol/L] and >250 mg/dL [13.9 mmol/L]), and 5% and 2% for time below range (TBR) with SG <70 mg/dL (3.9 mmol/L) and SG <54 mg/dL (3.0 mmol/L), respectively.

To control for multiplicity, the following endpoints were tested in an ordered sequence at level $\alpha = 0.05$ until a first non-statistically significant result was observed: (1) Change in HbA1c; (2) TAR with SG >250 mg/dL (13.9 mmol/L); (3) TAR with SG >180 mg/dL (10.0 mmol/L); (4) TIR 70-180 mg/dL (3.9 to 10.0 mmol/L); (5) TBR with SG <54 mg/dL (3.0 mmol/L); and (6) TBR with SG <70 mg/dL (3.9 mmol/L). The full sequence of statistical testing per treatment group is available in Appendix S1. Adjustment for multiplicity was not applied to other endpoints. All continuation phase analyses were exploratory and *P* values less than 0.05 were considered statistically significant.

Safety endpoints included the number of episodes of severe hypoglycaemia, diabetic ketoacidosis (DKA), serious adverse events, serious adverse device effects, and unanticipated serious adverse device effects. Study registration is available at [ClinicalTrials.gov](https://clinicaltrials.gov): NCT04235504.

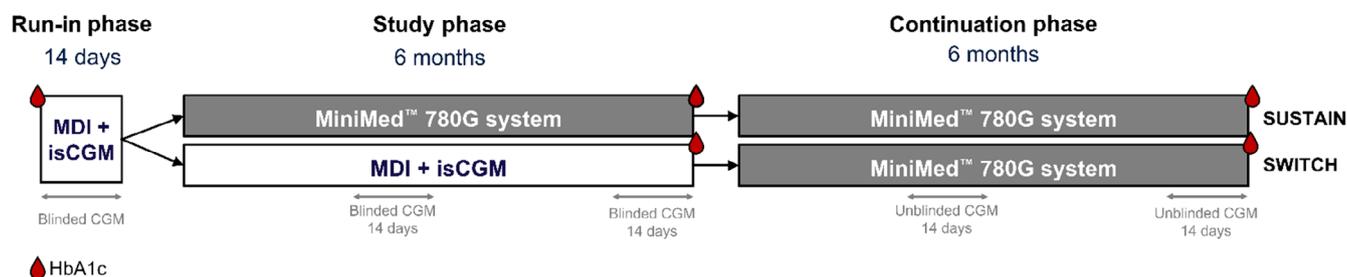


FIGURE 1 Study design consisting of run-in, study and continuation phases. CGM, continuous glucose monitoring; HbA1c, glycated haemoglobin; isCGM, intermittently scanned continuous glucose monitoring; MDI, multiple daily injections.

3 | RESULTS

3.1 | Baseline demographics

Of the 105 individuals assessed for eligibility, 82 were randomized at the start of the study phase (Figure 2). Of these, seven participants discontinued during the study phase, with 39 participants (15 female) in the SWITCH group and 36 participants (18 female) in the SUSTAIN group completing the 6-month study phase and entering the continuation phase.

Baseline characteristics for all randomized participants ($n = 82$, previously presented⁹) and for those participants who entered the continuation phase ($n = 75$) are presented in Table 1.

During the continuation phase, seven participants dropped out from the SWITCH group, four withdrew themselves, one was withdrawn due to physician decision, and one was withdrawn due to an adverse event. From the SUSTAIN group, one subject withdrew themselves from the study during the continuation phase.

3.2 | Glycated haemoglobin

In the SWITCH group, HbA1c was significantly decreased at 12 months by a mean of -1.4% (95% CI -1.7% to -1.1% ; $P < 0.001$) (-14.9 mmol/mol [95% CI: -18.0 to -11.8 mmol/mol]) compared to at 6 months (Figure 3) from a mean \pm SD of $8.9\% \pm 0.8\%$ (73.9 ± 8.6 mmol/mol) to $7.5\% \pm 0.6\%$ (58.5 ± 6.9 mmol/mol; Table 2). Mean HbA1c increased by 0.1% (95% CI -0.05 to 0.25%) (1.1 mmol/mol [95% CI: -0.6 to 2.7 mmol/mol]) from $7.3\% \pm 0.6\%$ (56.5 ± 6.7 mmol/mol) at 6 months to $7.4\% \pm 0.8\%$ (57.7 ± 9.1 mmol/mol) at 12 months in the SUSTAIN group, meeting the noninferiority criteria ($+0.3\%$).

For the descriptive analysis of HbA1c, mean \pm SD change in HbA1c from baseline to 12 months was $-1.6\% \pm 0.83\%$ in the SWITCH group, decreasing from $9.1\% \pm 0.7\%$ (75.7 ± 7.8 mmol/mol) to $7.5\% \pm 0.63\%$ (58.5 ± 6.9 mmol/mol), and $-1.5\% \pm 0.83\%$ in the SUSTAIN group, decreasing from $9.0\% \pm 0.97\%$ (74.9 ± 10.6 mmol/mol) to $7.4\% \pm 0.83\%$ (57.7 ± 9.1 mmol/mol).

Five (15.6%) of the SWITCH group participants achieved an HbA1c level $<7\%$ at 12 months, compared to none at 6 months. In the SUSTAIN group, 12 participants (35.3%) achieved an HbA1c level $<7\%$ at 12 months, compared to 10 (27.8%) at 6 months.

3.3 | Sensor glucose, system usage and patient-reported outcomes

Secondary endpoint results for the two treatment groups are shown in Table 2. TIR significantly increased by 28.1% (95% CI 22.8% to 33.4%; $P < 0.001$) in the SWITCH group from 6 to 12 months, whereas TAR (>180 mg/dL [10.0 mmol/L]) significantly decreased by -27.2% (95% CI -32.9% to -21.6% ; $P < 0.001$). In the same group, time in TBR (<70 mg/dL [3.9 mmol/L]) was unchanged from 6 to 12 months, meeting noninferiority (-0.5% [95% CI -1.5% to 0.1%]).

From 6 to 12 months, mean SG and standard deviation of SG both significantly decreased in the SWITCH group ($P < 0.001$). In the SUSTAIN group, all glycaemic control endpoints met noninferiority criteria for changes from 6 to 12 months of the continued use of the AID system.

In the SWITCH group, during the continuation phase, mean \pm SD percentage sensor use was $79.0\% \pm 24.7\%$. The SUSTAIN group had a percentage sensor use of $88.8\% \pm 9.8\%$ during the continuation phase as compared to $92.2\% \pm 4.2\%$ during the study phase. During the continuation phase, participants in the SWITCH group spent $77.1\% \pm 24.1\%$ time in automation, whereas SUSTAIN group participants spent $95.8\% \pm 3.4\%$ time in automation during the study phase and $93.7\% \pm 8.1\%$ time in automation during the continuation phase.

Of the participants in the SWITCH group, 15 (44.1%) selected the glucose target of 100 mg/dL (5.6 mmol/L), and no participants selected the glucose target of 120 mg/dL (6.7 mmol/L) for at least 95% of the continuation phase; the remaining 19 participants (55.9%) used a mixture of glucose targets. Ten SWITCH group participants (29.4%) selected an active insulin time of 2 hours, and five (14.7%) selected 2 to 3 hours, for at least 95% of the continuation phase; the remaining 19 participants (55.9%) used a mixture of active insulin times. In the SUSTAIN group, 21 (58.3%) selected the glucose target of 100 mg/dL (5.6 mmol/L), and eight participants (22.2%) selected the glucose target of 120 mg/dL (6.7 mmol/L), for at least 95% of the continuation phase; the remaining seven participants (19.4%) used a mixture of glucose targets. Nineteen (52.8%) SUSTAIN group participants selected an active insulin time of 2 hours, 11 (30.6%) selected 2 to 3 hours, and two (5.6%) selected 3 to 4 hours, for at least 95% of the continuation phase. The remaining four participants (11.1%) used a mixture of active insulin times.

The mean \pm SD number of SMBG readings per day was 3.5 ± 0.9 for the SWITCH group during the continuation phase; in the SUSTAIN group, the number of SMBG readings per day was 3.8 ± 1.2 during the study phase and 3.3 ± 0.8 during the continuation phase. Change in weight from 6 to 12 months was 2.25 kg (95% CI 1.20 to 4.40 kg) in the SWITCH group and 0.55 kg (95% CI -0.25 to 1.50 kg) in the SUSTAIN group. The total daily insulin dose delivered by the pump was 47.7 ± 16.1 units in the SWITCH group during the continuation phase, while in the SUSTAIN group it was 54.6 ± 21.8 units in the study phase and 54.3 ± 22.5 units in the continuation phase, with no change in total daily insulin dose between the study phases (-0.3 units [95% CI -2.1 to 1.5]).

Twenty (60.6%) of the SWITCH group participants achieved $>70\%$ TIR (70-180 mg/dL [3.9 - 10.0 mmol/L]) during the continuation phase, compared to two participants (6.5%) during the study phase. Thirty of the SWITCH participants (90.9%) achieved $<4\%$ TBR (<70 mg/dL [<3.9 mmol/L]) during the continuation phase, compared to 24 participants (77.4%) in the study phase. In the SUSTAIN group during the continuation phase, 16 participants (44.4%) achieved $>70\%$ TIR and 33 (91.7%) achieved $<4\%$ TBR, compared to 19 participants (52.8%) achieving $>70\%$ TIR and 30 (83.3%) achieving $<4\%$ TBR during the study phase. In the SWITCH group, patient-reported outcomes significantly improved from 6 to 12 months based on the Hypoglycaemia Fear Survey (mean change in total score of -6.5 [95%

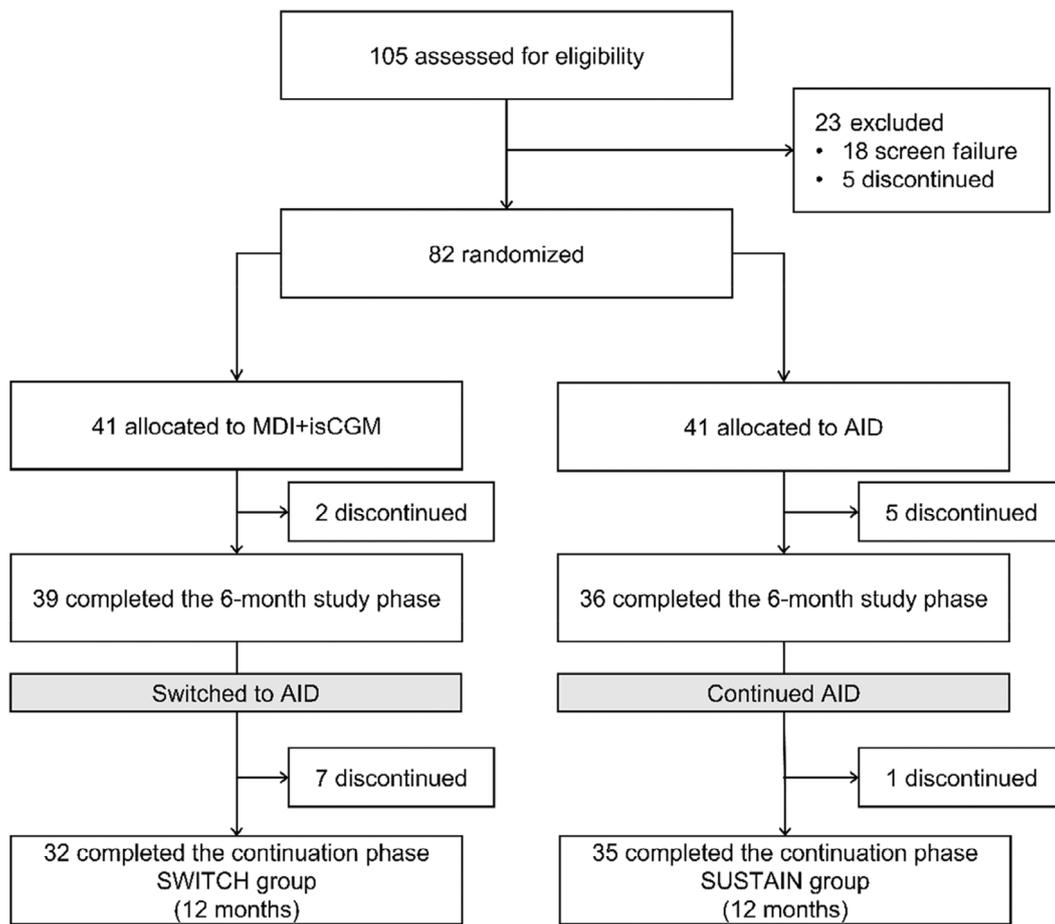


FIGURE 2 Flowchart of study inclusion. AID, automated insulin delivery; isCGM, intermittently scanned continuous glucose monitoring; MDI, multiple daily injections.

TABLE 1 Participant characteristics at time of randomization

	Baseline characteristics of all randomized participants, n = 82		Baseline characteristics of participants entering the continuation phase, n = 75	
	MDI+isCGM, n = 41	AID, n = 41	MDI+isCGM (SWITCH), n = 39	AID (SUSTAIN), n = 36
Age, years	39.7 ± 13.1	41.5 ± 11.6	40.6 ± 12.7	40.9 ± 12.1
Female, n (%)	16 (39.0)	22 (53.7)	15 (38.5)	18 (50.0)
Duration of diabetes, years	18.1 ± 10.0	18.8 ± 11.4	18.4 ± 9.9	17.8 ± 11.4
Weight, kg	78.4 ± 14.7 ^a	79.9 ± 15.1	79.7 ± 14.1 ^b	81.4 ± 14.6
BMI, kg/m ²	25.8 ± 4.9 ^a	27.0 ± 4.4	26.1 ± 4.9 ^b	27.3 ± 4.4
HbA1c, mmol/mol	75.7 ± 7.8	74.9 ± 10.6	76.0 ± 7.9	73.3 ± 7.4
HbA1c, %	9.1 ± 0.7	9.00 ± 1.0	9.1 ± 0.7	8.9 ± 0.7
Insulin total daily dose, U	53.3 ± 22.3 ^c	54.3 ± 25.9	53.2 ± 22.6	56.0 ± 26.2
Sensor readings, %	87.3 ± 16.2 ^a	90.1 ± 8.8 ^c	87.6 ± 16.3 ^d	90.8 ± 8.5 ^e
isCGM scans in the previous month, n/day	9.0 ± 5.2 ^a	8.8 ± 7.4	9.1 ± 5.25 ^d	8.8 ± 7.5

Note: Values reported as mean ± SD unless otherwise noted.

^an = 39.

^bn = 37.

^cn = 40.

^dn = 38.

^en = 35.

TABLE 2 Continuation phase glycaemic control and patient-reported outcomes in the SWITCH and SUSTAIN groups

Outcome	SWITCH group (switched to AID)			SUSTAIN group (remained on AID)		
	Study phase 6 months mean \pm SD N	Continuation phase 12 months mean \pm SD N	Estimate of change (95% CI; P) N	Study phase 6 months, mean \pm SD N	Continuation phase 12 months, mean \pm SD N	Estimate of change (95% CI) N
HbA1c, %	8.9 \pm 0.8 38	7.5 \pm 0.6 32	-1.4 (-1.7 to -1.1; <0.001) 31	7.3 \pm 0.6 36	7.4 \pm 0.8 34	0.1 (-0.1 to 0.25) ^a 33
HbA1c, mmol/mol	73.9 \pm 8.6 38	58.5 \pm 6.9 32	-14.9 (-18.0 to -11.8; <0.001) 31	56.5 \pm 6.7 36	57.7 \pm 9.1 34	1.1 (-0.6 to 2.7) ^a 33
TIR 70-180 mg/dL (3.9-10.0 mmol/L), %	43.6 \pm 15.4 31	70.7 \pm 9.5 33	28.1 (22.8 to 33.4; <0.001) 28	70.4 \pm 9.9 36	69.7 \pm 9.0 36	-0.7 (-2.1 to 0.7) ^a 36
TAR > 180 mg/dL (10.0 mmol/L), %	53.8 \pm 16.5 31	27.6 \pm 9.5 33	-27.2 (-32.9 to 21.6; <0.001) 28	27.1 \pm 10.4 36	28.0 \pm 9.6 36	0.9 (-0.5 to 2.3) ^a 36
TAR > 250 mg/dL (13.9 mmol/L), %	22.5 \pm 13.2 31	6.6 \pm 4.3 33	-16.6 (-21.7 to -11.6; <0.001) 28	6.7 \pm 4.6 36	7.2 \pm 4.9 36	0.5 (0.0 to 1.1) ^a 36
TBR <70 mg/dL (3.9 mmol/L), %	2.6 \pm 2.5 31	1.8 \pm 1.4 33	-0.5 (-1.5 to 0.1; 0.135) ^a 28	2.5 \pm 1.9 36	2.3 \pm 1.9 36	-0.2 (-0.7 to 0.2) ^a 36
TBR <54 mg/dL (3.0 mmol/L), %	0.7 \pm 1.2 31	0.4 \pm 0.4 33	-0.2 (-0.4 to 0.0; 0.060) ^a 28	0.6 \pm 0.6 36	0.5 \pm 0.5 36	-0.1 (-0.2 to 0.0) ^a 36
Mean SG, mg/dL	194.7 \pm 29.5 31	155.0 \pm 13.8 33	-41.4 (-51.7 to -31.0; <0.001) 28	152.7 \pm 16.0 36	154.4 \pm 15.6 36	1.76 (-0.4 to 3.9) 36
Standard deviation of SG, mg/dL	69.4 \pm 12.8 31	53.8 \pm 8.7 33	-14.7 (20.7 to -10.9; <0.001) 28	54.8 \pm 9.8 36	56.0 \pm 10.0 36	1.3 (-0.2 to 2.8) 36
Hypoglycaemia Fear Survey						
Total score	47.4 \pm 22.9 39	35.3 \pm 23.8 32	-6.5 (-16.0 to -0.5; 0.031) 32	35.7 \pm 23.4 35	29.7 \pm 20.8 34	-4.1 (-9.4 to 1.2) 33
Behaviour	21.8 \pm 8.6 39	16.3 \pm 10.1 32	-4.0 (-7.5 to -0.5; 0.016) 32	15.8 \pm 9.5 35	12.9 \pm 8.9 35	-2.3 (-4.8 to 0.3) 34
Worry	25.6 \pm 16.0 39	18.9 \pm 15.2 32	-2.5 (-11.0 to 1.0; 0.173) 32	19.9 \pm 15.3 35	17.1 \pm 13.7 34	-2.0 (-4.5 to 0.0) 33
DQoL						
Total score	66.4 \pm 14.3 25	75.2 \pm 10.6 22	5.0 (1.5 to 10.5; 0.007) 22	68.2 \pm 16.8 24	71.3 \pm 17.5 25	2.3 (-2.0 to 6.5) 24
Treatment satisfaction score	59.3 \pm 20.6 25	76.0 \pm 14.5 22	15.0 (5.1 to 24.9; 0.005) 22	68.0 \pm 21.9 24	74.0 \pm 19.5 25	4.0 (0.0 to 10.0) 24
Treatment impact score	60.0 \pm 13.8 25	66.4 \pm 9.0 22	2.5 (-1.5 to 8.0; 0.306) 22	62.6 \pm 11.8 24	65.5 \pm 14.7 25	2.1 (-2.0 to 6.2) 24
Social worry score	79.3 \pm 16.4 22	84.0 \pm 14.2 22	1.1 (-4.1 to 6.2; 0.6725) 20	77.3 \pm 21.3 24	79.0 \pm 22.6 23	1.6 (-3.4 to 6.4) 22

(Continues)

TABLE 2 (Continued)

Outcome	SWITCH group (switched to AID)			SUSTAIN group (remained on AID)		
	Study phase 6 months mean \pm SD N	Continuation phase 12 months mean \pm SD N	Estimate of change (95% CI; P) N	Study phase 6 months, mean \pm SD N	Continuation phase 12 months, mean \pm SD N	Estimate of change (95% CI) N
Diabetes worry score	67.5 \pm 19.4 24	74.5 \pm 14.9 22	6.0 (0.0 to 9.5; 0.1028) 21	64.5 \pm 22.4 24	68.6 \pm 24.7 23	3.3 (–5.9 to 12.5) 22
General well-being score	50.8 \pm 24.0 25	58.9 \pm 21.0 21	0.0 (0.0 to 17.0; 0.063) 21	50.0 \pm 20.2 22	44.4 \pm 25.6 24	0.0 (0.0 to 0.0) 21
DTSQs						
Treatment satisfaction	21.9 \pm 7.5 39	29.9 \pm 5.7 32	8.0 (4.4 to 11.6; <0.001) 32	29.7 \pm 5.8 35	31.6 \pm 4.7 34	1.5 (–0.04 to 3.1) 33
Frequency of hyperglycaemia	3.9 \pm 1.3 39	2.1 \pm 1.2 32	–1.8 (–2.5 to –1.1; <0.001) 32	2.3 \pm 1.4 35	2.1 \pm 1.5 35	–0.2 (–0.7 to 0.4) 34
Frequency of hypoglycaemia	2.8 \pm 1.3 39	1.9 \pm 1.3 32	–0.9 (–1.6 to –0.1; 0.021) 32	2.3 \pm 1.5 35	2.3 \pm 1.4 35	0.0 (–0.5 to 1.0) 34
DTSQc						
Treatment satisfaction change	3.7 \pm 7.2 38	12.9 \pm 6.4 32	9.0 (5.2 to 12.9; <0.001) 31	13.7 \pm 4.4 35	15.4 \pm 3.6 35	1.4 (0.3 to 2.4) 34
Frequency of hyperglycaemia change	0.8 \pm 1.4 38	–1.3 \pm 1.5 32	–2.2 (–2.9 to –1.5; <0.001) 31	–1.1 \pm 1.8 35	–1.2 \pm 1.9 35	0.0 (–0.5 to 1.0) 34
Frequency of hypoglycaemia change	0.1 \pm 1.3 38	–0.7 \pm 1.7 32	–0.7 (–1.6 to 0.2; 0.102) 31	–0.5 \pm 1.8 35	–0.7 \pm 1.8 35	0.0 (–0.5 to 0.5) 34

Abbreviations: CI, confidence interval; DQoL, Diabetes Quality of Life questionnaire; DTSQs/c, Diabetes Treatment Satisfaction Questionnaire status/change; SG, sensor glucose; TAR, time above range; TBR, time below range; TIR, time in range.

^aNoninferiority tested with noninferiority met.

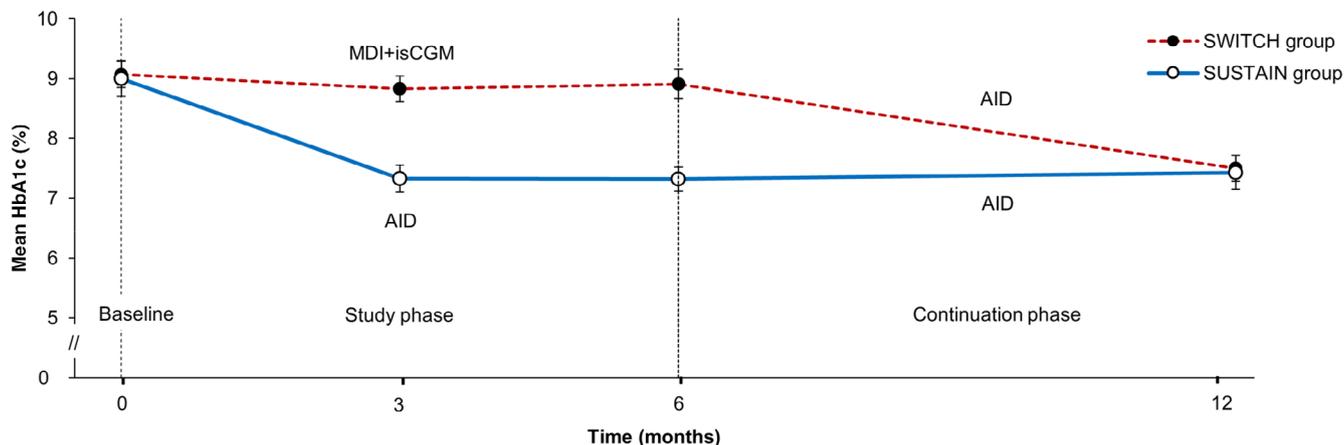


FIGURE 3 Mean glycated haemoglobin (HbA1c) throughout the study and continuation phases in the SWITCH and SUSTAIN groups. Error bars represent 95% confidence intervals. Figure shows all available data. AID, automated insulin delivery; isCGM, intermittently scanned continuous glucose monitoring; MDI, multiple daily injections.

CI -16.0 to -0.5]; $P = 0.03$), DQoL (mean change in total score of 5.0 [95% CI 1.5 to 10.5]; $P = 0.007$), DTSQ status (DTSQs; mean change in treatment satisfaction of 8.0 [95% CI 4.4 to 11.6]; $P < 0.001$), and DTSQ change (DTSQc; mean change in treatment satisfaction of 9.0 [95% CI 5.2 to 12.9]; $P < 0.001$). In the SUSTAIN group, the DTSQc treatment satisfaction change increased from 6 to 12 months by 1.4 (95% CI 0.3 to 2.4). No other significant changes between 6 and 12 months in patient-reported outcomes in the SUSTAIN group were observed. All patient-reported outcome data can be found in Table 2.

3.4 | Safety

Three severe hypoglycaemic episodes occurred in two participants in the SWITCH group during the continuation phase while receiving treatment with the AID system, two of which were classified as serious adverse events. In one patient, both severe hypoglycaemic episodes occurred due to incorrect use of the cannula fill function on the pump. In these cases, the participant used the pump feature that is intended for filling the cannula with insulin when initiating a new infusion set in order to administer a bolus that is not factored into the AID algorithm. No cause was determined for the third severe hypoglycaemic episode. No severe hypoglycaemic episodes occurred in the SUSTAIN group during the continuation phase. No DKA, serious adverse events, serious adverse device effects, nor unanticipated serious adverse device effects were reported during the continuation phase.

4 | DISCUSSION

The continuation phase of the ADAPT trial reproduced the results observed during the study phase,⁹ demonstrating that, in people with type 1 diabetes using MDI+isCGM therapy and experiencing suboptimal glycaemic control, switching to the AID system significantly improved HbA1c, with a -1.4% reduction from 8.9% (74 mmol/mol) to 7.5% (59 mmol/mol), and increased TIR by 28.1% from 43.6% to 70.7% . Switching to AID from MDI+isCGM increased the proportion of participants achieving the recommended glycaemic targets of HbA1c $<7\%$ and $>70\%$ TIR¹⁵ from 6.5% to 60.6% and from 0% to 15.6% , respectively. Additionally, the continuation phase data confirmed the sustained efficacy of the AID system up to 12 months, with no change in HbA1c (from 7.3% to 7.4% [56 to 57 mmol/mol]) nor proportion of time spent in range (from 70.4% to 69.7%) between the study phase and the continuation phase in those participants randomized at baseline to receive AID treatment. Importantly, the observed sustained glycaemic outcomes were achieved in a setting consistent with clinical practice, in which participants had only one in-clinic follow-up visit during the 6 -month continuation phase at 9 months (in addition to an end-of-study visit at 12 months to return study materials). The results of the ADAPT continuation phase corroborate previously observed glycaemic control benefits of the MiniMed™ 780G AID system in clinical trials^{6,16–18} and real-world settings,^{19–23}

and up to 1 year after initiation,¹⁷ demonstrating that the AID system can provide sustained benefits to people living with type 1 diabetes. Such sustained improvements in glycaemic control represent clinically meaningful changes¹⁵ that could profoundly reduce the risks of long-term cardiovascular and microvascular damage associated with type 1 diabetes.^{24,25}

The patient-reported outcome data also support the overall benefits of the AID system. Participants in the SWITCH group reported reduced fear and perceived frequency of hypo- and hyperglycaemia, were generally more satisfied with their diabetes treatment, and had improved quality of life after having used the AID system for 6 months. Furthermore, previously reported improvements seen at 6 months in the SUSTAIN group were maintained at 12 months.⁹ This adds to the growing evidence that beginning diabetes treatment with an AID system, switching from either MDI or previous generations of pump therapies, is not prohibitively burdensome and provides improvements to the user's daily experience with diabetes.^{26–28}

Patient satisfaction with the system was also reflected in the attrition rates, which mimicked those seen in the study phase. Of the 41 participants randomized to receive AID, five dropped out during the study phase (12% attrition).⁹ In comparison, in the continuation phase, seven of the 39 participants who switched from MDI+isCGM to AID dropped out (18% attrition). Importantly, only one of the 36 SUSTAIN group participants dropped out during the continuation phase, signifying sustained, long-term satisfaction with system use.

It can be noted that, while there were significant improvements in glycaemic outcomes with AID therapy, mean HbA1c remained greater than the recommended target of $<7\%$.¹⁵ However, previous studies show that people with type 1 diabetes consistently achieve HbA1c levels $<7\%$ with this AID system,¹⁶ and these data indicate the need for enhanced education for the studied population, especially regarding pump settings and CGM usage. In fact, only six (17.6%) of the SWITCH participants and 11 (30.6%) of the SUSTAIN participants used the recommended glucose target of 100 mg/dL (5.6 mmol/L) and active insulin time of 2 hours for at least 95% of the time, and these settings have been shown to be significant predictors of better glucose control.²⁰ Furthermore, SWITCH group participants spent only 77.1% of time in automation in the continuation phase, compared to the 95.8% in the SUSTAIN group during their first 6 months of system use (study phase), which may be attributable to the lower CGM sensor usage time in this group (79.0%). While study visits and training sessions were identical between treatment arms when starting the AID system, these results emphasize the need for adequate and recurrent training on pump settings and CGM use for optimal results.²⁹

While the mean TIR was unchanged in the SUSTAIN group between 6 and 12 months, the achievement rate of $>70\%$ TIR was lower in the SUSTAIN group at 12 months compared to 6 months (44.4% vs. 52.8%). This decline was not statistically significant ($P = 0.169$), with the mean TIR (69.7% at 12 months) being nearly equivalent to the 70% target threshold. Indeed, sensitivity analyses indicated that 50.0% of participants achieved $>69\%$ TIR during the continuation phase (Figure S3). It can thus be concluded that

achievement of glycaemic control remained stable in the SUSTAIN group between 6 and 12 months of AID use.

In general, the reported safety events were relatively low during the continuation phase, with no reported DKA events nor serious adverse device effects. In the 12-month follow-up period, no severe hypoglycaemic events occurred in the SUSTAIN group. However, three severe hypoglycaemic events occurred during the continuation phase, all occurring in the SWITCH group, as compared to no such events occurring during the study phase in either treatment arm. With the cause of two of these three severe hypoglycaemic episodes being the incorrect use of the cannula fill function, these findings highlight the importance of patient education surrounding infusion set changes and setup.

Analysis and interpretation of the continuation phase data is inherently limited by the lack of an independent control group for direct comparison and because the study was not specifically powered for the continuation phase. However, participants switching from MDI+isCGM to AID therapy served as their own controls and confirmed the benefits of the AID system in this population with significant, clinically meaningful improvements to diabetes treatment outcomes. Additionally, data presented here were only from participants on MDI and isCGM starting with the AID system, rather than those on MDI and real-time CGM, which may be more representative of standard of care in some geographical regions. Results from this cohort (MDI+ real-time CGM users) of the ADAPT study are presented elsewhere.³⁰ The ADAPT study is strengthened by its testing of a representative sample of people with diabetes who are engaged with MDI+isCGM therapy yet experiencing suboptimal glucose control. Furthermore, the study design (randomized control trial), duration, and primary outcome (HbA1c) ensure robust and relevant results that can be readily translated into clinical practice.

In summary, the continuation phase of the ADAPT study reproduced the glucose control benefits of the AID system versus MDI +isCGM previously seen in the study phase and revealed the sustained efficacy of the AID system after 12 months of use without meaningful attrition nor reduced treatment satisfaction. Furthermore, these benefits were observed after 6 months of AID use, regardless of beginning AID immediately after randomization or 6 months later, suggesting that a lengthy observation period using a therapy providing suboptimal glucose control is not necessary before beginning AID therapy. Taken together, the ADAPT study data indicate that AID therapy should be considered early on for people with type 1 diabetes on MDI therapy with suboptimal glucose control.

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AUTHOR CONTRIBUTIONS

JC, RR, JC, SDP, LV, JS, OC were involved in study design, PC, RK, WK, JK, CT and ME were trial investigators, JC performed Statistical analysis of study data, All authors were involved in data interpretation and the preparation and critical review of the first and all subsequent drafts of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Pratik Choudhary has received consulting fees from Medtronic, Dexcom, Insulet Corporation, Abbott Diabetes, Lilly Diabetes, and Sanofi; honoraria or payment for lectures, presentations, speaker bureaus, manuscript writing, and educational events from Novo Nordisk, Medtronic, Insulet Corporation, Lilly Diabetes, Sanofi Diabetes, and Glooko; payment for expert testimony and support for travel and attending meetings from Abbott Diabetes; participation on Data Safety Monitoring Boards or Advisory Boards for Medtronic; is the Chair of the Diabetes Technology Network-UK and the Lead for Type 1 Diabetes Midlands UK; was supported by NIHR Wellcome Trust clinical Research facility at King's College Hospital and the NIHR patient recruitment centre at University Hospitals Leicester, UK. Winfried Keuthage has received speaker fees from Medtronic and support for travel and attending ADAPT study meetings from Medtronic. Jens Kroeger has received payment and honoraria for lectures and presentations from Abbott, Dexcom, Medtronic, Astra Zeneca, Novo Nordisk, Lilly, Sanofi Aventis, Berlin Chemie, MSD, Boehringer Ingelheim, and Insulet Corporation; support for travel and attending meetings from Abbott, Dexcom, Medtronic, Novo Nordisk, Lilly, Sanofi Aventis, Berlin Chemie, MSD, and Boehringer Ingelheim; has participated in Data Safety Monitoring or Advisory Boards for Abbott, Dexcom, Insulet Corporation, Astra Zeneca and Novo Nordisk; and is the head of German Diabetes Aid. Charles Thivolet has received consulting fees from Medtronic Insulet Corporation and Sanofi; payment and honoraria for lectures, presentations, speaker bureaus, manuscript writing, and educational events from Novo Nordisk and Lilly; and support for travel and attending meetings from Abbott and Sanofi. Mark Evans has received grants for his participation in the HypoRESOLVE and INNODIA consortiums (from EU, charity and industry collaborator, including Medtronic for the HypoRESOLVE consortium); has received consulting fees from Medtronic, Dexcom, Novo Nordisk, Abbott

Diabetes Care, and Zucara Therapeutics; has consulted for Pila Pharma; has received payment and honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Medtronic, Novo Nordisk, Dexcom, Ypsomed, Abbott Diabetes Care, and Eli Lilly; has participated in Data Safety Monitoring Boards for the TACTIC E platform study and the HARP DOC study; is the chair of the advisory panel on driving and diabetes for the UK Government Department of Transport; and was supported by the NIHR Cambridge Biomedical Research Centre. The University of Cambridge has received salary support for ME from the National Health Service in the East of England through the Clinical Academic Reserve. Shannon N. Edd, Javier Castañeda, Roseline Ré, Jessica Cellot, Simona de Portu, Linda Vorrink, John Shin, Tim van den Heuvel, and Ohad Cohen are current employees and shareholders of Medtronic. Ralf Kolassa declares no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing requests by researchers who provide a methodologically sound proposal will be considered and should be addressed to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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