# Advanced hybrid closed loop therapy versus conventional treatment in adults with type 1 diabetes (ADAPT): a randomised controlled study

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## Summary

**Background** Adults with type 1 diabetes who are treated with multiple daily injections of insulin plus intermittently scanned continuous glucose monitoring (isCGM) can have suboptimal glucose control. We aimed to assess the efficacy of an advanced hybrid closed loop (AHCL) system compared with such therapy in this population.

**Methods** The Advanced Hybrid Closed Loop Study in Adult Population with Type 1 Diabetes (ADAPT) trial is a prospective, multicentre, open-label, randomised controlled trial that involved 14 centres in three European countries (France, Germany, and the UK). We enrolled patients who were at least 18 years of age, had a type 1 diabetes duration of at least 2 years, $HbA_{1c}$ of at least 8% (64 mmol/mol), and were using multiple daily injections of insulin plus isCGM (cohort A) or real time continuous glucose monitoring (cohort B) for at least 3 months. Here, only results for cohort A are reported. Participants were randomly allocated 1:1 to AHCL therapy or continuation of multiple daily injections of insulin plus continuous glucose monitoring for 6 months with an investigator-blinded block randomisation procedure. Participants and treating clinicians could not be masked to the arm assignment. The primary endpoint was the between-group difference in mean $HbA_{1c}$ change from baseline to 6 months in the intention-to-treat population using AHCL therapy and those using multiple daily injections of insulin plus isCGM. The primary endpoint was analysed using a repeated measures random-effects model with the study arm and period as factors. Safety endpoints included the number of device deficiencies, severe hypoglycaemic events, diabetic ketoacidosis, and serious adverse events. This study is registered with ClinicalTrials.gov, NCT04235504.

**Findings** Between July 13, 2020, and March 12, 2021, 105 people were screened and 82 randomly assigned to treatment (41 in each arm). At 6 months, mean $HbA_{1c}$ had decreased by 1·54% (SD 0·73), from 9·00% to 7·32% in the AHCL group and 0·20% (0·80) in the multiple daily injections of insulin plus isCGM from 9·07% to 8·91% (model-based difference –1·42%, 95% CI –1·74 to –1·10; p<0·0001). No diabetic ketoacidosis, severe hypoglycaemia, or serious adverse events related to study devices occurred in either group; two severe hypoglycaemic events occurred in the run-in phase. 15 device-related non-serious adverse events occurred in the AHCL group, compared with three in the multiple daily injections of insulin plus isCGM group. Two serious adverse events occurred (one in each group), these were breast cancer (in one patient in the AHCL group) and intravitreous haemorrhage (in one patient in the multiple daily injections of insulin plus isCGM group).

**Interpretation** In people with type 1 diabetes using multiple daily injections of insulin plus isCGM and with $HbA_{1c}$ of at least 8%, the use of AHCL confers benefits in terms of glycaemic control beyond those that can be achieved with multiple daily injections of insulin plus isCGM. These data support wider access to AHCL in people with type 1 diabetes not at target glucose levels.

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## Introduction

Medical devices, such as insulin pumps and continuous glucose monitors, have become an integral component of disease management for many people with type 1 diabetes. There has been a steady increase in the use of such technology over the past two decades,[1] which has contributed to the improvements in disease management seen in some long-term studies.[2] Systems combining insulin delivery with continuous glucose monitoring and with either low glucose suspend or hybrid closed loop algorithms have been shown to result in better glycaemic control than multiple daily injections of insulin plus self-monitoring of blood glucose.[3] In randomised controlled trials, automated insulin delivery systems that take glucose readings from a continuous glucose monitor and use an algorithm to continuously adjust insulin delivery have shown substantial improvements in glucose control when compared with sensor-augmented pumps.[4] Despite this benefit, in Europe and in other parts of the world, access to such systems is sometimes scarce and some

## Research in context

### Evidence before this study

The technology underpinning medical devices used in type 1 diabetes has advanced rapidly over the past decade. A 2020 systematic review and network meta-analysis by Pease and colleagues compared the findings of randomised controlled trials of different insulin delivery and glucose monitoring devices published up to 2019. They reported that integrated insulin delivery and continuous glucose monitoring systems including hybrid closed-loop or low glucose suspend systems were associated with lower $HbA_{1c}$ levels relative to multiple daily injections of insulin plus either intermittently scanned continuous glucose monitoring (isCGM) or self-monitoring of blood glucose. However, improvements in the technology continued, meaning that notable improvements in devices, and consequently clinical outcomes, might have occurred since 2019. Literature searches using Embase and Medline were performed to identify randomised controlled trials published from 2019 to 2022 using the search string ("insulin dependent diabetes mellitus"/exp OR "insulin dependent diabetes mellitus") AND ("randomised controlled trial"/exp OR "randomised controlled trial") AND ("automated insulin delivery system"/exp OR "automated insulin delivery system" OR "closed loop" OR "artificial pancreas"/exp OR "artificial pancreas") NOT ("pregnancy"/exp OR "pregnancy" OR "children"/exp OR "children" OR "real world") AND [2019-2022]/py). Searches returned a total of 118 hits. After title and abstract screening was done to exclude reviews and studies including people with type 2 diabetes or end stage renal disease, 26 articles were identified for full-text review. Only one study partially met the criteria for a randomised controlled trial comparing automated insulin delivery systems with multiple daily injections of insulin with continuous glucose monitoring. The identified study used a hybrid closed loop system rather than the advanced hybrid closed loop (AHCL) system used here, and the control group consisting of a mix of different therapies (continuous subcutaneous insulin infusion or multiple daily injections of insulin, with or without continuous glucose monitoring) and different criteria in terms of baseline $HbA_{1c}$. AHCL insulin delivery systems currently represent the state-of-the-art therapy, whereas real-time continuous glucose monitoring (rtCGM) or isCGM with multiple daily injections represents the standard of care for many patients. The rapid pace of innovation means that head-to-head comparisons of the devices at the forefront of technology are often lacking.

### Added value of this study

The MiniMed 780G AHCL reflects the latest generation of automated insulin delivery systems, and the ADAPT trial provides a head-to-head comparison of the efficacy of the MiniMed 780G AHCL algorithm system versus multiple daily injections of insulin plus isCGM, which is representative of the standard of care across many countries in western Europe for people with type 1 diabetes with baseline $HbA_{1c}$ levels of at least 8% (64 mmol/mol). Previous studies of multiple daily injections of insulin plus isCGM and multiple daily injections of insulin plus rtCGM in type 1 diabetes have shown beneficial effects in disease management but have consistently not shown benefits in terms of achieving the combined outcome of time-in-range of more than 70%, low time below range, and a $HbA_{1c}$ of less than 7%. This study added the comparison of the MiniMed 780G AHCL algorithm to the outcomes of multiple daily injections of insulin plus isCGM. The efficacy data from ADAPT in combination with the patient reported outcomes that were investigated could in turn be used to inform future cost-effectiveness analyses of AHCL versus multiple daily injections of insulin plus isCGM.

### Implications of all the available evidence

The findings of ADAPT are in line with previous findings showing benefit of earlier generation automated insulin delivery systems relative to comparators in terms of glycaemic control, although the magnitude of the treatment effect in terms of $HbA_{1c}$ reduction seen in ADAPT was larger than that reported by previous investigators. However, the large treatment effect is likely to be at least partly attributable to the characteristics of the study population (ie, high baseline $HbA_{1c}$ despite at least 3 months of isCGM use before study enrolment). Moreover, ADAPT also showed that AHCL was associated with substantial benefits relative to multiple daily injections of insulin plus isCGM in terms of time-in-range and some patient reported outcomes. The insight gained from ADAPT, combined with that from previously published studies of other automated insulin delivery systems suggests that, particularly for patients struggling to achieve good glycaemic control, AHCL could represent a valuable treatment option. The combined benefits in terms of $HbA_{1c}$, time-in-range, patient reported outcomes, and the potential long-term implications of this further suggest that AHCL should be considered early in the course of the disease when the use of multiple daily injections of insulin plus isCGM fails to achieve targets.

recommendations advocate the integration of technological solutions in a stepwise approach starting from multiple daily injections of insulin and self-monitoring of blood glucose, and gradually progressing to automated insulin delivery systems.[5,6]

The MiniMed 780G advanced hybrid closed loop system (AHCL; Medtronic, Northridge, CA, USA) is the latest generation automated insulin delivery system for use in people living with type 1 diabetes and incorporates several advanced features, such as auto basal and auto corrections. A single-arm study has showed AHCL to be safe and has been associated with improvements in both $HbA_{1c}$ and time-in-range (ie, the amount of time spent with glucose levels in the target range of 70–180 mg/dL [3·9–10·0 mmol/L]) in adults and adolescents with type 1 diabetes.[7] Similarly, a crossover study comparing the AHCL algorithm with the earlier MiniMed 670G device showed that, in people with

type 1 diabetes (aged 14–29 years and mean baseline $HbA_{1c}$ 7·9%), AHCL use led to a significantly lower proportion of time spent in hyperglycaemia relative to the 670G system, without increasing the proportion of time spent in hypoglycaemia.[8] Furthermore, real-world data from more than 12 000 users showed that targets of time-in-range of more than 70% and a glucose management indicator of less than 7% were achieved by more than 75% of users.[9] However, available real-world data provide little insight on the prior management of patients, and the Advanced Hybrid Closed Loop Study in Adult Population with Type 1 Diabetes (ADAPT) study was specifically designed to assess the performance of the AHCL in individuals struggling to achieve glucose targets with conventional treatment (multiple daily injections of insulin plus intermittently scanned continuous glucose monitoring [isCGM] or real-time continuous glucose monitoring [rtCGM]) for a period of 6 months. We aimed to assess the efficacy of an AHCL system compared with multiple daily injections of insulin plus isCGM in adults with type 1 diabetes with suboptimal glucose control.

## Methods

### Study design

The ADAPT study design is described in detail elsewhere;[10] briefly, it was a prospective, multicentre, open-label, randomised controlled trial consisting of a 2-week run-in phase and a 6-month study phase followed by a 6-month continuation phase. Two separate cohorts were included, with a separate randomisation for each. Cohort A (confirmatory cohort) consisted of participants randomly assigned to continue with multiple daily injections of insulin plus isCGM or to initiate AHCL, and cohort B (exploratory cohort) consisted of participants randomly assigned to either continue with multiple daily injections of insulin plus rtCGM or to initiate AHCL. The findings presented here pertain to the 6-month study phase in cohort A only; results for cohort B will be published separately.

ADAPT was conducted in 14 centres across three European countries (France [n=6 centres], Germany [n=4 centres], and the UK [n=4 centres]), and was conducted in line with the principles of the Declaration of Helsinki, those of good clinical practice, and in line with local legislation in all three countries. Approval from competent authorities and ethics committees was obtained for all study centres.

### Participants

Eligible participants were aged at least 18 years, had been diagnosed with type 1 diabetes for 2 years or more, had $HbA_{1c}$ of at least 8·0% (64 mmol/mol), and were on multiple daily injections of insulin for at least 2 years at the time of the screening visit. For cohort A participants were required to have been using isCGM for at least 3 months, with an average of at least five scans per day, and sensor readings available for more than 70% of the time in the month prior to screening. Exclusion criteria included a use of pramlintide, dipeptidyl-peptidase-4 inhibitors, glucagon-like peptide-1 agonists or mimetics, metformin, or sodium-glucose cotransporter-2 inhibitors at screening, women of childbearing potential who were either pregnant at screening, or planning to become pregnant during the study period, subject planning to switch from isCGM to rtCGM during screening, history of hearing or visual impairment that would hinder perception of glucose display and alarms, and unresolved skin conditions around the area of sensor placement. A complete list of the inclusion and exclusion criteria are provided elsewhere.[10] Study participants were recruited from the pool of eligible people with type 1 diabetes seen regularly at participating study centres. All participants provided written informed consent.

### Randomisation and masking

Participants were allocated 1:1 to use either AHCL or multiple daily injections of insulin plus isCGM. Randomisation was done electronically via case report forms using an investigator-blinded block randomisation procedure with blocks of different sizes according to a sequence prepared by the study statistician. Study enrolment and group assignment (based on the randomisation procedure described) were performed by investigators at participating centres who were already involved in patients' care and continued to be involved throughout the study period.[10] Due to the nature of the intervention, participants and treating clinicians could not be masked to the arm assignment.

### Procedures

The study included a 2-week run-in phase, during which participants were required to show tolerance to wearing the Guardian Sensor 3 (Medtronic, CA, USA) and compliance with the blinded continuous glucose monitoring procedure, which was performed using the Guardian Sensor 3 attached to a Guardian Link 3 transmitter (Medtronic; CA, USA) acting as a recorder. Participants with a satisfactory run-in phase were randomly assigned to either AHCL therapy or continuation with multiple daily injections of insulin plus isCGM for the 6-month study phase. For the AHCL arm, use of optimal AHCL settings was recommended (ie, glucose target of 100 mg/dL and active insulin time of 2 h) unless there was concern relating to hypoglycaemia. 2-week blinded continuous glucose monitoring periods (using the same procedure as in the run-in phase) were repeated at 3 months and 6 months for individuals in the multiple daily injections of insulin plus isCGM group. At 6 months, participants in the multiple daily injections of insulin plus isCGM arm were crossed over to the AHCL arm for a continuation phase of 6 months, while participants in the AHCL group continued with AHCL. The AHCL used in the

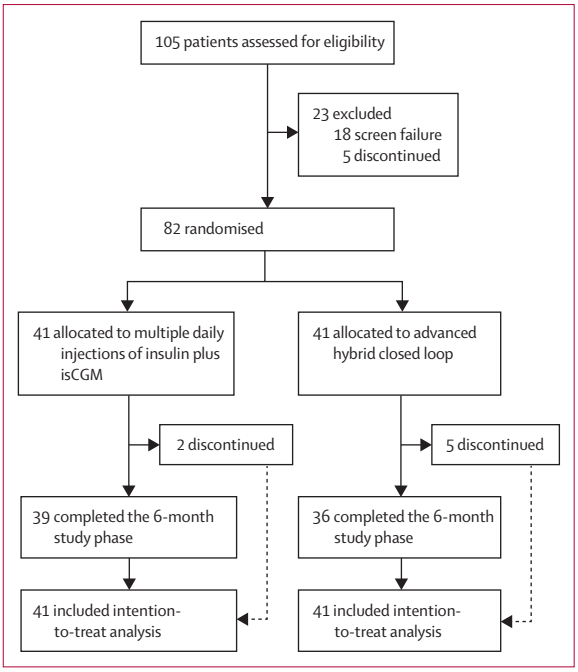


***Figure 1:*** **Trial profile**
Five participants in the advanced hybrid closed loop arm and two participants in the multiple daily injections of insulin plus isCGM arm discontinued during the study phase; in all cases the reason for discontinuation was withdrawal by the participant.

| | Multiple daily injections of insulin plus isCGM group (n=41) | Advanced hybrid closed loop group (n=41) |
|---|---|---|
| Age, years | | |
| Mean | 39·7 (13·12) | 41·5 (11·63) |
| Range | 19–69 | 23–63 |
| Sex | | |
| Male, n (%) | 25 (61%) | 19 (46%) |
| Female, n (%) | 16 (39%) | 22 (54%) |
| Duration of type 1 diabetes, years | 18·1 (9·97) | 18·8 (11·42) |
| Weight, kg | 78·4 (14·77)* | 79·9 (15·09) |
| BMI, kg/m$^2$ | 25·8 (4·92)* | 27·0 (4·37) |
| $HbA_{1c}$, % | 9·07% (0·72) | 9·00% (0·97) |
| $HbA_{1c}$, mmol/mol | 75·7 (7·83) | 74·9 (10·64) |
| isCGM scans, n per day | 9·0 (5·23)* | 8·8 (7·37) |
| Insulin total daily dose, units | 53·3 (22·33) | 54·3 (25·89) |

Values are mean (SD) unless otherwise stated. HbA1c=glycated haemoglobin. isCGM=intermittently scanned continuous glucose monitoring. *Data were missing for two participants.

***Table 1:*** **Baseline characteristics**

study was the MiniMed 670G (version 4.0), which is an investigational system with an AHCL algorithm equivalent to the MiniMed 780G system, which does not include Bluetooth connectivity and glucose target of 110 mg/dL.[7] There were a total of five planned follow-up visits for each arm during the study period.

## Outcomes

The primary endpoint was the between-group difference in mean change in $HbA_{1c}$ from baseline to 6 months. $HbA_{1c}$ was measured at a centralised laboratory at baseline and at the end of months 3 and 6. Secondary endpoints were percentage time spent in the hyperglycaemic range (time spent with sensor glucose levels >250 mg/dL [13·9 mmol/L] and >180 mg/dL [10·0 mmol/L]), percentage time spent in the euglycaemic range (70–180 mg/dL [3·9–10·0 mmol/L]), and percentage time spent in hypoglycaemic ranges (<54 mg/dL [3·0 mmol/L] and <70 mg/dL [3·9 mmol/L]) using continuous glucose monitoring data. Safety endpoints included the number of severe hypoglycaemic events, diabetic ketoacidosis, serious adverse events, serious adverse device effects, and unanticipated serious adverse devices effects. All adverse events were assessed by the study investigators. A Clinical Events Committee was responsible for assessing all serious adverse events, serious adverse device effects, unanticipated serious adverse device effects, severe hypoglycaemia, diabetic ketoacidosis and deaths. Ancillary endpoints included time spent in closed loop and open loop in the AHCL arm and frequency of self-monitoring of blood glucose in the AHCL arm, number of scans in the multiple daily injections of insulin plus isCGM group, sensor use (which in the multiple daily injections of insulin plus isCGM group was determined from glucose reports obtained as per the manufacturer's instructions), measures of glycaemic variability, change in weight, change in BMI, and measures of medical resource use in both arms. A complete list of ancillary endpoints is provided in the study protocol.[10]

The analysis of time spent in the hyperglycaemic, euglycaemic, and hypoglycaemic ranges, and number of hypoglycaemic events, mean sensor glucose levels, and time spent in open-loop and closed-loop was also done specifically for daytime (0600 h to 2359 h) and night time (0000 h to 0559 h).

Patient-reported outcomes included fear of hypoglycaemia, quality of life, and treatment satisfaction assessed using the Hypoglycemia Fear Survey, the Diabetes Quality of Life Questionnaire, and the Diabetes Treatment Satisfaction Questionnaire.

## Statistical analysis

The sample size calculation assumed a 0·5% difference in the mean change from baseline in the AHCL versus the multiple daily injections of insulin plus isCGM group, with an SD of 0·7% and a 7·5% attrition rate during the 6-month study phase.[11] For an α level of 0·05 and a power of 80% based on a two-sided, two-sample *t*-test, a sample size of 70 participants was required.

A reassessment of sample size based on an interim analysis was done by an independent data monitoring committee after 44 participants had completed the 6-month study phase; the committee recommended the completion of the study with no changes in the initial sample size.

The primary endpoint was analysed using a repeated measures random-effects model with the study arm and period as factors. Treatment effects were referred to as model-based estimates. The repeated measures random-effects model used all available data and accounted for missing data. Sensitivity analyses were also performed, which were per protocol analysis, multiple imputation considering baseline characteristics, and baseline observation carried forward. The secondary endpoints and sensor glucose-based ancillary endpoints were calculated for each of the two 2-week measurement periods at the end of months 3 and 6. These were analysed using a repeated measures random effects model with study arm and period (within the study phase) as factors and adjusted by the baseline value of the variable associated with the endpoint as a covariate. The method of White and Thompson[12] was used to adjust for incomplete baseline measurements.

To adjust for multiple statistical comparisons for primary and secondary endpoints, a prespecified hierarchical test procedure was used. First, a superiority test for the change in $HbA_{1c}$ was conducted at 0·05. The secondary endpoints were then tested in a prespecified order until one of the null hypotheses was non-rejected.[10] Superiority and non-inferiority tests were performed (appendix p 10) for secondary endpoints. Ancillary endpoint testing was performed in an exploratory manner. All effectiveness analyses were performed on an intention-to-treat basis, which included all randomly assigned participants. All statistical analyses were performed using SAS software, version 9.4, and p values less than 0·05 were considered statistically significant. This study is registered with ClinicalTrials.gov, NCT04235504.

### Role of the funding source

The study was funded by Medtronic. Medtronic was involved in the design of the study protocol, study conduct, data collection, and data analysis.

## Results

Between July 13, 2020, and March 12, 2021, 105 patients were screened for eligibility. 41 (39%) of 105 participants were randomly assigned to treatment in each arm. 36 (88%) of 41 participants in the AHCL arm and 39 (95%) of 41 participants in the multiple daily injections of insulin plus isCGM group completed the 6-month treatment phase (figure 1). Five patients in the AHCL arm and two patients in the multiple daily injections of insulin plus isCGM group discontinued during the study phase; all of which were due to withdrawal by subject.

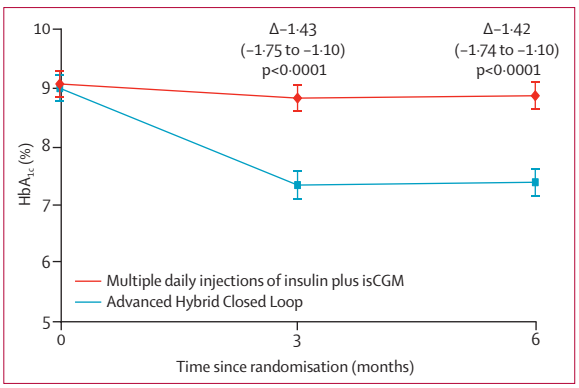


***Figure 2:*** **Mean change in $HbA_{1c}$**
Error bars are 95% CIs.

At baseline, randomly assigned participants in the AHCL arm had a mean (SD) age of 41·5 years (11·63 years), $HbA_{1c}$ of 9·00% (0·97% [74·9 mmol/mol SD 10·64 mmol/mol]), bodyweight of 79·9 kg (15·09 kg) and type 1 diabetes duration of 18·8 years (11·42 years). Participants in the multiple daily injections of insulin plus isCGM group had a mean age of 39·7 years (13·12 years), $HbA_{1c}$ of 9·07% (0·72% [75·7 mmol/mol SD 7·83 mmol/mol]), bodyweight of 78·4 kg (14·77 kg) and type 1 diabetes duration of 18·1 years (9·97 years; table 1).

At 6 months, the mean change from baseline in $HbA_{1c}$ was –1·54% (SD 0·73; –16·8 mmol/mol [SD 8·0]) in the AHCL group and –0·20% (0·80; –2·2 mmol/mol [8·7]) in the multiple daily injections of insulin plus isCGM group, resulting in a model-based treatment effect of –1·42% (95% CI –1·74 to –1·10; –15·5 mmol/mol [–19·0 to –12·0]; p<0·0001) in favour of AHCL (figure 2, table 2).

See Online for appendix

Participants in the AHCL group spent a greater percentage of time with sensor glucose levels between 70–180 mg/dL (3·9–10·0 mmol/L) compared with the multiple daily injections of insulin plus isCGM group (time-in-range: 70·6% [SD 9·7] in the AHCL group *vs* 43·6% [SD 15.37] in the multiple daily injections of insulin plus isCGM group; model-based treatment effect 27·6%, 95% CI 21·6 to 33·6; p<0·0001; table 2). During the study phase participants in the AHCL group spent a mean of 6·6% (SD 5·02) of the time with sensor glucose levels of more than 250 mg/dL and 26·7% (SD 10·44) of the time with sensor glucose levels more than 180 mg/dL, whereas the corresponding values for the multiple daily injections of insulin plus isCGM arm were 22·5% (13·19) for time spent with sensor glucose levels of more than 250 mg/dL and 53·8% (16·47) for time spent with sensor glucose levels of more than 180 mg/dL. This resulted in model-based treatment effects of –16·9% (95% CI –21·4 to –12·4; p<0·0001) for time spent with glucose levels of more than 250 mg/dL and –27·9% (–34·2 to –21·6; p<0·0001) for time spent with glucose levels of more than 180 mg/dL (table 2). The percentage of time spent in the hypoglycaemic range in the AHCL group did not differ (was non-inferior)

| | Multiple daily injections of insulin plus isCGM group (n=41) | | | | Advanced hybrid closed loop group (n=41) | | | | Model-based treatment effect* |
|---|---|---|---|---|---|---|---|---|---|
| | N | Run-in | N | Study | N | Run-in | N | Study | |
| **Primary endpoint** | | | | | | | | | |
| Change in $HbA_{1c}$ from baseline, % | .. | .. | 38 | −0·20 (0·80) | .. | .. | 36 | −1·54 (0·73) | −1·42 (−1·74 to −1·10; p<0·0001) |
| **Secondary endpoints** | | | | | | | | | |
| Time in range, % | | | | | | | | | |
| >250 mg/dL (13·9 mmol/L) | 35 | 23·2% (10·84) | 31 | 22·5% (13·19) | 35 | 28·9% (13·87) | 36 | 6·6% (5·02) | −16·9% (−21·4 to −12·4; p<0·0001) |
| >180 mg/dL (10·0 mmol/L) | 35 | 54·2% (12·59) | 31 | 53·8% (16·47) | 35 | 61·3% (14·71) | 36 | 26·7% (10·44) | −27·9% (−34·2 to −21·6; p<0·0001) |
| 70–180 mg/dL (3·9–10·0 mmol/L) | 35 | 42·6% (11·20) | 31 | 43·6% (15·37) | 35 | 36·4% (13·60) | 36 | 70·6% (9·70) | 27·6% (21·63 to 33·6; p<0·0001) |
| <54 mg/dL (3·0 mmol/L) | 35 | 1·0% (1·83) | 31 | 0·7% (1·17) | 35 | 0·8% (1·12) | 36 | 0·6% (0·67) | −0·1% (−0·4% to 0·3%; non-inferiority met)† |
| <70 mg/dL (3·9 mmol/L) | 35 | 3·2% (3·37) | 31 | 2·6% (2·55) | 35 | 2·2% (2·12) | 36 | 2·6% (2·01) | 0·1% (−0·7% to 1·0%; non-inferiority met)‡ |
| **Ancillary endpoints** | | | | | | | | | |
| Mean of sensor glucose, mg/dL | 35 | 195·1 (23·75) | 31 | 194·7 (29·53) | 35 | 208·8 (29·01) | 36 | 152·2 (16·49) | −44·9 (−55·8 to −34·1; p<0·0001) |
| Mean of sensor glucose, mmol/L | 35 | 10·8 (1·3) | 31 | 10·8 (1·6) | 35 | 11·6 (1·6) | 36 | 8·5 (0·9) | −2·5 (−3·1 to −1·9; p<0·0001) |
| Standard deviation of sensor glucose values, mg/dL | 35 | 73·3 (12·01) | 31 | 69·4 (12·80) | 35 | 73·3 (13·25) | 36 | 54·2 (9·66) | −15·4 (−20·1 to −10·7; p<0·0001) |
| Standard deviation of sensor glucose values, mmol/L | 35 | 4·1 (0·7) | 31 | 3·9 (0·7) | 35 | 4·1 (0·7) | 36 | 3·0 (0·5) | −0·9 (−1·1 to −0·6); p<0·0001) |
| Coefficient of variation of sensor glucose values, % | 35 | 37·8% (5·63) | 31 | 35·9% (5·74) | 35 | 35·4% (5·81) | 36 | 35·5% (4·46) | 0·6% (−1·4 to 2·5; p=0·57) |
| Mean amplitude of glycaemic excursion, mg/dL | 35 | 153·8 (29·97) | 31 | 145·0 (31·21) | 35 | 156·8 (33·43) | 36 | 121·4 (20·50) | −24·9% (−35·9 to −13·8; p<0·0001) |
| Glucose management indicator, %§ | 35 | 8·0% (0·57) | 31 | 8·0% (0·71) | 35 | 8·3% (0·69) | 36 | 7·0% (0·40) | −1·1% (−1·3 to −0·8; p<0·0001) |
| Users achieving $HbA_{1c}$ <7·0%, % (n/N)§ | 41 | 0% (0/41) | 38 | 0% (0/38) | 41 | 0% (0/41) | 36 | 27·8% (10/36) | 25·2% (10·1 to 40·4; p=0·0011) |
| Users achieving glucose management indicator <7·0%, % (n/N)§ | 35 | 0% (0/35) | 31 | 6·5% (2/31) | 35 | 2·9% (1/35) | 36 | 58·3% (21/36) | 49·0% (31·7 to 66·3; p<0·0001) |
| Users achieving time in range >70%, % (n/N)§ | 35 | 0% (0/35) | 31 | 6·5% (2/31) | 35 | 0% (0/35) | 36 | 52·8% (19/36) | 51·1% (35·0 to 67·3; p<0·0001) |
| Users achieving time below range <4%, % (n/N)§ | 35 | 68·6% (24/35) | 31 | 77·4% (24/31) | 35 | 80·0% (28/35) | 36 | 80·6% (29/36) | −0·6% (−17·4 to 16·3; p=0·95) |

Values are mean (SD) unless otherwise stated. *Model-based treatment effect (95% CI; p value for superiority test unless otherwise indicated). †Model-based treatment effect (95% CI; non-inferiority result), non-inferiority is met when the upper confidence limit is less that the non-inferiority margin of 2%. ‡Model-based treatment effect (95% CI; non-inferiority result), non-inferiority is met when the upper confidence limit is less that the non-inferiority margin of 5%. §Post hoc analysis.

***Table 2:*** **$HbA_{1c}$ and continuous glucose monitoring derived endpoints of glycaemic control**

compared with multiple daily injections of insulin plus isCGM. Specifically, the mean percentage of time spent with sensor glucose levels of less than 70 mg/dL was 2·6% (SD 2·01) for AHCL and 2·6% (SD 2·55) for multiple daily injections of insulin plus isCGM (model-based treatment effect 0·1% (95% CI −0·7 to 1·0; non-inferiority met). The mean percentage of time spent with sensor glucose levels of less than 54 mg/dL was 0·6% (SD 0·67) for AHCL and 0·7% (SD 1·17) for multiple daily injections of insulin plus isCGM (model-based treatment −0·1% (95% CI −0·4 to 0·3; non-inferiority met; table 2).

Ten (27·8%) of 36 of participants in the AHCL group versus no participants in the multiple daily injections of insulin plus isCGM group achieved an $HbA_{1c}$ of less than 7·0% at 6 months (table 2).

19 (52·8%) of 36 participants in the AHCL group achieved a time-in-range of more than 70% at 6 months versus two (7%) of 31 participants in the multiple daily injections of insulin plus isCGM group (table 2). A time below range of less than 4% was achieved by 29 (80·6%) of 36 participants in the AHCL group versus 24 (77·4%) of 31 in the multiple daily injections of insulin plus isCGM group (table 2).

Participants randomly assigned to the AHCL group used the sensor 92·2% of the time, spent 95·8% of the time in AHCL (the difference between sensor use and time in the AHCL is due to the algorithm-driven automation continuing for a limited time without continuous glucose monitoring input), experienced 0·9 (SD 0·63) AHCL exits per week, and performed a mean of 3·8 (SD 1·24) self-monitoring of blood glucose measurements per day (appendix p 2). Participants selected the glucose target of 100 mg/dL (5·5 mmol/L) for 68·3% of the time or 120 mg/dL (6·7 mmol/L) for 31·7% of the time and an active insulin time of 2 h for 54·4%, 2–3 h for 40·8%, 3–4 h for 4·8%, or more than 4 h for 0·0% of the time. For the multiple daily injections of insulin plus isCGM group, mean sensor use was 87·3% and participants performed a mean of 9·7 scans per day (appendix p 2).

Mean sensor glucose levels were 152·2 mg/dL (SD 16·49; 8·5 mmol/L [SD 0·9 mmol/L]) for the AHCL group versus 194·7 mg/dL (SD 29·53; 10·8 mmol/L [SD 1·6 mmol/L]) for the multiple daily injections of insulin plus isCGM group (model-based treatment effect –44·9 mg/dL, 95% CI –55·8 to –34·1; p<0·0001), corresponding to a glucose management indicator of 7·0% for the AHCL group and 8·0% for the multiple daily injections of insulin plus isCGM group (model-based treatment effect –1·1%, 95% CI –1·3 to –0·8%; p<0·0001; table 2). 21 (58·3%) of 36 participants in the AHCL group achieved a glucose management indicator less than 7·0% at 6 months compared with two (6·5%) of 31 in the multiple daily injections of insulin plus isCGM group. Measures of variability showed that the coefficient of variation of sensor glucose levels did not differ between groups, but there was a reduction in the mean amplitude of glycaemic excursions in favour of AHCL (table 2). Participants in the AHCL group had a mean weight increase of 2·8 kg from baseline versus 0·8 kg in the multiple daily injections of insulin plus isCGM group (model-based treatment effect 2·0 kg, 95% CI 0·3–3·7 kg; p=0·023). Participants in the AHCL group had a mean decrease in total daily dose of insulin of 0·6 units from baseline versus a mean total daily dose decrease of 0·3 units in the multiple daily injections of insulin plus isCGM group, which was not statistically significant (appendix p 3).

Participants in the AHCL group had increased Diabetes Treatment Satisfaction Questionnaire scores for treatment satisfaction after 6 months compared with multiple daily injections of insulin plus isCGM (mean difference 6·2, 95% CI 2·9 to 9·4; p=0·0003; table 3), which was accompanied by a decrease in perceived hyperglycaemia with AHCL (p<0·0001). Perceived frequency of hypoglycaemia did not differ between groups. These findings were consistent across both the Diabetes Treatment Satisfaction Questionnaire status and change versions (table 3). Fear of hypoglycaemia (Hypoglycemia Fear Survey total score) decreased from baseline in both groups, but the magnitude of the decrease was greater with AHCL (table 3). At 6 months, mean Hypoglycemia Fear Survey total scores decreased by 10·2 points (SD 15·51) from baseline in the AHCL group and 2·7 points (13·08) from baseline in the multiple daily injections of insulin plus isCGM group (model-based treatment effect –6·9, 95% CI –13·5 to –0·3: p=0·041). Most results from the Diabetes Quality of Life Questionnaire did not show any significant between group difference in the change from baseline, with the quality of life total scores improving by a mean of 5·9 (SD 10·60) points in the AHCL group and 1·5 (SD 10·08) points in the multiple daily injections of insulin plus isCGM group (model-based treatment effect 3·8; 95% CI –2·1 to 9·7; p=0·20). However, the treatment satisfaction subscore significantly improved in the AHCL

| | N | Multiple daily injections of insulin plus isCGM group | N | Advanced hybrid closed loop group | Model-based treatment effect |
|---|---|---|---|---|---|
| **Change in DTSQs scores from baseline** | | | | | |
| Treatment satisfaction score | 39 | 0·2 (6·84) | 35 | 6·1 (7·55) | 6·2 (2·9 to 9·4; p=0·0003) |
| Perceived frequency of hyperglycaemia score | 39 | −0·3 (1·49) | 35 | −2·0 (1·69) | −1·8 (−2·5 to −1·0; p<0·0001) |
| Perceived frequency of hypoglycaemia score | 39 | 0·2 (1·44) | 35 | −0·4 (1·80) | −0·5 (−1·2 to 0·3; p=0·22) |
| **Change in DTSQc scores from baseline** | | | | | |
| Treatment satisfaction score | 38 | 3·7 (7·24) | 35 | 13·7 (4·39) | 9·8 (7·04 to 12·64; p<0·0001) |
| Perceived frequency of hyperglycaemia score | 38 | 0·8 (1·42) | 35 | −1·1 (1·77) | −2·0 (−2·7 to −1·2; p<0·0001) |
| Perceived frequency of hypoglycaemia score | 38 | 0·1 (1·27) | 35 | −0·5 (1·80) | −0·5 (−1·2 to 0·3; p=0·22) |
| **Change in Hypoglycaemia Fear Survey scores from baseline** | | | | | |
| Behaviour | 39 | −0·7 (7·52) | 35 | −4·8 (8·73) | −3·8 (−7·5 to −0·1; p=0·047) |
| Worry | 39 | −2·0 (8·58) | 35 | −5·4 (10·42) | −3·0 (−7·4 to 1·4; p=0·18) |
| Total score | 39 | −2·7 (13·08) | 35 | −10·2 (15·51) | −6·9 (−13·5 to −0·3; p=0·041) |
| **Change in DQoL scores from baseline*** | | | | | |
| Treatment satisfaction score | 25 | −2·7 (13·57) | 24 | 10·3 (16·35) | 12·4 (3·9 to 21·0; p=0·0052) |
| Treatment impact score | 24 | 0·1 (6·69) | 24 | 4·4 (8·05) | 4·0 (−0·2 to 8·3; p=0·062) |
| Social worry score | 13 | 2·3 (10·64) | 19 | −0·3 (14·78) | −2·1 (−11·2 to 7·0; p=0·64) |
| Diabetes worry score | 16 | 6·7 (12·99) | 19 | 5·4 (15·41) | −1·7 (−11·3 to 7·8; p=0·72) |
| Total score | 25 | 1·5 (10·08) | 24 | 5·9 (10·60) | 3·8 (−2·1 to 9·7; p=0·20) |
| General well-being score | 24 | −1·3 (11·96) | 22 | 6·1 (16·96) | 7·2 (−1·4 to 15·8; p=0·10) |

Values are mean (SD) unless otherwise stated. DTSQs=Diabetes Treatment Satisfaction Questionnaire–status. DTSQc=Diabetes Treatment Satisfaction Questionnaire–change. isCGM=intermittently scanned continuous glucose monitoring. *QoL assessment was only conducted in study centres in France and the UK owing to the absence of a German validation of the Diabetes Quality of Life Questionnaire (DQoL).

*Table 3:* **Patient-reported outcomes during the 6-month study phase**

arm compared with the multiple daily injections of insulin plus isCGM group (model-based treatment effect 12·4; p=0·0052; table 3).

No severe hypoglycaemic or diabetic ketoacidosis event occurred during the 6-month study phase. Two severe hypoglycaemic events occurred during the run-in phase (appendix p 4). Two serious adverse events, not related to the devices, occurred during the study phase (these were one case of breast cancer in the AHCL group and one patient in the multiple daily injections of insulin plus isCGM group experienced an intra-vitreous haemorrhage). 66 non-serious adverse events occurred in the AHCL group and 39 occurred in the multiple daily injections of insulin plus isCGM group (appendix p 5). 15 (22·7%) of the 66 non-serious adverse events occurring in the AHCL group, were considered to be related to the study device; these were classed as lipohypertrophy (n=5), cannula site reaction (n=3), sensor site reaction (n=2), severe hyperglycaemia (n=1), topical adhesive reaction (n=1), bleeding at sensor site insertion (n=1), skin reaction to infusion set (n=1), and infusion site rash (n=1; appendix 5–7). By contrast, only three non-serious adverse events in the multiple daily injections of insulin plus isCGM group were considered to be device-related (n=1 each for itching at injection site, bleeding at sensor insertion site, and device site erythema; appendix p 8). Device deficiencies, which include issues specifically related to the devices, such as adhesive issues related to the sensor for both groups and issues such as cannula site failure or a failure in communication between the insulin pump and the transmitter for the AHCL group, were more frequent in the AHCL group. There were a total of 56 device deficiencies in the AHCL group compared with eight in the multiple daily injections of insulin plus isCGM group (appendix p 5). The higher number of device deficiencies in the AHCL group was anticipated, as the study device was used in this group and participants in the AHCL group were new to AHCL therapy. Hospitalisations, emergency room visits, and events requiring ambulance assistance were low in both groups (appendix p 9).

## Discussion

ADAPT is the first randomised controlled trial to evaluate the clinical benefits of the MiniMed 780G algorithm AHCL system in adults with type 1 diabetes, in which the current conventional therapy of multiple daily injections of insulin plus isCGM is unable to control glucose levels. Over a 6-month period, the use of AHCL was associated with a statistically significant 1·42% reduction in $HbA_{1c}$ relative to multiple daily injections of insulin plus isCGM and 1·54% decrease relative to baseline. Glycaemic control is established as a key determinant of the risk for long-term microvascular and cardiovascular complications in type 1 diabetes.[13,14] As such, it is feasible that if the improved glycaemic control observed with AHCL can be sustained over the long-term, the use of AHCL could have benefits in terms of reducing the risk for long-term complications. Moreover, there is some suggestion that achieving good glycaemic control early in the course of disease could be particularly beneficial in terms of the effects on long-term complication risk.[15]

The magnitude of the effect observed in ADAPT suggests that a wider use of AHCL should be considered. The health economic implications of such warrant future cost-effectiveness analyses, although previous health economic analyses based on earlier data suggest that AHCL is cost-effective relative to multiple daily injections of insulin plus isCGM over a long-term time horizon.[16,17]

In studies such as ADAPT, the choice of comparator is a crucial consideration. Multiple daily injections of insulin plus isCGM was chosen as this represents the standard of care or first-line treatment for type 1 diabetes across most of western Europe. Insulin pump therapy could have been considered as a third comparator, but previous studies have shown only small incremental benefits of adding continuous subcutaneous insulin infusion to continuous glucose monitors without automation. For example, Beck and colleagues[18] randomised 75 people on continuous glucose monitors to use continuous subcutaneous insulin infusion or continue with multiple daily injections of insulin and found only a 0·3% reduction in $HbA_{1c}$ with continuous subcutaneous insulin infusion plus continuous glucose monitors, with an increase in time below range.

Real-world studies evaluating isCGM, such as the UK-based ABCD audit,[19] French RELIEF study,[20] and the Swedish[21] and Belgian[22] registry studies, have consistently reported a reduction in hypoglycaemia and reduced hospital admissions, providing further evidence for the effectiveness of isCGM relative to self-monitoring of blood glucose. However, in these studies, as well as large registry studies such as the type 1 diabetes exchange[23] and Diabetes Prospective Follow-up Registry,[24] mean $HbA_{1c}$ levels remained close to 8%. The real-world FLARE-NL4 study showed that with isCGM, the greatest $HbA_{1c}$ reductions were observed in those with the highest baseline $HbA_{1c}$ levels.[25] However, although some patients can achieve good glycaemic control with isCGM, the attainment of $HbA_{1c}$ target levels (ie, HbA1c <7% for most people) is an elusive goal for a substantial proportion of patients who do not use automated insulin delivery devices.

Although the participants underwent a shift in the therapeutic approach—from multiple daily injections of insulin plus isCGM to an integrated AHCL system—analysis of safety data showed an overall low incidence of serious adverse events and no serious adverse device effects, diabetic ketoacidosis, or severe hypoglycaemic events. This finding could help to alleviate concerns that people treating themselves with multiple daily injections of insulin can find it challenging to adapt to new

technologies, which has formed part of the rationale for a stepped-care approach that has culminated in the delayed adoption of advanced technologies.[26] Participant withdrawal from the AHCL group (attrition rate of 12%) occurred early in the trial reflecting an a priori higher reluctance to use pump therapy and the finger-pricking required for calibration, and that pump therapy is not universally accepted by all people with type 1 diabetes. The high time spent in AHCL (95·8%) by most participants who continued the trial, and the significant improvement in treatment satisfaction, provides testament to the user satisfaction and usability of the AHCL system.

Time-in-range was a secondary endpoint and there is an increasing recognition of its value as an endpoint alongside $HbA_{1c}$.[27] In ADAPT, AHCL was associated with a higher percentage of time spent in the target range of 70–180 mg/dL (3·9–10·0 mmol/L) and the between group difference in time-in-range was 27·6%, which is considerably greater than the 5% increase considered to be clinically significant.[28] The increase in time-in-range seen in the AHCL arm was primarily attributable to a reduction in time above range. Baseline time below range was low in both arms and remained below the recommended threshold of 4%,[28] again providing further evidence that algorithm-based therapy was successful in achieving target glycaemic levels without increasing sensor-detected or clinical hypoglycaemia. This finding contrasts with multiple daily injections of insulin or non-automated continuous subcutaneous insulin infusion-based therapy, in which achievement of $HbA_{1c}$ target levels can lead to increased hypoglycaemia. For example, in the landmark DCCT trial,[29] which pre-dated the widespread use of technologies such as continuous glucose monitors and insulin pumps and wherein glucose levels were monitored by self-monitoring of blood glucose, intensive therapy was associated with a three-times higher rate of severe clinical hypoglycaemia.[29] Within the past 5–6 years, trials of multiple daily injections of insulin plus isCGM and multiple daily injections of insulin plus rtCGM in type 1 diabetes have shown beneficial effects in disease management but have consistently not shown benefits in terms of achieving the combined outcome of time-in-range of more than 70%, low time below range, and a $HbA_{1c}$ of less than 7%. In particular, a 2016 study[30] showed that in adults with well controlled type 1 diabetes, isCGM was associated with a significant reduction in time spent in the hypoglycaemic range relative to self-monitoring of blood glucose but no difference in $HbA_{1c}$. Similarly, trials of multiple daily injections of insulin plus rtCGM versus multiple daily injections of insulin plus self-monitoring of blood glucose have shown a reduction in time spent in hypoglycaemia and improved $HbA_{1c}$ in people with uncontrolled type 1 diabetes (baseline $HbA_{1c}$ of 8·6%), but the HbA1c treatment effects were in the region of decreases of 0·4–0·6% relative to the control group, which was insufficient to allow the majority of participants to reach glycaemic goals.[31,32] Visser and colleagues[33] presented findings from a randomised controlled trial in adults with type 1 diabetes who previously used isCGM, including 81% treated with multiple daily injections of insulin and mean baseline $HbA_{1c}$ of 7·4%. At 6 months, use of rtCGM led to improved time-in-range, reduced $HbA_{1c}$, and a reduction in time below range, but only 28% people on rtCGM (and 15% on isCGM) achieved time-in-range targets as defined by international consensus guidelines,[28] suggesting there could be a ceiling effect for non-automated algorithm-based therapies, even with best practices.

Although no participant in the control arm of ADAPT achieved a $HbA_{1c}$ of less than 7%, the percentage of treatment arm participants who achieved $HbA_{1c}$ less than 7% was 27·8%, whereas 58·3% achieved a glucose management indicator of less than 7%, and 52·8% achieved a time-in-range of more than 70%. The time-in-range and glucose management indicator outcomes are lower than the corresponding outcomes reported for real-world users of the MiniMed 780G algorithm system.[9] The differences are probably attributable to the ADAPT inclusion criteria, which focused on people with high baseline $HbA_{1c}$. Some of the behaviours associated with raised baseline $HbA_{1c}$ could have also contributed to the lower percentage of people achieving target levels with AHCL. These include missed or late boluses, more errors in carbohydrate counting, or greater fear or anxiety relating to hypoglycaemia resulting in higher glucose levels or increased carbohydrate intake when in the lower levels of target range. An example of this is the lower proportion of people using optimal settings for AHCL.

The data presented here are in line with a descriptive study that showed that switching from sensor augmented pump therapy to AHCL resulted in an increase in time-in-range in people with type 1 diabetes.[34] Similarly, randomised controlled trials of other advanced systems have also shown improvements in glycaemic control but not of the scale seen in ADAPT and not focused on this specific population.[35,36] However, the high baseline $HbA_{1c}$ is likely to be a contributing factor in the large treatment effect seen in ADAPT. The findings of the ADAPT study also lend weight to a commentary by Forlenza and colleagues[37] pertaining to the process of user selection for closed-loop systems, wherein the authors suggest that there is a need to "shake up provider assumptions that we should restrict technology to only those we deem to be 'good candidates'" (ie, those who are highly engaged). The findings of ADAPT provide a robust, quantitative evidence base to affirm the suggestion that access to AHCL should be widened beyond those traditionally considered as good candidates.

Several patient-reported outcome measures were investigated in ADAPT. Significant between-group differences in favour of AHCL were reported in the treatment satisfaction questionnaires results and in

fear of hypoglycaemia. Overall quality of life scores did not differ between the two groups, which suggests that the added technological burden and finger-prick testing does not negatively influence quality of life. However, quality of life findings should be interpreted with caution owing to low patient numbers as the Diabetes Quality of Life Questionnaire was not used in study centres in Germany. Nevertheless, the findings of ADAPT are in line with those of a previous study showing that AHCL was associated with improved glucose monitoring satisfaction relative to an earlier generation hybrid closed-loop system.[38]

The ADAPT study has several limitations. Firstly, there was no optimisation of therapy at baseline, which was in part mitigated by the fact that for study entry all participants were required to have been treated at study sites and using isCGM appropriately for at least 3 months before screening, and they continued to be seen for optimisation during the study with minimal improvements. Individuals in the control arm continued to show a high degree of engagement with therapy using isCGM 87·3% of the time with an average of 9·7 scans a day, which is in line with international data on isCGM use and UK guidance, which recommends at least eight scans per day.[39–41]Indeed, the study effect in the control group was minimal and it also identifies the control group as people who had raised $HbA_{1c}$ despite a high degree of engagement and self-management.

Additionally, although blinded continuous glucose monitoring data for the control group were not available for the duration of the 6-month study phase, with data limited to two 2-week periods at months 3 and 6, 2 weeks of continuous glucose monitoring data has been shown to be representative of long-term glycaemic control,[42] and to minimise the effect, the comparisons in continuous glucose monitoring data were appropriately matched between the two arms in the statistical analyses. The control arm treatment was limited to multiple daily injections of insulin plus isCGM, which is representative of the current standard of care in Europe. However, the trial also included an exploratory analysis in a smaller cohort of rtCGM users; the findings of this analysis will be published separately. A further limitation pertains to the study duration, which might not be of sufficient length to capture any rare safety events. Strengths of the study include the randomised controlled trial design and the fact that the participants are likely to be representative of people with type 1 diabetes with challenging glycaemic control encountered in routine clinical practice.

In conclusion, the findings of the ADAPT study suggest that for people with type 1 diabetes using multiple daily injections of insulin plus isCGM and with a $HbA_{1c}$ of at least 8·0%, the use of AHCL confers benefits in terms of $HbA_{1c}$ and time-in-range beyond those that can be achieved with multiple daily injections of insulin plus isCGM, which represents the standard of care in the countries in which the study was conducted. Improvements in patient reported outcomes were observed in both treatment groups but the use of AHCL was associated with significant benefits relative to multiple daily injections of insulin plus isCGM in terms of treatment satisfaction and fear of hypoglycaemia. The extent of the benefit observed with AHCL is likely to be translated into long-term benefits in terms of reduced risk of long-term complications and suggests that AHCL should be considered at the early stages in the type 1 diabetes treatment pathway. Future health economic analyses are warranted to determine the long-term health economic implications of the use of AHCL relative to multiple daily injections of insulin plus isCGM.

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**Contributors**

PC, RK, WK, JK, CT, and ME were trial investigators. SdP, LV, RR, JS, JC, AH, JdS, and OC were involved in the design of the trial. Statistical analysis of study data was performed by AH and JC. All authors had access to the study data, and all authors were involved in data interpretation and the preparation and critical review of the first and all subsequent drafts of the manuscript. OC was responsible for the final decision to submit the manuscript. PC and JC had direct access to and verified the data.

**Declaration of interests**

PC 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 Welcome Trust clinical Research facility at King's College Hospital and the NIHR patient recruitment centre at University Hospitals Leicester, UK. WK has received speaker fees from Medtronic and support for travel and attending ADAPT study meetings from Medtronic. JK 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. CT 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. ME has received grants for his participation in the HypoRESOLVE and INNODIA consortiums (from EU,charity andindustry 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. RR, SdP, LV, JS, AH, JC, JdS, and OC are current employees and shareholders of Medtronic. RK declares no competing interests.

### Data sharing

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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