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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 injection plus intermittent scanning glucose monitoring (MDI+isCGM) in people with type 1 diabetes not meeting glucose targets.

Methods: The ADAPT study was a prospective, multi-center, open-label, randomized control trial in people with type 1 diabetes, with an HbA1c of at least 8%, 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 non-inferiority in the SUSTAIN group (ClinicalTrials.gov: NCT04235504).

Results: 39 SWITCH and 36 SUSTAIN participants entered the continuation phase. In the SWITCH group, HbA1c was significantly decreased by -1.4% (95% CI: -1.7 to -1.1%; p<0.001) from a mean±SD of 8.9±0.8% (73.9±8.6 mmol/mol) at 6 months to 7.5±0.6% (58.5±6.9 mmol/mol) at 12 months. Mean HbA1c increased by 0.1% (CI: -0.05 to +0.25%) from 7.3±0.6% (56.5±6.7 mmol/mol) to 7.4±0.8% (57.7±9.1 mmol/mol) in the SUSTAIN group, meeting non-inferiority criteria. Three severe hypoglycemia events occurred in two SWITCH participants during the continuation phase.

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

Background

In the care 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 favorable glycemic control compared to multiple daily injection 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 multiple daily injection (MDI) therapy and self-monitoring blood glucose (SMBG) or intermittent scanning continuous glucose monitoring (CGM) before progressing to MDI therapy with real-time 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 to support 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 multiple daily injections (MDI) with intermittent scanning continuous glucose monitoring (isCGM)[7].

Therefore, 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 (HbA1c≥8%)[8]. The primary results of the ADAPT trial showed that the AID system safely provided a 1.4% reduction in HbA1c and a 26.7% increase in time in range (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 intermittent scanning CGM (MDI+isCGM) therapy.[9] As such, these data suggest

the use of the AID system earlier in the treatment pathway for type 1 diabetes, 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 in 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 aim of the continuation phase of the ADAPT study was two-fold: (1) to test if improvements in glycemic control observed in the main study phase were reproduced in the SWITCH group, and (2) to confirm long-term sustained glycemic control benefits of AID therapy up to 12 months in the SUSTAIN group.

Methods

Study design and participants

Details of the ADAPT parallel randomized control 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 control trial. Eligible participants had an HbA1c at baseline of at least 8.0% (64 mmol/mol) and were diagnosed with type 1 diabetes at least two years, had been on multiple daily injection (MDI) therapy for at least two years, and were using isCGM for at least three 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, DPP-4 inhibitor, GLP- 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 six-month continuation phase (Figure 1). During the two-week run-in phase, baseline sensor glucose data were recorded using the Guardian Link 3 transmitter (data recorder only) with the Guardian Sensor 3 (Medtronic, CA, USA), while participants continued with their MDI therapy. Participants who demonstrated tolerance to continuous wear of the CGM and compliance with study procedures were 1:1 randomized (investigator-blinded, block randomization procedure, conducted electronically) to either continue with MDI+isCGM (control arm) therapy 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, CA, USA). 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 hypoglycemia 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 UK (N=4 sites). The study was

conducted in accordance with the Declaration of Helsinki, good clinical practice, and local legislation. Competent authority and ethics committee approvals were obtained for all study sites.

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 non-inferiority test where the upper limit of the confidence interval for the mean change was compared to the non-inferiority 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 include CGM-based metrics of glycemic 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 sensor glucose (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[11,12], Diabetes Treatment Satisfaction Questionnaire[13], and the Hypoglycaemic Fear Survey[14]. The statistical analyses of within-group changes in continuous endpoints used paired t-tests and 95% confidence intervals (95%CI) in cases where the normality assumption was met, otherwise endpoints were reported as median and 95%CI (estimated using Hodges-Lehmann method) and compared using a Wilcoxon signed rank test. Non-

inferiority test margins were set at 6% for time in range (TIR; 70-180 mg/dL (3.9-10.0 mmol/L)) and time above range (TAR; >180 mg/dL (10.0 mmol/L) and >250mg/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 α=0.05 until a first non-statistically significant results was observed: 1. Change in HbA1c; Percentage of 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 (3.9-10.0 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 Supplemental Materials. 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 hypoglycemia, diabetic ketoacidosis (DKA), serious adverse events, serious adverse device effects, and unanticipated serious adverse device effects.

Study registration is available on ClinicalTrials.gov, NCT04235504.

Results

Baseline demographics

Of the 105 patients assessed for eligibility, 82 participants 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 presented[9]) and for 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 due to withdrawal by the subject, one due to physician decision, and one due to adverse event. From the SUSTAIN group, one subject withdrew themselves from the study during the continuation phase.

HbA1c

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) compared to at 6 months (Figure 3), from a mean±SD of 8.9±0.8% (73.9±8.6 mmol/mol) to 7.5±0.6% (58.5±6.9 mmol/mol) (Table 2). Mean HbA1c increased by 0.1% (CI: -0.05 to 0.25) from 7.3±0.6% (56.5±6.7 mmol/mol) at 6 months to 7.4±0.8% (57.7±9.1 mmol/mol) at 12 months in the SUSTAIN group, meeting the non-inferiority criteria (+0.3%).

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

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

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 (CI:22.8 to 33.4)% (p<0.001) in the SWITCH group from 6 to 12 months, whereas TAR (above 180 mg/dL) significantly decreased by -27.2 (CI: -32.9 to -21.6%; p<0.001). In the same group, time in TBR (below 70 mg/dL (3.9 mmol/L)) was unchanged from 6 to 12 months, meeting non-inferiority (-0.5 (CI: -1.5 to 0.1)%). From 6 to 12 months, mean sensor glucose and standard deviation of sensor

glucose both significantly decreased in the SWITCH group (p<0.001). In the SUSTAIN group, all glycemic control endpoints met non-inferiority 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±SD percentage sensor use was 79.0±24.7%. The SUSTAIN group had a percentage sensor use of 88.8±9.8% during the continuation phase as compared to 92.2±4.2% during the study phase. During the continuation phase, participants in the SWITCH group spent 77.1±24.1% time in automation, whereas SUSTAIN group participants spent 95.8±3.4% time in automation during the study phase and 93.7±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 (55.9%) participants used a mixture of glucose targets. Ten (29.4%) SWITCH group participants selected an active insulin time of 2 hours, and 5 (14.7%) selected 2-3 hours, for at least 95% of the continuation phase; the remaining 19 (55.9%) participants 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 8 (22.2%) participants selected the glucose target of 120 mg/dL (6.7 mmol/L), for at least 95% of the continuation phase; the remaining 7 (19.4%) participants used a mixture of glucose targets. Nineteen (52.8%) SWITCH group participants selected an active insulin time of 2 hours, 11 (30.6%) selected 2-3 hours, and 2 (5.6%) selected 3-4 hours, for at least 95% of the continuation phase. The remaining 4 (11.1%) participants used a mixture of active insulin times.

Mean±SD number of SMBG readings per day was 3.5±0.9 for the SWITCH group during the continuation phase; in the SUSTAIN group, 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 (CI: 1.20 to 4.40) kg in

the SWITCH group and 0.55 (-0.25 to 1.50) kg in the SUSTAIN group. Total daily insulin dose (TDD) delivered by the pump was 47.7±16.1 units in the SWITCH group during the continuation phase. TDD in the SUSTAIN group was 54.6±21.8 units in the study phase and 54.3±22.5 units in the continuation phase, with no TDD change between the study phases (-0.3 (CI: -2.1 to 1.5) units).

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 2 (6.5%) participants during the study phase. Thirty (90.9%) of the SWITCH participants achieved <4% TBR (<70 mg/dL (<3.9 mmol/L)) during the continuation phase, compared to 24 (77.4%) participants in the study phase. In the SUSTAIN group during the continuation phase, 16 (44.4%) participants achieved >70% TIR and 33 (91.7%) achieved <4% TBR, compared to 19 (52.8%) achieving <70% TIR and 30 (83.3%) participants achieving <4% TBR during the study phase. In the SWITCH group, patient reported outcomes significantly improved from 6 to 12 months in Hypoglycemia Fear Survey (mean change in total score of -6.5 (CI: -16.0 to -0.5); p=0.03), DQoL (mean change in total score of 5.0 (CI: 1.5 to 10.5); p=0.007), DTSQ status (DTSQs, mean change in treatment satisfaction of 8.0 (CI: 4.4 to 11.6); p<0.001), and DTSQ change (DTSQc, mean change in treatment satisfaction of 9.0 (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 (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.

Safety

Three severe hypoglycemic 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 hypoglycemic 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 hypoglycemic episode. No severe hypoglycemic episodes occurred in the SUSTAIN group during the continuation phase. No diabetic ketoacidosis (DKA), serious adverse events, serious adverse device effects, nor unanticipated serious adverse device effects were reported during the continuation phase.

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 glycemic 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 glycemic targets of HbA1c<7% and >70% TIR[15] 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 glycemic 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 glycemic control benefits of the MiniMed™ 780G AID system in clinical trials[6,16-18] and real-world settings[19-23], and up to one year after initiation[17], demonstrating that the AID system can provide sustained benefits to people living with type 1 diabetes. Such sustained improvements in glycemic control represent clinically meaningful changes[15] 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 a reduced fear and perceived frequency of hypo- and hyperglycemia, 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 users' daily experiences with diabetes[26-28].

Patient satisfaction with the system was reflected also 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, 7 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 glycemic 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<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 6 (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% time in automation in the continuation phase, compared to the 95.8% seen in the SUSTAIN group during their first six 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 (see Supplemental Materials, Figure S3). It can thus be concluded that achievement of glycemic control remained stable in the SUSTAIN group from 6 to 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 hypoglycemic events occurred in the SUSTAIN group. However, three severe hypoglycemic 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 hypoglycemic 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 control 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 AID system, rather than on MDI and real-time CGM, which may be more representative of standard of care in some geographies. 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 over 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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Tables and Figures

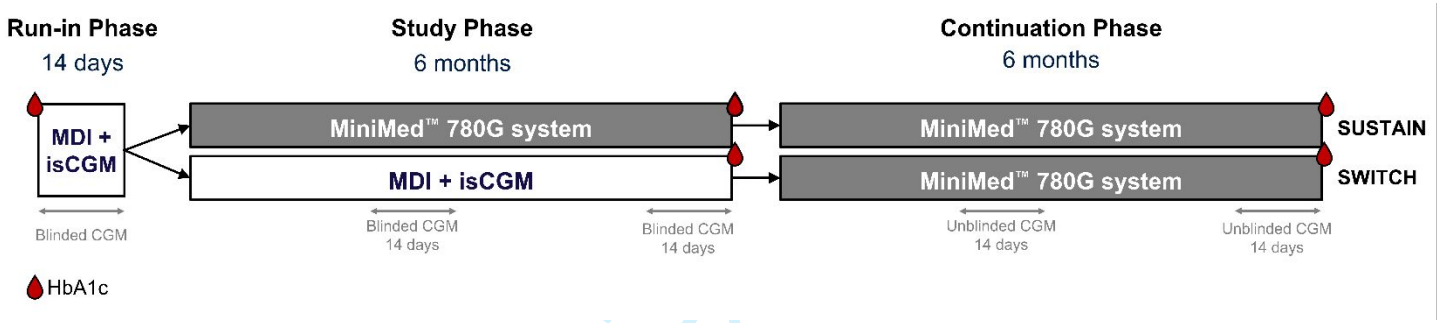

Figure 1: Study design consisting of a run-in, study, and continuation phases.

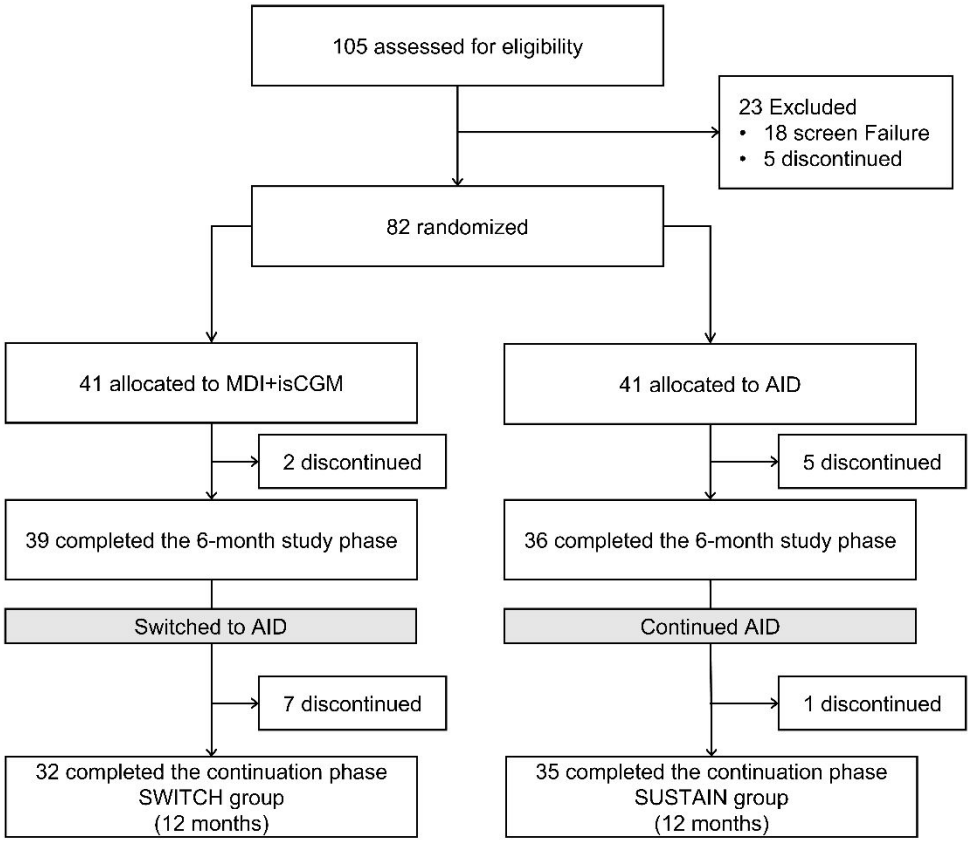

Figure 2: Flowchart of study inclusion. MDI+isCGM: multiple daily injection + intermittently scanned continuous glucose monitoring. AID: automated insulin delivery.

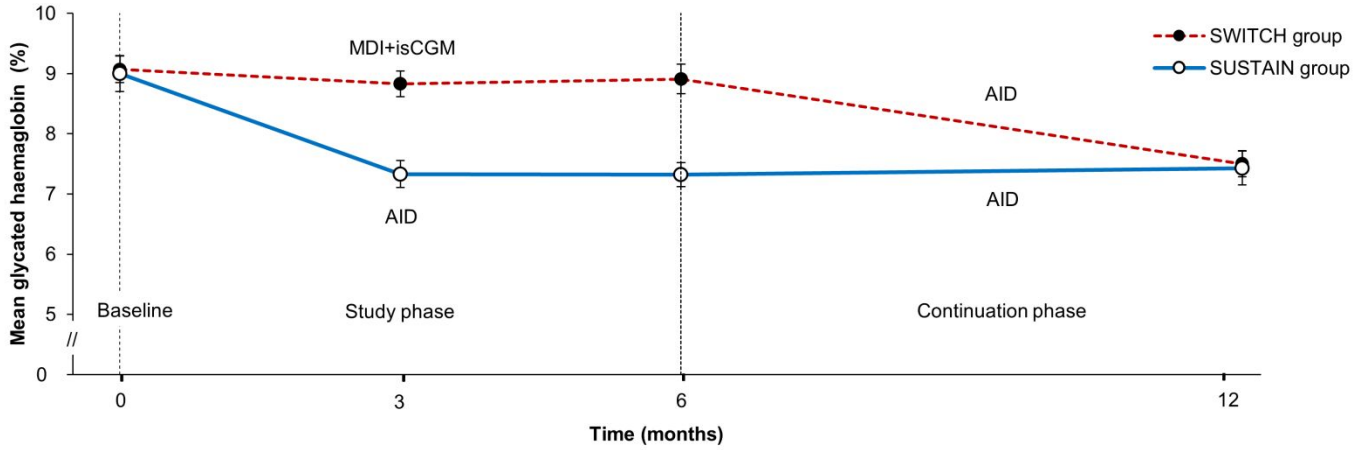

Figure 3: Mean HbA1c throughout study and continuation phases in SWITCH and SUSTAIN groups. Error bars represent 95% CIs. MDI+isCGM: multiple daily injection + intermittently scanned continuous glucose monitoring. AID: automated insulin delivery. Figure shows all available data.

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†	79.9 ± 15.1	79.7 ± 14.1‡	81.4 ± 14.6
BMI, kg/m²	25.8 ± 4.92†	27.0 ± 4.4	26.1 ± 4.9‡	27.3 ± 4.4
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††	54.3 ± 25.9	53.2 ± 22.6	56.0 ± 26.2
Sensor readings, %	87.3 ± 16.2†	90.1 ± 8.8††	87.6 ± 16.3§	90.8 ± 8.5¶
isCGM scans in the previous month, n per day	9.0 ± 5.2†	8.8 ± 7.4	9.1 ± 5.25§	8.8 ± 7.5

Values reported as mean ± SD unless otherwise noted

† n=39; ‡ n=37; § n=38; ¶ n=35; †† n=40

Table 2: Continuation phase glycemic control and patient reported outcomes in SWITCH and SUSTAIN groups

	SWITCH group (switched to AID)			**SUSTAIN group (remained on AID)**		
Outcome	**Study phase 6 months** Mean ± SD	**Continuation phase 12 months** Mean ± SD	**Estimate of change (95% CI; p)**	**Study phase 6 months** Mean ± SD	**Continuation phase 12 months** Mean ± SD)	**Estimate of change (95% CI)**
	N	N	N	N	N	N
HbA1C, %	8.9 ± 0.8	7.5 ± 0.6	-1.4 (-1.7 to -1.1; <0.001)	7.3 ± 0.6	7.4 ± 0.8	0.1 (-0.1 to 0.25)*
	38	32	31	36	34	33
TIR 70-180 mg/dL, %	43.6 ± 15.4	70.7 ± 9.5	28.1 (22.8 to 33.4; <0.001)	70.4 ± 9.9	69.7 ± 9.0	-0.7 (-2.1 to 0.7)*
	31	33	28	36	36	36
TAR >180 mg/dL, %	53.8 ± 16.5	27.6 ± 9.5	-27.2 (-32.9 to 21.6; <0.001)	27.1 ± 10.4	28.0 ± 9.6	0.9 (-0.5 to 2.3)*
	31	33	28	36	36	36
TAR >250 mg/dL, %	22.5 ± 13.2	6.6 ± 4.3	-16.6 (-21.7 to -11.6; <0.001)	6.7 ± 4.6	7.2 ± 4.9	0.5 (0.0 to 1.1)*
	31	33	28	36	36	36

TBR <70 mg/dL, %	2.6 ± 2.5	1.8 ± 1.4	-0.5 (-1.5 to 0.1; 0.135)*	2.5 ± 1.9	2.3 ± 1.9	-0.2 (-0.7 to 0.2)*
	31	33	28	36	36	36
TBR <54 mg/dL, %	0.7 ± 1.2	0.4 ± 0.4	-0.2 (-0.4 to 0.0; 0.060)*	0.6 ± 0.6	0.5 ± 0.5	-0.1 (-0.2 to 0.0)*
	31	33	28	36	36	36
Mean sensor glucose, mg/dL	194.7 ± 29.5	155.0 ± 13.8	-41.4 (-51.7 to -31.0; <0.001)	152.7 ± 16.0	154.4 ± 15.6	1.76 (-0.4 to 3.9)
	31	33	28	36	36	36
Standard deviation of SG, mg/dl	69.4 ± 12.8	53.8 ± 8.7	-14.7 (20.7 to -10.9; <0.001)	54.8 ± 9.8	56.0 ± 10.0	1.3 (-0.2 to 2.8)
	31	33	28	36	36	36
Hypoglycemia Fear						
Total score	47.4 ± 22.9	35.3 ± 23.8	-6.5 (-16.0 to -0.5; 0.031)	35.7 ± 23.4	29.7 ± 20.8	-4.1 (-9.4 to 1.2)
	39	32	32	35	34	33
Behavior	21.8 ± 8.6	16.3 ± 10.1	-4.0 (-7.5 to -0.5; 0.016)	15.8 ± 9.5	12.9 ± 8.9	-2.3 (-4.8 to 0.3)

	39	32	32	35	35	34
Worry	25.6 ± 16.0	18.9 ± 15.2	-2.5 (-11.0 to 1.0; 0.173)	19.9 ± 15.3	17.1 ± 13.7	-2.0 (-4.5 to 0.0)
	39	32	32	35	34	33
DQoL						
Total score	66.4 ± 14.3	75.2 ± 10.6	5.0 (1.5 to 10.5; 0.007)	68.2 ± 16.8	71.3 ± 17.5	2.3 (-2.0 to 6.5)
	25	22	22	24	25	24
Treatment satisfaction score	59.3 ± 20.6	76.0 ± 14.5	15.0 (5.1 to 24.9; 0.005)	68.0 ± 21.9	74.0 ± 19.5	4.0 (0.0 to 10.0)
	25	22	22	24	25	24
Treatment impact score	60.0 ± 13.8	66.4 ± 9.0	2.5 (-1.5 to 8.0; 0.306)	62.6 ± 11.8	65.5 ± 14.7	2.1 (-2.0 to 6.2)
	25	22	22	24	25	24
Social worry score	79.3 ± 16.4	84.0 ± 14.2	1.1 (-4.1 to 6.2; 0.6725)	77.3 ± 21.3	79.0 ± 22.6	1.6 (-3.4 to 6.4)
	22	22	20	24	23	22
Diabetes worry score	67.5 ± 19.4	74.5 ± 14.9	6.0 (0.0 to 9.5; 0.1028)	64.5 ± 22.4	68.6 ± 24.7	3.3 (-5.9 to 12.5)
	24	22	21	24	23	22

General well-being score	50.8 ± 24.0	58.9 ± 21.0	0.0 (0.0 to 17.0; 0.063)	50.0 ± 20.2	44.4 ± 25.6	0.0 (0.0 to 0.0)
	25	21	21	22	24	21
DTSQs						
Treatment satisfaction	21.9 ± 7.5	29.9 ± 5.7	8.0 (4.4 to 11.6; <0.001)	29.7 ± 5.8	31.6 ± 4.7	1.5 (-0.04 to 3.1)
	39	32	32	35	34	33
Frequency of hyperglycemia	3.9 ± 1.3	2.1 ± 1.2	-1.8 (-2.5 to -1.1; <0.001)	2.3 ± 1.4	2.1 ± 1.5	-0.2 (-0.7 to 0.4)
	39	32	32	35	35	34
Frequency of hypoglycemia	2.8 ± 1.3	1.9 ± 1.3	-0.9 (-1.6 to -0.1; 0.021)	2.3 ± 1.5	2.3 ± 1.4	0.0 (-0.5 to 1.0)
	39	32	32	35	35	34
DTSQc						
Treatment satisfaction change	3.7 ± 7.2	12.9 ± 6.4	9.0 (5.2 to 12.9; <0.001)	13.7 ± 4.4	15.4 ± 3.6	1.4 (0.3 to 2.4)
	38	32	31	35	35	34
Frequency of hyperglycemia change	0.8 ± 1.4	-1.3 ± 1.5	-2.2 (-2.9 to -1.5; <0.001)	-1.1 ± 1.8	-1.2 ± 1.9	0.0 (-0.5 to 1.0)
	38	32	31	35	35	34

Frequency of hypoglycemia change	0.1 ± 1.3	-0.7 ± 1.7	-0.7 (-1.6 to 0.2; 0.102)	-0.5 ± 1.8	-0.7 ± 1.8	0.0 (-0.5 to 0.5)
	38	32	31	35	35	34

* non-inferiority tested with non-inferiority met

TIR: Time in Range, TAR: Time Above Range, TBR: Time Below Range, DQoL: Quality of Life Questionnaire, DTSQs/c: Diabetes Treatment Satisfaction Questionnaire status/change

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

Supplemental materials

Statistical testing sequence

Hierarchical test procedure for SWITCH group

The following hierarchical test procedure reflects the relative importance of the endpoints and controls for multiplicity.

Fixed sequential testing of primary and selected secondary endpoints

For the following endpoints, the procedure test hierarchically the ordered hypotheses in sequence at level $\alpha=0.05$ until a first hypothesis is non-rejected.

Primary endpoint

1. Change in HbA1c

    Change in HbA1c will be tested for superiority and a p-value < 0.05 will be considered statistically significant. If p-value < 0.05, continue to next test, else stop.

Secondary endpoints

2. Percentage of time spent in hyperglycemic range with SG > 250 mg/dL

    Non-inferiority test with non-inferiority margin of 6%, if p-value < 0.05 reject null hypothesis and continue, else stop

3. Percentage of time spent in hyperglycemic range with SG > 250 mg/dL

    Superiority test, if p-value<0.05 reject null hypothesis and continue, else stop

4. Percentage of time spent in hyperglycemic range with SG > 180 mg/dL

Non-inferiority test with non-inferiority margin of 6%, if p-value < 0.05 reject null hypothesis and continue, else stop

5. Percentage of time spent in hyperglycemic range with SG > 180 mg/dL

Superiority test, if p-value<0.05 reject null hypothesis and continue, else stop

6. Percentage of time spent within range 70 - 180 mg/dL

Non-inferiority test with non-inferiority margin of 6%, if p-value<0.05 reject null hypothesis and continue, else stop

7. Percentage of time spent within range 70 - 180 mg/dL

Superiority test, if p-value<0.05 reject null hypothesis and continue, else stop

8. Percentage of time spent in hypoglycemic range with SG < 54 mg/dL

Non-inferiority test with non-inferiority margin of 2 %, if p-value < 0.05 reject null hypothesis and continue, else stop

9. Percentage of time spent in hypoglycemic range with SG < 70 mg/dL

Non-inferiority test with non-inferiority margin of 5 %, if p-value < 0.05 reject null hypothesis and continue, else stop

Additional analysis

Superiority test for percentage of time spent in hypoglycemic range with SG < 54 mg/dL, < 70 mg/dL and analyses on ancillary endpoints and safety endpoints may be performed, and p-values will be reported but may not be claimed.

Hierarchical test procedure for SUSTAIN group

The following hierarchical test procedure reflects the relative importance of the endpoints and controls for multiplicity.

Fixed sequential testing of primary and selected secondary endpoints

For the following endpoints, the procedure test hierarchically the ordered hypotheses in sequence at level α=0.05 until a first hypothesis is non-rejected.

Primary endpoint

1. Change in HbA1c

    Change in HbA1c will be tested using a non-inferiority test with margin of 0.3% and a p-value < 0.05 will be considered statistically significant. If p-value < 0.05, continue to next test, else stop.

Secondary endpoints

2. Percentage of time spent in hyperglycemic range with SG > 250 mg/dL

    Non-inferiority test with non-inferiority margin of 6%, if p-value < 0.05 reject null hypothesis and continue, else stop

3. Percentage of time spent in hyperglycemic range with SG > 180 mg/dL

    Non-inferiority test with non-inferiority margin of 6%, if p-value < 0.05 reject null hypothesis and continue, else stop

4. Percentage of time spent within range 70 - 180 mg/dL

    Non-inferiority test with non-inferiority margin of 6%, if p-value<0.05 reject null hypothesis and continue, else stop

5. Percentage of time spent in hypoglycemic range with SG < 54 mg/dL

Non-inferiority test with non-inferiority margin of 2 %, if p-value < 0.05 reject null hypothesis and continue, else stop

6. Percentage of time spent in hypoglycemic range with SG < 70 mg/dL

Non-inferiority test with non-inferiority margin of 5 %, if p-value < 0.05 reject null hypothesis and continue, else stop

Additional analysis

Analyses on ancillary endpoints and safety endpoints may be performed, and p-values will be reported but may not be claimed.

Achievement rate sensitivity analyses

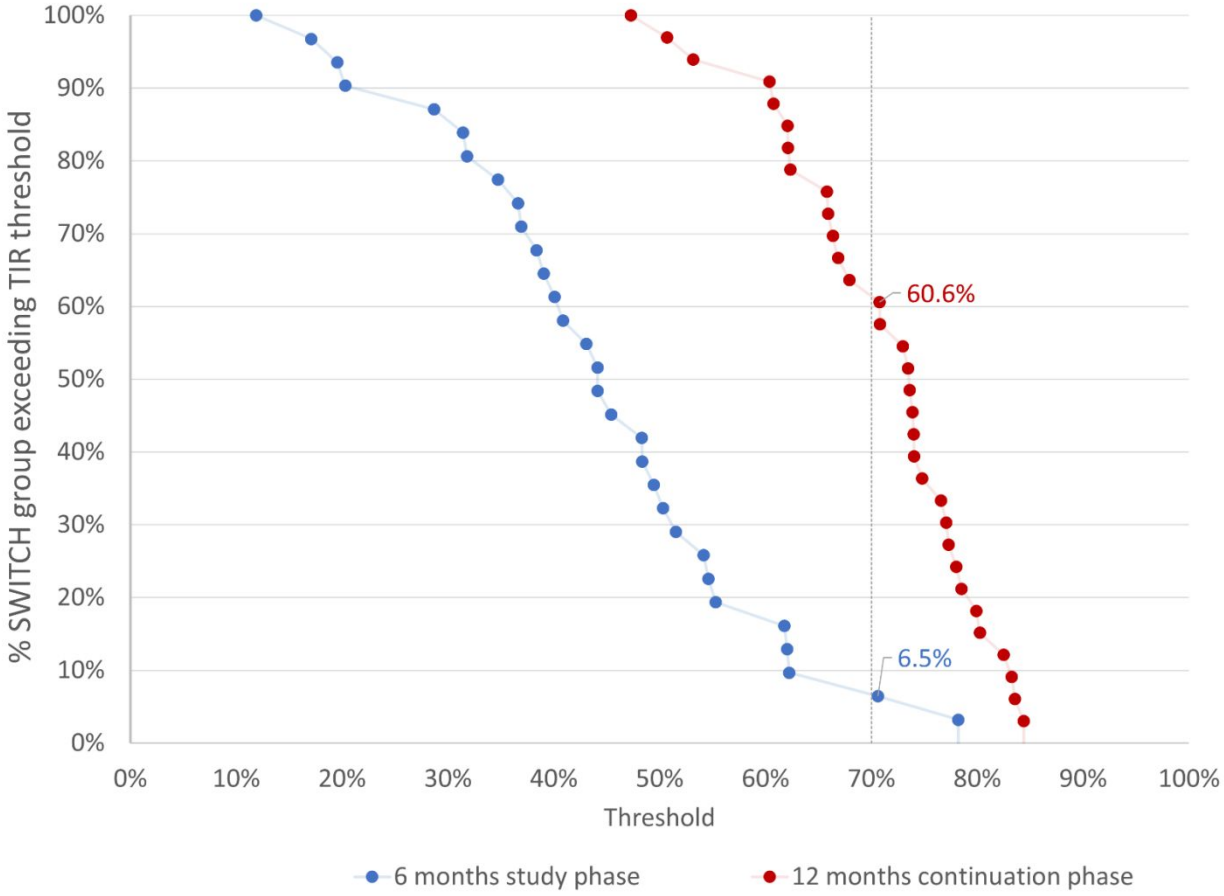

Figure S1: Percentage of SWITCH group participants exceeding a given time in 70-180 mg/dL range (TIR) threshold

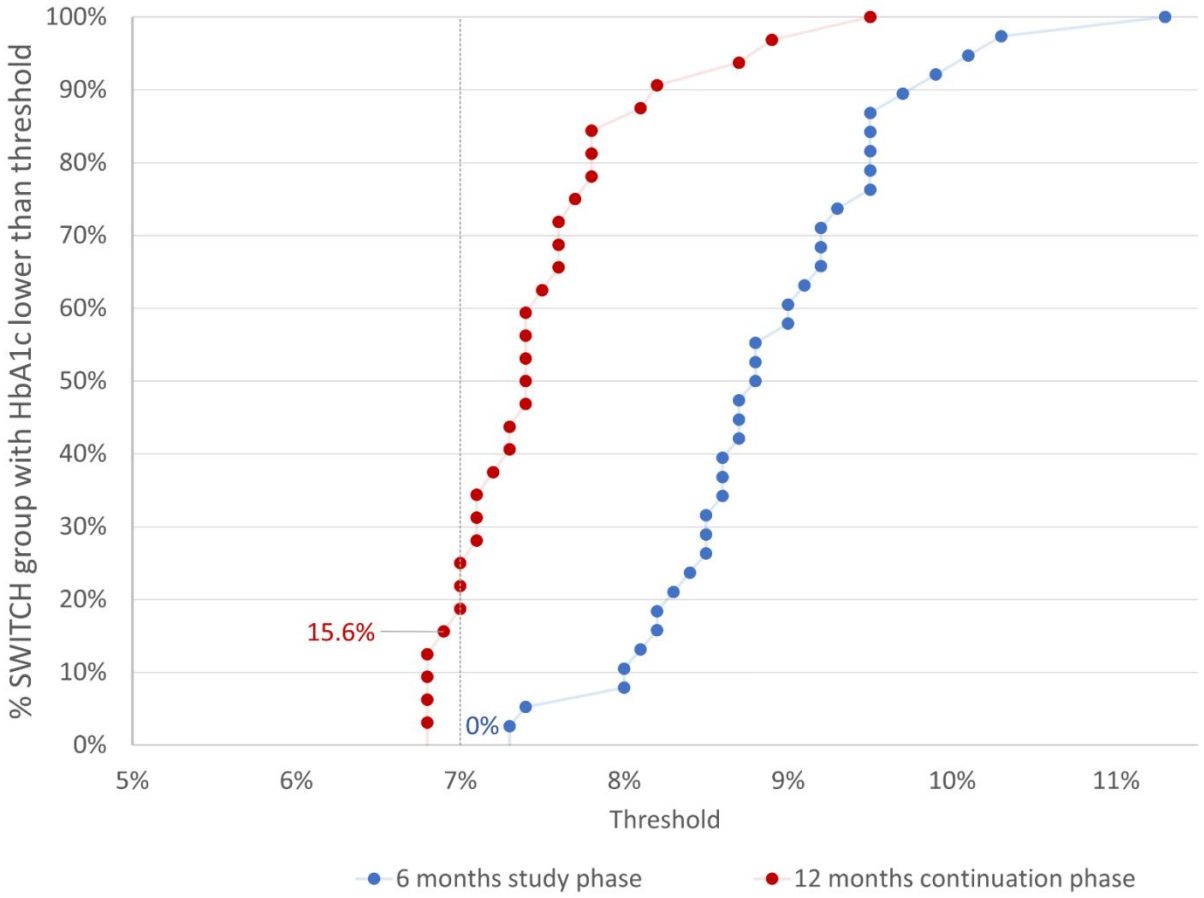

Figure S2: Cumulative distribution of SWITCH group participants achieving an HbA1c lower than a given threshold

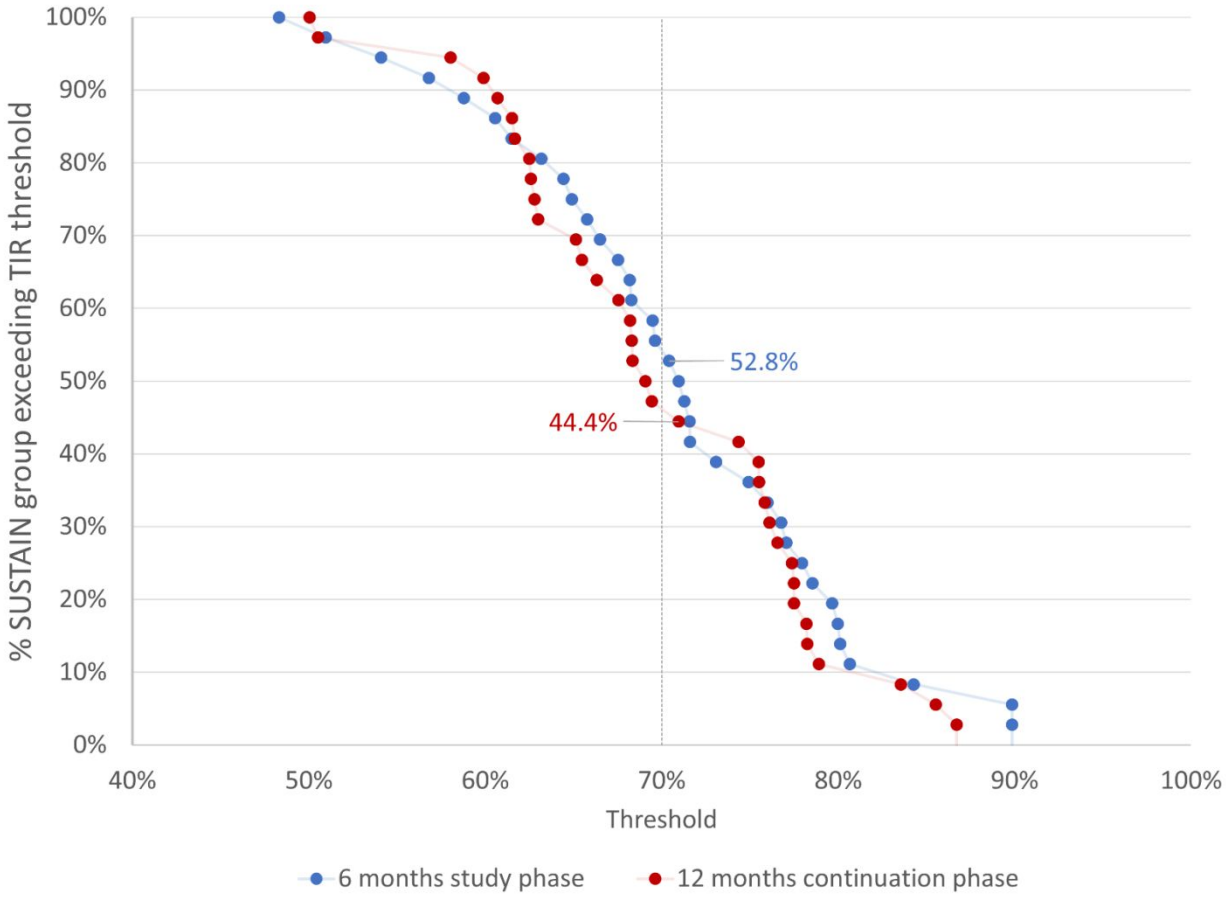

Figure S3: Percentage of SUSTAIN group participants exceeding a given time in 70-180 mg/dL range (TIR) threshold

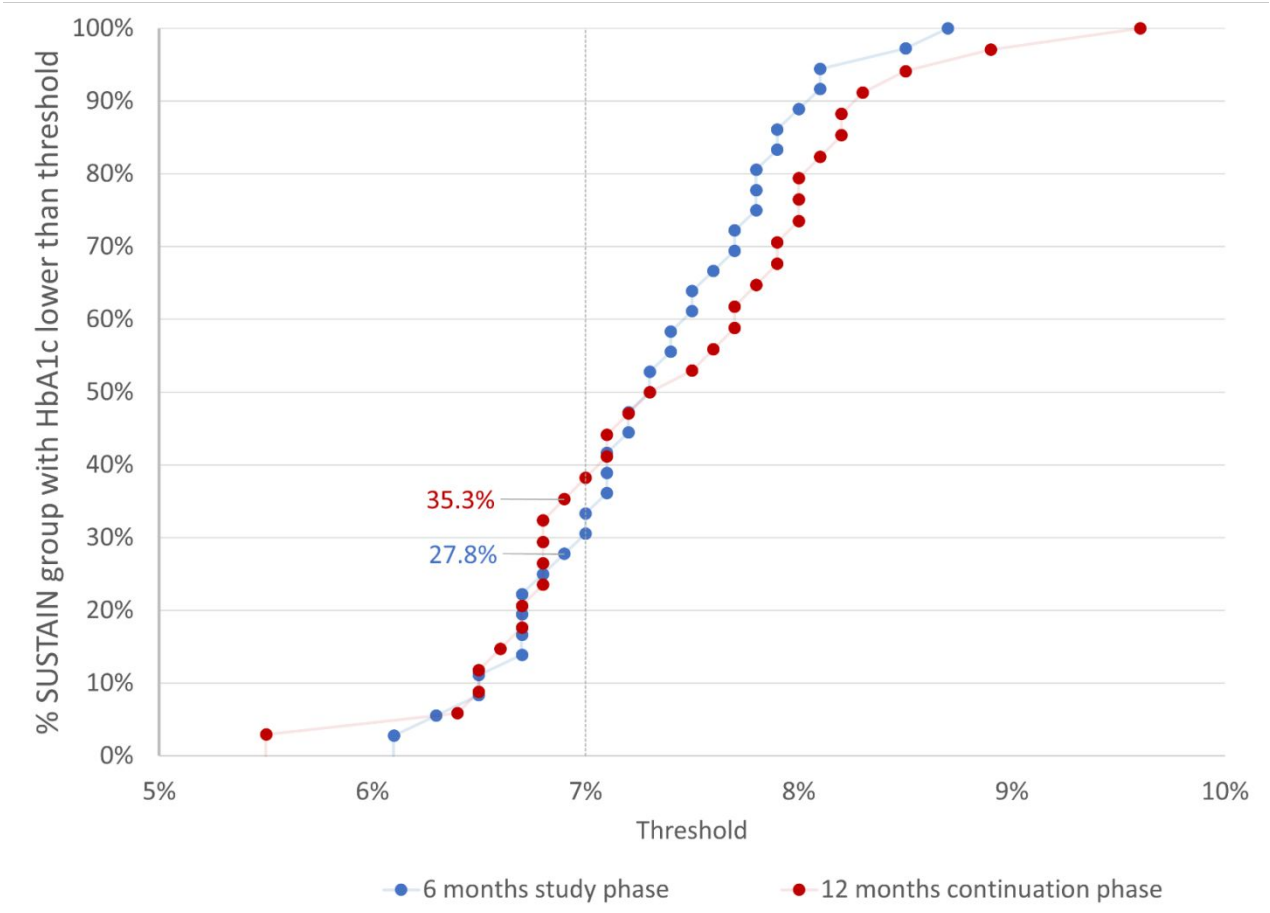

Figure S4: Cumulative distribution of SUSTAIN group participants achieving an HbA1c lower than a given threshold.