BMJ Open

ADVANCED HYBRID CLOSED-LOOP STUDY IN ADULT POPULATION WITH TYPE 1 DIABETES (ADAPT): STUDY PROTOCOL AND RATIONALE

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-050635
Article Type:	Protocol
Date Submitted by the Author:	11-May-2021
Complete List of Authors:	de Portu, Simona; Medtronic International Trading Sarl, Reimbursement and GA Diabetes Vorrink, Linda; Medtronic International Trading Sarl, Medtronic Diabetes Re, Roseline; Medtronic International Trading Sarl, Medtronic Diabetes Shin, John; Medtronic Diabetes, Clinical Research, Biostatistics, and Bioinformatics Castaneda, Javier ; Medtronic Bakken Research Center BV, Statistics Habteab, Aklilu; Medtronic Bakken Research Center BV Cohen, Ohad; Medtronic International Trading Sarl, Medtronic Diabetes
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, DIABETES & ENDOCRINOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A RANDOMISED CONTROLLED TRIAL OF ADVANCED HYBRID CLOSED-LOOP IN ADULT POPULATION WITH TYPE 1 DIABETES (ADAPT): STUDY PROTOCOL AND RATIONALE

Authors: de Portu S[1], Vorrink L[1], Ré R[1], Shin J[2], Castañeda J[3], Habteab A[3], Cohen O[1]

Affiliations: [1] Medtronic International Trading Sàrl, Tolochenaz, Switzerland

[2] Medtronic, Northridge, United States.

[3] Bakken Research Center, Maastricht, The Netherlands.

Corresponding author: Ohad Cohen

Medtronic International Trading Sàrl

Route du Molliau 31, CH-1131 Tolochenaz

Switzerland

E-mail: ohad.cohen@medtronic.com

Running header: Advanced hybrid closed loop system versus multiple daily injections plus flash glucose monitoring

Key words: Hybrid closed loop; insulin pump; flash glucose monitoring; type 1 diabetes

ABSTRACT

Introduction

For many people with type 1 diabetes (T1D) who struggle to achieve glycemic control with multiple daily injections (MDI) plus self-monitoring of blood glucose (SMBG), the use of MDI plus medical devices such as intermittently scanned continuous glucose monitoring (IS-CGM), real-time continuous glucose monitoring (RT-CGM) or alternatively insulin administration using insulin pump therapy now represent optimized care in many geographies. Continual advances in pump technology have led to the development of an advanced hybrid closed loop (AHCL) systems; however, to date, studies examining the incremental effects of an AHCL system relative to MDI plus IS-CGM are lacking.

Methods and analysis

The Advanced Hybrid Closed Loop study in Adult Population with Type 1 Diabetes (ADAPT) study is a multinational, prospective, open-label, confirmatory and exploratory randomized controlled trial that will examine outcomes with the MiniMed 670G version 4.0 AHCL system (with an equivalent algorithm and commercialized as the MiniMed 780G system, referred to throughout the manuscript as AHCL) relative to MDI plus IS-CGM in adults with sub-optimally controlled T1D (baseline HbA1c of ≥8.0%). The study will be conducted in approximately 124 adults on MDI plus either IS-CGM or RT-CGM for at least 3 months prior to screening. The primary endpoint will be the difference in mean HbA1c change from baseline to 6 months between the AHCL arm and the MDI plus IS-CGM arm. Secondary endpoints will include the proportion of time spent in the hypoglycemic, euglycemic and hyperglycemic range.

Ethics and dissemination

The ADAPT study will be conducted in accordance with the requirements of the Declaration of Helsinki as well as local laws and regulations of the countries in which the study will be conducted. The trial will provide valuable information on the incremental benefits that may be provided by AHCL for patients failing to achieve glycemic targets on MDI plus IS-CGM or RT-CGM as well as providing a clinical evidence base for future health economic evaluations to support market access.

Registration details

The trial is registered with clinicaltrials.gov with the registration number NCT04235504 (https://clinicaltrials.gov/ct2/show/NCT04235504).

Strengths and limitations of this study

- To date long-term, head-to-head studies of AHCL versus MDI plus IS-CGM (or RT-CGM) are lacking and the ADAPT study has been designed to directly address this need
- The inclusion criteria limit trial enrollment to subjects with a baseline HbA1c of ≥8.0% (64 mmol/mol), i.e. subjects failing to achieve good glycemic control as stipulated by HbA1c targets recommended in major guidelines, in line with the patient population utilizing insulin pumps and CGM in many settings
- Many previous studies of HCL systems have been of a duration of 12 weeks or less[1,2,3] but the ADAPT study will evaluate the durability of outcomes over a study phase of 6 months, with a further 6-month follow-up continuation phase in a home setting
- A limitation of the study is that the comparator arms represent the current standard of care for patients with T1D and as a result it may not fully quantify the benefits of AHCL compared with the frequent, stepwise changes in treatment and/or addition of supplementary technologies in patients failing to achieve glycemic targets or experiencing problematic hypoglycemia in routine clinical practice
- The ADAPT study will assess patient reported outcomes, including fear of hypoglycemia, quality of life and treatment satisfaction, and provide valuable input data for future health economic analyses, allowing better informed decision making amongst healthcare payers, for whom the acquisition costs of new technologies can represent a barrier to their uptake or reimbursement

INTRODUCTION

Type 1 diabetes (T1D) is a chronic lifelong condition that is associated with a risk of long-term complications including cardiovascular disease, renal disease, and ophthalmic complications. The standard of care for people with T1D has evolved greatly over time, with each advance offering stepwise incremental improvements in glycemic control and/or the risk of hypoglycemic events. Improvements in disease management include both drug treatments and advances in technology. Advances in technology include the development of real-time continuous glucose monitoring (RT-CGM), intermittently scanned continuous glucose monitoring (IS-CGM) and continuous subcutaneous insulin infusion (CSII) with each generation of insulin pumps becoming progressively more sophisticated, with advanced hybrid closed loop (AHCL) systems representing the latest and most advanced generation of insulin pumps.[4,5,6]

Despite improvements in the standard of care increasing life expectancy for people with T1D over the last two decades, life expectancy for young people with T1D remains around 8–13 years below that of the general population, suggesting there is still much to be achieved in terms of improving long-term outcomes for people with T1D.[7,8,9] In an increasing number of countries, multiple daily injections of insulin (MDI) plus either RT-CGM or IS-CGM are emerging as the standard of care for many patients, particularly for those struggling with either glycemic control or hypoglycemia.[10,11] Moreover, recently published national and international guidelines are increasingly moving towards advocating the use of CGM in people with T1D, particularly those with a history of severe hypoglycemic events or unawareness of hypoglycemia.[12,13] Both CGM methods utilize a sensor placed subcutaneously but whereas with RT-CGM sensor readings are transmitted to the receiver every 5 minutes, with IS-CGM the receiver must be scanned directly over the sensor. Real-world studies have shown that IS-CGM use can lead to improved glycemic control measures for some patients, with improvements linked to a higher frequency of scanning.[14,15] In parallel, insulin pumps are also becoming more widely used.[16] One of the most recently developed and commercialized insulin pumps is the MiniMed 780G, which is an AHCL system approved for use in Europe in individuals with T1D aged 7–80 years, has been shown to significantly improve time in range [TIR] relative to previous generation systems.[6]

The ADAPT study will examine potential improvements associated with the use of the AHCL system in people with T1D with sub-optimal glycemic control on a non-automated system. Previous studies of insulin pumps, including hybrid closed loop (HCL) systems, have largely utilized a comparator arm of MDI plus self-monitoring of blood glucose (SMBG). However, uptake of RT-CGM and IS-CGM, particularly among patients struggling with disease management, is increasing and this now represents the standard of care for some difficult-to-manage patients. The ADAPT study has been designed to provide insights into the potential incremental improvement in outcomes that could be achieved with the use of an AHCL system.

METHODS AND ANALYSIS

Study design

The ADAPT study will be a prospective open-label, multi-center, adaptive, confirmatory and randomized controlled trial in adults with T1D. The study will be conducted at multiple sites with experience in CSII use in adults with T1D in France, Germany, and the UK. The primary objective is to compare the mean change in HbA1c from baseline to 6 months between the active intervention arm (MiniMed™ 670G version 4.0 AHCL) and the control arm (MDI plus IS-CGM). The study will comprise three phases: a 2-week run-in phase, a 6-month study phase and a 6-month continuation phase (**Error! Reference source not found.**). In the run-in phase subjects will continue on their current baseline therapy of MDI plus blinded CGM to collect baseline CGM data and determine subject's ability to tolerate wearing the sensor and transmitter continuously. Patients who successfully complete blinded CGM during the run-in phase, including wearing and acceptable tolerance to the sensor plus at least two fingerstick blood glucose measurements per day and compliance with study procedures will undergo randomization. Blinded CGM will be performed at baseline for all patients and at two additional timepoints for patients in the control MDI plus CGM (IS-CGM or RT-CGM) arm (at Month 3 and Month 6 of the study phase).

At the start of the 6-month study phase, subjects will be randomly allocated to either the AHCL arm or the control arm. The study will consist of two cohorts (Cohort A: confirmatory part of study and Cohort B: exploratory part of study) as follows:

Cohort A:	Treatment arm – begin treatment with AHCL
	Control arm – continue treatment with MDI plus IS-CGM
Cohort B:	Treatment arm – begin treatment with AHCL
	Control arm – continue treatment with MDI plus RT-CGM

In each cohort, participants will be randomly allocated to treatment in a 1:1 ratio using an investigator-blinded block randomization procedure with blocks of different sizes. The order of the block sizes will be selected randomly at a country level. Participants who are allocated to AHCL will receive training on how to use the pump and will be expected to use the device in closed loop with Auto Basal and Auto Correction at all times as well as regularly upload pump and sensor glucose data into CareLink™ therapy management software.

The AHCL used in this study incorporates a hybrid close loop algorithm. In closed loop, basal insulin is delivered every 5 minutes, with the basal insulin delivery rate calculated and adjusted as required based on CGM, users in the ADAPT study are also able to customize their target glucose level to either 120 mg/dL (6.7 mmol/L) or 100 mg/dL (5.6 mmol/L). During the ADAPT study, the recommended settings are a target glucose level of 100 mg/dL (5.6 mmol/L) and an active insulin time of 2 hours. The AHCL also delivers automatic correction boluses based on CGM data, with this feature designed to increase the proportion of time spent in the euglycemic range. In closed loop, the user is still required to record pre-meal carbohydrates. When used in open loop, SmartGuard™ features such as suspend before low (which temporarily suspends basal insulin delivery if sensor glucose levels go below a pre-defined threshold level) can be used. Subjects in the MDI plus IS-CGM arm will use an Abbott FreeStyle Libre IS-CGM device. With the Abbott FreeStyle Libre IS-CGM device, the sensor is placed on the arm subcutaneously and glucose levels are obtained by manually scanning the reader over the sensor. While several commercially available glucose sensors are available, in the ADAPT trial the comparator arm will use Abbott FreeStyle Libre IS-CGM device for the primary analysis.

The duration of the study phase will be 6 months. Following completion of the study phase subjects will enter a 6-month continuation phase, during which all subjects will use the 670G version 4.0 AHCL system (**Error! Reference source not found.**). The overall duration of the study from initiation to completion of all patients is anticipated to be a maximum of 13 months.

Study eligibility and key inclusion/exclusion criteria

For inclusion in the ADAPT study, subjects will be required to be aged ≥18 years with a diagnosis of T1D made at least 2 years prior to screening, on MDI therapy, using IS-CGM or RT-CGM for ≥3 months (with daily average of ≥5 scans for IS-CGM) and sensor readings >70% of time in the month prior to screening to ensure the proper utilization of the CGM device and have a HbA1c ≥8.0% (64 mmol/mol). Measurement of HbA1c will be performed in accordance with the National Glycohemoglobin Standardization Program at a centralized laboratory. Full details of inclusion and exclusion criteria are provided in **Error! Reference source not found.**.

Patient involvement

Patients were not involved in the development of research question, outcomes measures and design of the study, but they were actively involved in the recruitment process and intervention implementation. The participants will be informed once the trial results are published.

Study endpoints

The primary and confirmatory analyses will be performed in Cohort A and the primary endpoint of the study will be the difference in the mean HbA1c change (baseline versus 6 months) between the AHCL arm and the MDI plus IS-CGM arm. Secondary endpoints will include the proportion of time spent in hyperglycemic range with sensor glucose (SG) >250 mg/dL (13.9 mmol/L) and SG >180 mg/dL (>10.0 mmol/L), proportion of time spent within range with sensor glucose (SG) between 70–180 mg/dL (3.9–10.0 mmol/L) and the proportion of time spent in hypoglycemic range with SG <54 mg/dL (3.0 mmol/L) and <70 mg/dL (3.9 mmol/L) (**Error! Reference source not found.**). Safety

endpoints will include the number of severe hypoglycemic events (defined as an event requiring assistance due to altered consciousness), the number of diabetic ketoacidosis events, number of serious adverse events, number of serious adverse device effects, number of unanticipated serious adverse device effects and the number of device deficiencies. Ancillary endpoints will include the proportion of time spent in closed loop and open loop in the AHCL arm and number of days lost from work or school, the coefficient of variation of SG values, change in total daily dose of insulin from baseline to end of study, change in weight, change in body mass index (BMI), and mean change in HbA1c from baseline to 12 months (**Error! Reference source not found.**). The primary, secondary and ancillary endpoints will be assessed in Cohort B in an exploratory fashion. Several patient-reported outcomes (PROs) will also be assessed including quality of life, assessed using the Diabetes Quality of Life Questionnaire (DQOL),[17] treatment satisfaction, assessed using the Diabetes Treatment Satisfaction Questionnaire (DTSQ)[18] and fear of hypoglycemia (FoH), assessed using the Hypoglycemia Fear Survey (HFS).[19]

Sample size

For Cohort A (670G version 4.0 AHCL versus MDI plus IS-CGM) it is anticipated that a total enrollment of 84 subjects will be required. It is also assumed that, based on a drop-out rate of 10% at screening, 5% following the run-in phase and 7.5% during the 6-month study phase, approximately 70 subjects will undergo randomization and 64 will complete the 6-month study phase. The sample size calculation also assumes an alpha of 0.05, a power of 80% and a minimum difference in mean (SD) reduction of 0.5 (0.7)% in HbA1c in the treatment arm versus the control arm. The value of 0.5% in terms of HbA1c change also constitutes the minimum clinically meaningful difference, and is based on the findings of a 2011 study by Hermanides *et al.* 2011.[20] Due to uncertainty about the magnitude of the SD and the effect of treatment, the study has been designed to allow for a reassessment of sample size based on an interim analysis to be performed by an independent Data Monitoring Committee (DMC) after at least 30 patients have completed the 6-month study phase in Cohort A. The interim analysis for sample size reassessment with one interim look, protecting the overall two-sided type 1 error of 0.05, is based on the conditional power approach of Li *et al*.[21] and Chen *et al*.[22] as extended by Mehta and Pocock.[23] On the basis of this interim analysis, the DMC will recommend termination or completion of the study, and if appropriate an increase in the sample size. Drop-out

rates will also be reassessed. For Cohort B (670G version 4.0 AHCL versus MDI plus RT-CGM) a total enrollment of 40 subjects will be required to achieve approximately 34 subjects undergoing randomization and 30 subjects completing the 6-month study phase for exploratory analysis.

Statistical analysis

HbA1c measurements will be performed at baseline, the end of Month 3 and the end of Month 6. The primary endpoint (change in HbA1c from baseline to 6 months) will be analyzed using a repeated measures random effects model that accounts for subjects who dropout of the study and for possible missing at random data. All analyses will be performed using the intention-to-treat (ITT) population, which will consist of all randomized patients. To preserve the overall type I error and claim significance, a hierarchical test procedure will be performed for the predefined secondary endpoints (**Error! Reference source not found.**). The study statistician analyzing the data will be masked to group assignment until final database lock. Patient baseline demographics and characteristics will be collected and presented using descriptive statistics for continuous variables and counts or percentages for categorical variables.

Ethics and dissemination

The ADAPT study will be conducted in accordance with the requirements of the Declaration of Helsinki as well as local laws and regulations of the countries in which the study will be conducted. The study will also be conducted in compliance with the principles of good clinical practice, which includes review and approval by an independent ethics committee or institutional review board, and is aligned with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Statement.[24] Each participating center will not commence any patient-related study activities until approval by the relevant ethics committee or institutional review board has been received and the study center has received clearance from the sponsor to commence the study. The study is registered with clinicaltrials.gov (NCT04235504).

DISCUSSION

The aim of the ADAPT study will be to determine the change in HbA1c from baseline to 6 months for adults with T1D using the AHCL system relative to those using MDI plus IS-CGM. The clinical benefits as well as the convenience of technologies such as CGM and insulin pumps are increasingly recognized by payers and policy makers as well as treating physicians. International and national level guidelines also frequently recommend the use of CGM and/or insulin pumps in people with T1D struggling to achieve good glycemic control. For example, the French national guidelines recommend the use of IS-CGM as an alternative or replacement for SMBG in patients with type 1 or type 2 diabetes on intensified insulin therapy.[25] Similarly, the current ADA guidelines note that the use of technology should be individualized based on a combination of need, desire, skill level and availability.[13]

The inclusion criteria limit trial enrollment to subjects with a baseline HbA1c of ≥8.0% (64 mmol/mol), i.e. subjects failing to achieve good glycemic control as stipulated by HbA1c targets recommended in major guidelines.[26] This aligns with the patient population utilizing insulin pumps and CGM in many settings, where reimbursement of medical devices such as CGM is often limited to those with poor glycemic control or frequent severe hypoglycemic events.[27] The use of MDI plus IS-CGM as the comparator/standard of care arm in the ADAPT study has both clinical and economic implications. Clinical studies have consistently shown that both IS-CGM, RT-CGM and SAP or AHCL can improve glycemic control and increase the proportion of patients obtaining these goals, while reducing the proportion of time spent in the hypoglycemic range relative to SMBG.[28] However, to date, long-term, head-to-head studies of AHCL versus MDI plus IS-CGM (or RT-CGM) are lacking.

Given the continued evolution of medical devices in the management of people with T1D payers and policy makers must determine whether the incremental clinical benefits provided by the latest advances in technology represent good value for money relative to the standard of care. It is therefore important that cost-effectiveness analyses utilize clinical input data that reflects contemporary clinical practice to avoid over- or underestimating long-term clinical or economic outcomes. ADAPT will provide valuable data in this regard by providing head-to-head data for future

economic evaluations of AHCL versus MDI plus IS-CGM. Additionally, the ADAPT study will include days of work/school lost as an ancillary endpoint, which will provide valuable input data for health economic analyses performed from the societal perspective. The ADAPT study will also assess several PROs including FoH, QoL and treatment satisfaction. The inclusion of PROs is important to give an accurate measure of the patient experience in both treatment arms. Moreover, health economic analyses have shown that factors such as reduced FoH can be a key driver of the cost-effectiveness of HCL systems.[29]

For many people with T1D there is frequently a stepwise change in treatment or addition of supplementary technologies such as CGM or insulin pump therapy only when people fail to achieve glycemic targets or experience problematic hypoglycemia.[30] Alongside this, a degree of therapeutic inertia has been reported in some settings, resulting in delays in intensification of treatment or addition of technology, which may potentially have implications in terms of the risk for long-term complications.[31] There is evidence of a legacy effect in T1D with good glycemic control early in the course of the disease reducing or delaying the incidence of serious long-term complications.[32] This may, in turn, have economic implications in terms of the medical costs associated with long-term complications. The importance of optimizing treatment for patients with T1D is clear and it is hoped that the ADAPT study will provide valuable information regarding the use of AHCL systems in adult with T1D.

The ADAPT study will address the issue of whether the AHCL system can provide incremental benefits over a period of 6 months in terms of glycemic control relative to MDI plus IS-CGM in adults with T1D. The study will also provide an important evidence base for future cost-effectiveness analyses of the one of the most advanced AHCL systems currently available to support market access.

REFERENCES

[1] Paldus B, Lee MH, Jones HM, McAuley SA, Horsburgh JC, Roem KL, Ward GM, MacIsaac RJ, Cohen N, Colman PG, Jenkins AJ, O'Neal DN. Glucose Control Using a Standard Versus an Enhanced Hybrid Closed Loop System: A Randomized Crossover Study. Diabetes Technol Ther. 2019 Jan;21(1):56-58

[2] Tauschmann M, Thabit H, Bally L, Allen JM, Hartnell S, Wilinska ME, Ruan Y, Sibayan J, Kollman C, Cheng P, Beck RW, Acerini CL, Evans ML, Dunger DB, Elleri D, Campbell F, Bergenstal RM, Criego A, Shah VN, Leelarathna L, Hovorka R; APCam11 Consortium. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet. 2018 Oct 13;392(10155):1321-1329

[3] Messer LH, Forlenza GP, Sherr JL, Wadwa RP, Buckingham BA, Weinzimer SA, Maahs DM, Slover RH. Optimizing Hybrid Closed-Loop Therapy in Adolescents and Emerging Adults Using the MiniMed 670G System. Diabetes Care. 2018 Apr;41(4):789-796.

[4] Brown SA, Kovatchev BP, Raghinaru D, et al. Six-Month Randomized, Multicenter Trial of Closed Loop in Type 1 Diabetes. N Engl J Med. 2019 Oct;381(18):1707-17

[5] Leelarathna L, Choudhary P, Wilmot EG, Lumb A, Street T, Kar P, Ng SM. Hybrid closed-loop therapy: Where are we in 2021? Diabetes Obes Metab. 2020 Dec; doi: 10.1111/dom.14273 (published online ahead of print)

[6] Collyns O, Meier R, Betts Z, et al. Improved Glycemic Outcomes with Medtronic MiniMed Advanced Hybrid Closed-Loop Delivery: Results from a Randomized Crossover Trial Comparing Automated Insulin Delivery with Predictive Low Glucose Suspend in People with Type 1 Diabetes. Diabetes Care. 2021. Online publication ahead of print; dc202250: https://doi.org/10.2337/dc20-2250

[7] Huo L, Harding JL, Peeters A, Shaw JE, Magliano DJ. Life expectancy of type 1 diabetic patients during 1997-2010: a national Australian registry-based cohort study. Diabetologia. 2016 Jun;59(6):1177-85

[8] Petrie D, Lung TW, Rawshani A, Palmer AJ, Svensson AM, Eliasson B, Clarke P. Recent trends in life expectancy for people with type 1 diabetes in Sweden. Diabetologia. 2016 Jun;59(6):1167-76

[9] Bjornstad P, Donaghue KC, Maahs DM. Macrovascular disease and risk factors in youth with type 1 diabetes: time to be more attentive to treatment? Lancet Diabetes Endocrinol. 2018 Oct;6(10):809-820

[10] Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, Maahs DM, Tamborlane WV, Bergenstal R, Smith E, Olson BA, Garg SK. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther. 2019 Feb;21(2):66-72

[11] NHS England 2019. Flash Glucose Monitoring: National Arrangements for Funding of Relevant Diabetes Patients. Available at: https://www.england.nhs.uk/wp-content/uploads/2020/02/national-arrangements-for-funding-of-relevant-diabetes-patients-v1.2.pdf [Last accessed August 11, 2020]

[12] Grunberger G, Handelsman Y, Bloomgarden ZT, Fonseca VA, Garber AJ, Haas RA, Roberts VL, Umpierrez GE. American Association of Clinical Endocrinologists and American College of Endocrinology 2018 Position Statement on Integration of Insulin Pumps and Continuous Glucose Monitoring in Patients with Diabetes Mellitus. Endocr Pract. 2018 Mar;24(3):302-30

[13] American Diabetes Association. 7. Diabetes Technology: *Standards of Medical Care in Diabetes-2019*. Diabetes Care. 2019 Jan;42(Suppl 1):S71-S80

[14] Jangam S, Dunn T, Xu Y, Hayter G, Ajjan RA. Flash glucose monitoring improves glycemia in higher risk patients: a longitudinal, observational study under real-life settings. BMJ Open Diabetes Res Care. 2019 Mar 25;7(1):e000611

[15] Landau Z, Abiri S, Gruber N, Levy-Shraga Y, Brener A, Lebenthal Y, Barash G, Pinhas-Hamiel O, Rachmiel M. Use of flash glucose-sensing technology (FreeStyle Libre) in youth with type 1 diabetes: AWeSoMe study group real-life observational experience. Acta Diabetol. 2018 Dec;55(12):1303-1310

[16] van den Boom L, Karges B, Auzanneau M, Rami-Merhar B, Lilienthal E, von Sengbusch S, Datz N, Schröder C, Kapellen T, Laimer M, Schmid SM, Müller H, Wolf J, Holl RW. Temporal Trends and Contemporary Use of Insulin Pump Therapy and Glucose Monitoring Among Children, Adolescents, and Adults With Type 1 Diabetes Between 1995 and 2017. Diabetes Care. 2019;42(11):2050-2056

[17] Reliability and validity of a diabetes quality-of-life measure for the diabetes control and complications trial (DCCT). The DCCT Research Group. Diabetes Care. 1988 Oct;11(9):725-32

[18] Bradley, 1994. The Diabetes Treatment Satisfaction Questionnaire: DTSQ. Handbook of Psychology and Diabetes.

[19] Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia: quantification, validation, and utilization. Diabetes Care. 1987 Sep-Oct;10(5):617-21

[20] Hermanides J, Nørgaard K, Bruttomesso D, Mathieu C, Frid A, Dayan CM, Diem P, Fermon C, Wentholt IM, Hoekstra JB, DeVries JH. Sensor-augmented pump therapy lowers HbA(1c) in suboptimally controlled Type 1 diabetes; a randomized controlled trial. Diabet Med. 2011 Oct;28(10):1158-67

[21] Li G, Shih WJ, Xie T, Lu J. A sample size adjustment procedure for clinical trials based on conditional power. Biostatistics. 2002 Jun;3(2):277-87

[22] Chen YH, DeMets DL, Lan KK. Increasing the sample size when the unblinded interim result is promising. Stat Med. 2004 Apr 15;23(7):1023-38

[23] Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med. 2011 Dec 10;30(28):3267-84

[24] SPIRIT Statement Website. Available at: https://www.spirit-statement.org [Last accessed March 29, 2021]

[25] Borot S, Benhamou PY, Atlan C, Bismuth E, Bonnemaison E, Catargi B, Charpentier G, Farret A, Filhol N, Franc S, Gouet D, Guerci B, Guilhem I, Guillot C, Jeandidier N, Joubert M, Melki V, Merlen E, Penfornis A, Picard S, Renard E, Reznik Y, Riveline JP, Rudoni S, Schaepelynck P, Sola-Gazagnes A, Tubiana-Rufi N, Verier-Mine O, Hanaire H; Société francophone du diabète (SFD), Société française d'endocrinologie (SFE); Évaluation dans le diabète des implants actifs Group (EVADIAC). Practical implementation, education and interpretation guidelines for continuous glucose monitoring: A French position statement. Diabetes Metab. 2018 Feb;44(1):61-72

[26] American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019 Jan;42(Suppl 1):S61-S70.

[27] Graham C. Continuous Glucose Monitoring and Global Reimbursement: An Update. Diabetes Technol Ther. 2017 Jun;19(S3):S60-S66

[28] De Ridder F, den Brinker M, De Block C. The road from intermittently scanned continuous glucose monitoring to hybrid closed-loop systems. Part B: results from randomized controlled trials. Ther Adv Endocrinol Metab. 2019 Aug 30;10:2042018819871903

[29] Jendle J, Pöhlmann J, de Portu S, Smith-Palmer J, Roze S. Cost-Effectiveness Analysis of the MiniMed 670G Hybrid Closed-Loop System Versus Continuous Subcutaneous Insulin Infusion for Treatment of Type 1 Diabetes. Diabetes Technol Ther. 2019 Mar;21(3):110-118

[30] Brunton S. Therapeutic Inertia is a Problem for All of Us. Clin Diabetes. 2019 Apr;37(2):105-106

[31] Brož J, Janíčková Žďárská D, Urbanová J, Brabec M, Doničová V, Štěpánová R, Martinka E, Kvapil M. Current Level of Glycemic Control and Clinical Inertia in Subjects Using Insulin for the Treatment of Type 1 and Type 2 Diabetes in the Czech Republic and the Slovak Republic: Results of a Multinational, Multicenter, Observational Survey (DIAINFORM). Diabetes Ther. 2018 Oct;9(5):1897-1906

[32] Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. JAMA. 2003 Oct 22;290(16):2159-67

AUTHORS CONTRIBUTIONS

All authors contributed to the design of the study and critically reviewed the present manuscript. All authors approved the final version of the manuscript. The authors are grateful to Jayne Smith-Palmer at Ossian Health Economics and Communications for medical writing support in the preparation of the manuscript.

FUNDING STATEMENT

The ADAPT Study is sponsored and funded by Medtronic International Trading Sàrl.

COMPETING INTEREST STATEMENT

SdP, LV, RR, JS, AH and OC are employees of Medtronic.

TABLES

Table 1 Inclusion and exclusion criteria for the ADAPT study

Inclusion criteria	Exclusion criteria
• Age ≥18 years at screening • Clinical diagnosis of T1D for ≥2 years prior to screening • On MDI therapy[a] for ≥2 years prior to screening • Subject has been followed and treated by investigator for at least ≥3 months prior to screening and has undergone local educational therapeutic programs • Subject is using: IS-CGM for ≥3 months with daily average of ≥5 scans with sensor readings > 70% of time over the previous month prior to screening Or, RT-CGM, ≥ 3 months with sensor use >70% of the time over the previous month • HbA1c of ≥8.0% (64 mmol/mol) at screening • Subject is willing to take or switch to Humalog™ (insulin lispro injection) or Novolog™ (insulin aspart) • Minimum daily insulin requirement of ≥8 units and maximum of 250 units per day • Subject is willing to upload data from the study pump and meter (subject must have internet access and computer system that meets the requirements for uploading study pump data at home • Subject is willing and able to provide informed consent comply with all study procedures and wear all study devices, as required during the study	• Untreated Addison's disease, thyroid disorder, growth hormone deficiency, hypopituitarism or definite gastroparesis • Use of pramlintide, DPP-4 inhibitor, GLP-1 agonists/mimetics, metformin, SGLT2 inhibitors at screening • Renal failure, defined as creatinine clearance <30 mL/min • Subject is planning to switch from IS-CGM to RT-CGM during the 6-month study phase • History of hearing or vision impairment hindering perception of glucose display and alarms, or otherwise incapable of using the study devices • Women of child bearing potential who are pregnant at screening or plan to become pregnant during the study period • Females who are sexually active and able to conceive not using an effective method of contraception and not agreeing to continue using an effective method of contraception for the duration of the study • Unresolved adverse skin conditions in the area of sensor placement (e.g. psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection). • Active participation in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or device in the last 2 weeks before enrollment into the study • Current abuse of illicit drugs, marijuana, alcohol or prescription drugs (other than nicotine) • Subject has any other disease or condition that may preclude the patient from participating in the study • Subject is legally incompetent, illiterate or vulnerable person • Research staff involved with the study

a Defined as ≥3 insulin injections per day and/or a basal/bolus regimen

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; IS-CGM, intermittently scanned MDI, multiple daily injections; RT-CGM, real-time continuous glucose monitoring; SGLT-2, sodium-glucose co-transporter-2; T1D, type 1 diabetes

Table 2 Secondary endpoints to be assessed in Cohort A

Secondary endpoints
Percentage time spent in hyperglycemic range with SG >250 mg/dL (13.9 mmol/L)
Percentage time spent in hyperglycemic range with SG >180 mg/dL (>10.0 mmol/L)
Percentage time spent within range with SG between 70–180 mg/dL (3.9–10.0 mmol/L)
Percentage time spent in hypoglycemic range with SG <54 mg/dL (3.0 mmol/L)
Percentage time spent in hypoglycemic range with SG <70 mg/dL (3.9 mmol/L)

SG, sensor glucose

Table 3 Ancillary endpoints

Endpoint
• Percentage time spent in 70–140 mg/dL (3.9–7.8 mmol/L) range
• AUC in hypoglycemic range with SG <54 mg/dL (3.0 mmol/L), <70 mg/dL (3.9 mmol/L)
• Percentage time and AUC in hyperglycemic range with SG >140 mg/dL (7.8 mmol/L), >350 mg/dL (19.4 mmol/L) and AUC in hyperglycemic range with SG >180 mg/dL (10 mmol/L), >250 mg/dL (13.9 mmol/L)
• Number of biochemical hypoglycemic events with SG <54 mg/dL (3.0 mmol/L), <70 mg/dL (3.9 mmol/L) (defined as sensor values below the threshold per 15 and 20 consecutive minutes)
• Mean of SG values (mg/dL)
• Percentage time spent in closed loop and open loop
All above endpoints will be categorized by daytime (06:01 to 23:59) and night-time (00:00 to 06:00) and overall (24h)
• Percentage time spent in hyperglycemic range with SG >250 mg/dL (13.9 mmol/L)
• Percentage time spent in hyperglycemic range with SG >180 mg/dL (>10.0 mmol/L)
• Percentage time spent within range with SG between 70–180 mg/dL (3.9–10.0 mmol/L)
• Percentage time spent in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L)
• Percentage time spent in hypoglycemic range with SG <70 mg/dL (3.9 mmol/L)
The above five endpoints will be categorized by daytime (06:01 to 23:59) and night-time (00:00 to 06:00)
• Number of scans and percentage of sensor readings for MDI plus IS-CGM control arm
• Percentage of sensor readings for MDI plus RT-CGM control arm only
• Number of SMBG tests in the AHCL arm
• Percentage of sensor use
• Excursion amplitudes of the glucose values measured by MAGE
• Coefficient of variation of SG values
• Change in total daily dose of insulin from baseline to EOS
• Change in weight from baseline to EOS
• Change in BMI from baseline to EOS
• Mean HbA1c change (from baseline to 12 months)
• Mean HbA1c change (baseline to 6 month) by age groups and duration of diabetes
• Diabetes-related number and mean duration of hospitalizations, number and mean duration intensive care unit care, number of emergency room admissions, number of events requiring ambulance assistance, categorized by reason of diagnosis
• Number of lost days from school or work.
• Hypoglycemia Fear Survey score
• Diabetes Treatment Satisfaction Questionnaire score
• Diabetes Quality of Life questionnaire score

AHCL, advanced hybrid closed loop; AUC, area under the curve; BMI, body mass index; EOS, end of study; IS-CGM, intermittently scanned continuous glucose monitoring; MAGE, mean amplitude of glycemic excursions; MDI, multiple daily injections; RT-CGM, real time continuous glucose monitoring; SG, sensor glucose; SMBG, self-monitoring of blood glucose

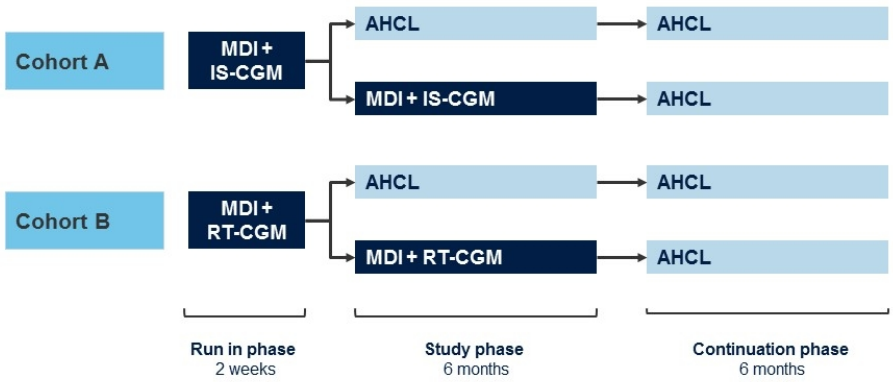


Figure 1 Study Design

AHCL, advanced hybrid closed loop; IS-CGM, intermittently scanned continuous glucose monitoring; MDI, multiple daily injections; RT-CGM, real-time continuous glucose monitoring

254x190mm (96 x 96 DPI)

BMJ Open

A RANDOMISED CONTROLLED TRIAL OF ADVANCED HYBRID CLOSED-LOOP STUDY IN ADULT POPULATION WITH TYPE 1 DIABETES (ADAPT): STUDY PROTOCOL AND RATIONALE

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-050635.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Oct-2021
Complete List of Authors:	de Portu, Simona; Medtronic International Trading Sarl, Reimbursement and GA Diabetes Vorrink, Linda; Medtronic International Trading Sarl, Medtronic Diabetes Re, Roseline; Medtronic International Trading Sarl, Medtronic Diabetes Shin, John; Medtronic Diabetes, Clinical Research, Biostatistics, and Bioinformatics Castaneda, Javier ; Medtronic Bakken Research Center BV, Statistics Habteab, Aklilu; Medtronic Bakken Research Center BV Cohen, Ohad; Medtronic International Trading Sarl, Medtronic Diabetes
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, DIABETES & ENDOCRINOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A RANDOMISED CONTROLLED TRIAL OF ADVANCED HYBRID CLOSED-LOOP IN ADULT POPULATION WITH TYPE 1 DIABETES (ADAPT): STUDY PROTOCOL AND RATIONALE

Authors: de Portu S[1], Vorrink L[1], Ré R[1], Shin J[2], Castañeda J[3], Habteab A[3], Cohen O[1]

Affiliations: [1] Medtronic International Trading Sàrl, Tolochenaz, Switzerland

[2] Medtronic, Northridge, United States.

[3] Bakken Research Center, Maastricht, The Netherlands.

Corresponding author: Ohad Cohen

Medtronic International Trading Sàrl

Route du Molliau 31, CH-1131 Tolochenaz

Switzerland

E-mail: ohad.cohen@medtronic.com

Running header: Advanced hybrid closed loop system versus multiple daily injections plus flash glucose monitoring

Key words: Hybrid closed loop; insulin pump; flash glucose monitoring; type 1 diabetes

ABSTRACT

Introduction

For many people with type 1 diabetes (T1D) who struggle to achieve glycemic control with multiple daily injections (MDI) plus self-monitoring of blood glucose (SMBG), MDI plus intermittently-scanned continuous glucose monitoring (IS-CGM) or real-time continuous glucose monitoring (RT-CGM), or insulin administration using insulin pump therapy represent optimized care in many regions. Through technological advances an advanced hybrid closed loop (AHCL) system has been developed; studies of incremental effects relative to MDI plus IS-CGM are lacking.

Methods and analysis

The Advanced Hybrid Closed Loop study in Adult Population with Type 1 Diabetes (ADAPT) study is a multinational, prospective, open-label, confirmatory and exploratory randomized controlled trial to examine outcomes with the MiniMed 670G version 4.0 AHCL system (with an equivalent algorithm and commercialized as the MiniMed 780G system, referred to as AHCL) relative to MDI plus IS-CGM in adults with baseline HbA1c ≥8.0%. An exploratory cohort will compare AHCL with MDI plus RT-CGM. The study will be conducted in approximately 124 adults on MDI plus either IS-CGM or RT-CGM for at least 3 months prior to screening. The primary endpoint will be the difference in mean HbA1c change from baseline to 6 months between the AHCL and the MDI plus IS-CGM arms. Secondary endpoints will include proportion of time spent in hypoglycemic, euglycemic and hyperglycemic ranges.

Ethics and dissemination

The ADAPT study will be conducted in accordance with the requirements of the Declaration of Helsinki and local laws and regulations, and has been approved by ethics committees. The trial will provide valuable information on the incremental benefits that may be provided by AHCL for patients failing to achieve glycemic targets on MDI plus IS-CGM or RT-CGM and a basis for health economic evaluations to support market access.

Registration details

The trial is registered with clinicaltrials.gov with the registration number NCT04235504 (https://clinicaltrials.gov/ct2/show/NCT04235504).

Strengths and limitations of this study

- To date long-term, head-to-head studies of AHCL versus MDI plus IS-CGM (or RT-CGM) are lacking and the ADAPT study has been designed to directly address this need
- The inclusion criteria limit trial enrollment to subjects with a baseline HbA1c of ≥8.0% (64 mmol/mol), i.e. subjects failing to achieve good glycemic control as stipulated by HbA1c targets recommended in major guidelines, in line with the patient population utilizing insulin pumps and CGM in many settings
- Many previous studies of HCL systems have been of a duration of 12 weeks or less but the ADAPT study will evaluate the durability of outcomes over a study phase of 6 months, with a further 6-month follow-up continuation phase in a home setting
- A limitation of the study is that the comparator arms represent the current standard of care for patients with T1D and as a result it may not fully quantify the benefits of AHCL compared with the frequent, stepwise changes in treatment and/or addition of supplementary technologies in patients failing to achieve glycemic targets or experiencing problematic hypoglycemia in routine clinical practice
- The ADAPT study will assess patient reported outcomes, including fear of hypoglycemia, quality of life and treatment satisfaction, and provide valuable input data for future health economic analyses, allowing better informed decision making amongst healthcare payers, for whom the acquisition costs of new technologies can represent a barrier to their uptake or reimbursement

INTRODUCTION

Type 1 diabetes (T1D) is a chronic lifelong condition that is associated with a risk of long-term complications including cardiovascular disease, renal disease, and ophthalmic complications. The standard of care for people with T1D has evolved greatly over time, with each advance offering stepwise incremental improvements in glycemic control and/or reduce the risk of hypoglycemic events. Improvements in disease management include both drug treatments and advances in technology. Advances in technology include the development of real-time continuous glucose monitoring (RT-CGM), intermittently scanned continuous glucose monitoring (IS-CGM) and continuous subcutaneous insulin infusion (CSII) with each generation of insulin pumps becoming progressively more sophisticated, with advanced hybrid closed loop (AHCL) systems representing the latest and most advanced generation of insulin pumps.[1,2,3,4]

Despite improvements in the standard of care increasing life expectancy for people with T1D over the last two decades, life expectancy for young people with T1D remains around 8–13 years below that of the general population, suggesting there is still much to be achieved in terms of improving long-term outcomes for people with T1D.[5,6,7] In an increasing number of countries, multiple daily injections of insulin (MDI) plus either RT-CGM or IS-CGM are emerging as the standard of care for many patients, particularly for those struggling with either glycemic control or hypoglycemia.[8,9] Moreover, recently published national and international guidelines are increasingly moving towards advocating the use of CGM in people with T1D, particularly those with a history of severe hypoglycemic events or unawareness of hypoglycemia.[10,11] Both CGM methods utilize a sensor placed subcutaneously but whereas with RT-CGM sensor readings are transmitted to the receiver every 5 minutes, with IS-CGM the receiver must be scanned directly over the sensor. Real-world studies have shown that IS-CGM use can lead to improved glycemic control measures for some patients, with improvements linked to a higher frequency of scanning.[12,13] In parallel, insulin pumps are also becoming more widely used.[14] One of the most recently developed and commercialized insulin pumps is the MiniMed 780G, which is an AHCL system approved for use in Europe in individuals with T1D aged 7–80 years, has been shown to significantly improve time in range [TIR] relative to previous generation systems.[3]

The ADAPT study will examine potential improvements associated with the use of the AHCL system in people with T1D with sub-optimal glycemic control on a non-automated system. Previous studies of insulin pumps, including hybrid closed loop (HCL) systems, have largely utilized a comparator arm of MDI plus self-monitoring of blood glucose (SMBG). However, uptake of RT-CGM and IS-CGM, particularly among patients struggling with disease management, is increasing and this now represents the standard of care for some patients with sub-optimally controlled T1D. The ADAPT study has been designed to provide insights into the potential incremental improvement in outcomes that could be achieved with the use of an AHCL system.

METHODS AND ANALYSIS

Study design

The ADAPT study will be a prospective open-label, multi-center, adaptive, confirmatory and randomized controlled trial in adults with T1D. The study will be conducted at multiple sites with experience in CSII use in adults with T1D in France, Germany, and the UK, with a study start date of July 13, 2020. The estimated primary completion date is December 15, 2021 and estimated study closure is July 30, 2022. The primary objective is to compare the mean change in HbA1c from baseline to 6 months between the active intervention arm (MiniMed™ 670G version 4.0 AHCL) and the control arm (MDI plus IS-CGM). There will also be an additional exploratory part of the study, with a separate cohort, comparing the same AHCL system with MDI plus RT-CGM to look for potential similarities in trends. The study will comprise three phases: a 2-week run-in phase, a 6-month study phase and a 6-month continuation phase (Figure 1 and Supplementary Material 1). In the run-in phase subjects will continue on their current baseline therapy of MDI plus blinded CGM (using the Guardian™ Link 3 attached to the Guardian™ Sensor 3) to collect baseline CGM data and determine subject's ability to tolerate wearing the sensor and transmitter continuously. Patients who successfully complete blinded CGM during the run-in phase, including wearing and acceptable tolerance to the sensor plus at least two fingerstick blood glucose measurements per day and compliance with study procedures will undergo randomization. Blinded CGM will be performed at baseline for all patients and at two additional timepoints for patients in the control MDI plus CGM (IS-

CGM or RT-CGM) arm (at Month 3 and Month 6 of the study phase). The same CGM system will be used in both arms to allow for comparisons of CGM data.

At the start of the 6-month study phase, subjects will be randomly allocated to either the AHCL arm or the control arm. The study will consist of two cohorts (Cohort A: confirmatory part of study and Cohort B: exploratory part of study) as follows:

Cohort A:	Treatment arm – begin treatment with AHCL
	Control arm – continue treatment with MDI plus IS-CGM
Cohort B:	Treatment arm – begin treatment with AHCL
	Control arm – continue treatment with MDI plus RT-CGM

Participants using IS-CGM will be randomized in cohort A, and those using RT-CGM will be randomized in cohort B. In each cohort, participants will be randomly allocated to treatment in a 1:1 ratio using an investigator-blinded block randomization procedure with blocks of different sizes. The order of the block sizes will be selected randomly at a country level. Participants who are allocated to AHCL will receive training on how to use the pump and will be expected to use the device in closed loop with Auto Basal and Auto Correction at all times as well as regularly upload pump and sensor glucose data into CareLink™ therapy management software.

The AHCL used in this study incorporates a hybrid closed loop algorithm. In closed loop, basal insulin is delivered every 5 minutes, with the basal insulin delivery rate calculated and adjusted as required based on CGM, users in the ADAPT study are also able to customize their target glucose level to either 120 mg/dL (6.7 mmol/L) or 100 mg/dL (5.6 mmol/L). During the ADAPT study, the recommended settings are a target glucose level of 100 mg/dL (5.6 mmol/L) and an active insulin time of 2 hours. The AHCL also delivers automatic correction boluses based on CGM data, with this feature designed to increase the proportion of time spent in the euglycemic range. In closed loop, the user is still required to record pre-meal carbohydrates. When used in open loop, SmartGuard™ features such as suspend before low (which temporarily suspends basal insulin delivery if sensor glucose levels go below, or are predicted to go below, a pre-defined threshold level) can be used.

Subjects in the MDI plus IS-CGM arm (cohort A) will use an Abbott FreeStyle Libre IS-CGM device. With the Abbott FreeStyle Libre IS-CGM device, the sensor is placed on the arm subcutaneously and glucose levels are obtained by manually scanning the reader over the sensor. While several commercially available glucose sensors are available, in the ADAPT trial the comparator arm will use Abbott FreeStyle Libre IS-CGM device for the primary analysis. Participants will use the IS-CGM device according to the specific model and to the current best clinical practice. Subjects in the MDI plus RT-CGM arm (cohort B) will use any RT-CGM model available at the study site, in line with standard of care.

The duration of the study phase will be 6 months. Following completion of the study phase subjects will enter a 6-month continuation phase, during which all subjects will use the 670G version 4.0 AHCL system (Figure 1). The overall duration of the study from initiation to completion of all patients is anticipated to be a maximum of 13 months.

Study eligibility and key inclusion/exclusion criteria

For inclusion in the ADAPT study, subjects will be required to be aged ≥18 years with a diagnosis of T1D made at least 2 years prior to screening, on MDI therapy, using IS-CGM or RT-CGM for ≥3 months (with daily average of ≥5 scans for IS-CGM) and sensor readings >70% of time in the month prior to screening to ensure the proper utilization of the CGM device and have a HbA1c ≥8.0% (64 mmol/mol). Measurement of HbA1c will be performed in accordance with the National Glycohemoglobin Standardization Program at a centralized laboratory. Full details of inclusion and exclusion criteria are provided in Table 1.

Patient involvement

Patients were not involved in the development of research question, outcome measures and design of the study. The participants will be informed once the trial results are published.

Study endpoints

The primary and confirmatory analyses will be performed in Cohort A and the primary endpoint of the study will be the difference in the mean HbA1c change (baseline versus 6 months) between the AHCL arm and the MDI plus IS-CGM arm. Secondary endpoints will include the proportion of time spent in hyperglycemic range with sensor glucose (SG) >250 mg/dL (13.9 mmol/L) and SG >180 mg/dL (>10.0 mmol/L), proportion of time spent within range with sensor glucose (SG) between 70–180 mg/dL (3.9–10.0 mmol/L) and the proportion of time spent in hypoglycemic range with SG <54 mg/dL (3.0 mmol/L) and <70 mg/dL (3.9 mmol/L) (Table 2). Safety endpoints will include the number of severe hypoglycemic events (defined as an event requiring assistance due to altered consciousness), the number of diabetic ketoacidosis events, number of serious adverse events, number of serious adverse device effects, number of unanticipated serious adverse device effects and the number of device deficiencies. Ancillary endpoints will include the proportion of time spent in closed loop and open loop in the AHCL arm and number of days lost from work or school, the coefficient of variation of SG values, change in total daily dose of insulin from baseline to end of study, change in weight, change in body mass index (BMI), and mean change in HbA1c from baseline to 12 months (Table 3). The primary, secondary and ancillary endpoints will be assessed in Cohort B in an exploratory fashion. Several patient-reported outcomes (PROs) will also be assessed including quality of life, assessed using the Diabetes Quality of Life Questionnaire (DQOL),[15,16] treatment satisfaction, assessed using the Diabetes Treatment Satisfaction Questionnaire (DTSQ)[17,18] and fear of hypoglycemia (FoH), assessed using the Hypoglycemia Fear Survey (HFS).[19]

Sample size

For Cohort A (670G version 4.0 AHCL versus MDI plus IS-CGM) it is anticipated that a total enrollment of 84 subjects will be required. It is also assumed that, based on a drop-out rate of 10% at screening, 5% following the run-in phase and 7.5% during the 6-month study phase, approximately 70 subjects will undergo randomization and 64 will complete the 6-month study phase. The sample size calculation also assumes an alpha of 0.05, a power of 80% and a minimum difference in mean (SD) reduction of 0.5 (0.7)% in HbA1c in the treatment arm versus the control arm. The value of 0.5% in terms of HbA1c change also constitutes the minimum clinically meaningful difference, and is based on

the findings of a 2011 study by Hermanides *et al.* 2011.[20] Due to uncertainty about the magnitude of the SD and the effect of treatment, the study has been designed to allow for a reassessment of sample size based on an interim analysis to be performed by an independent Data Monitoring Committee (DMC) after at least 30 patients have completed the 6-month study phase in Cohort A. The interim analysis for sample size reassessment with one interim look, protecting the overall two-sided type 1 error of 0.05, is based on the conditional power approach of Li *et al*.[21] and Chen *et al*.[22] as extended by Mehta and Pocock.[23] On the basis of this interim analysis, the DMC will recommend termination or completion of the study, and if appropriate an increase in the sample size. Drop-out rates will also be reassessed. For Cohort B (670G version 4.0 AHCL versus MDI plus RT-CGM) a total enrollment of 40 subjects will be required to achieve approximately 34 subjects undergoing randomization and 30 subjects completing the 6-month study phase for exploratory analysis.

Statistical analysis

HbA1c measurements will be performed at baseline, the end of Month 3 and the end of Month 6. The primary endpoint (change in HbA1c from baseline to 6 months) will be analyzed using a repeated measures random effects model that accounts for subjects who dropout of the study and for possible missing at random data. All analyses will be performed using the intention-to-treat (ITT) population, which will consist of all randomized patients. To preserve the overall type I error and claim significance, a hierarchical test procedure will be performed for the predefined secondary endpoints (Table 2). The study statistician analyzing the data will be masked to group assignment until final database lock. Patient baseline demographics and characteristics will be collected and presented using descriptive statistics for continuous variables and counts or percentages for categorical variables.

Ethics and dissemination

The ADAPT study will be conducted in accordance with the requirements of the Declaration of Helsinki as well as local laws and regulations of the countries in which the study will be conducted. The study will also be conducted in compliance with the principles of good clinical practice, which includes review and approval by an independent ethics committee or institutional review board in

France (Comité de Protection des Personnes Ile de France IV), Germany (Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster), and the UK (London-Dulwich Research Ethics Committee), and is aligned with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Statement (Supplementary Materials 2 and 3).[24] Each participating center will not commence any patient-related study activities until approval by the relevant ethics committee or institutional review board has been received and the study center has received clearance from the sponsor to commence the study. The study is registered with clinicaltrials.gov (NCT04235504).

DISCUSSION

The aim of the ADAPT study will be to determine the change in HbA1c from baseline to 6 months for adults with T1D using the AHCL system relative to those using MDI plus IS-CGM. The clinical benefits as well as the convenience of technologies such as CGM and insulin pumps are increasingly recognized by payers and policy makers as well as treating physicians. International and national level guidelines also frequently recommend the use of CGM and/or insulin pumps in people with T1D struggling to achieve good glycemic control. For example, the French national guidelines recommend the use of IS-CGM as an alternative or replacement for SMBG in patients with type 1 or type 2 diabetes on intensified insulin therapy.[25] Similarly, the current ADA guidelines note that the use of technology should be individualized based on a combination of need, desire, skill level and availability.[11]

The inclusion criteria limit trial enrollment to subjects with a baseline HbA1c of ≥8.0% (64 mmol/mol), i.e. subjects failing to achieve good glycemic control as stipulated by HbA1c targets recommended in major guidelines.[26] This aligns with the patient population utilizing insulin pumps and CGM in many settings, where reimbursement of medical devices such as CGM is often limited to those with poor glycemic control or frequent severe hypoglycemic events.[27] The use of MDI plus IS-CGM as the comparator/standard of care arm in the ADAPT study has both clinical and economic implications. Clinical studies have consistently shown that both IS-CGM, RT-CGM and SAP or AHCL can improve glycemic control and increase the proportion of patients obtaining these goals, while reducing the proportion of time spent in the hypoglycemic range relative to SMBG.[28] However, to date, long-term, head-to-head studies of AHCL versus MDI plus IS-CGM (or RT-CGM) are lacking.

Given the continued evolution of medical devices in the management of people with T1D payers and policy makers must determine whether the incremental clinical benefits provided by the latest advances in technology represent good value for money relative to the standard of care. It is therefore important that cost-effectiveness analyses utilize clinical input data that reflects contemporary clinical practice to avoid over- or underestimating long-term clinical or economic outcomes. ADAPT will provide valuable data in this regard by providing head-to-head data for future

economic evaluations of AHCL versus MDI plus IS-CGM. Additionally, the ADAPT study will include days of work/school lost as an ancillary endpoint, which will provide valuable input data for health economic analyses performed from the societal perspective. The ADAPT study will also assess several PROs including FoH, QoL and treatment satisfaction. The inclusion of PROs is important to give an accurate measure of the patient experience in both treatment arms. Moreover, health economic analyses have shown that factors such as reduced FoH can be a key driver of the cost-effectiveness of HCL systems.[29]

For many people with T1D there is frequently a stepwise change in treatment or addition of supplementary technologies such as CGM or insulin pump therapy only when people fail to achieve glycemic targets or experience problematic hypoglycemia.[30] Alongside this, a degree of therapeutic inertia has been reported in some settings, resulting in delays in intensification of treatment or addition of technology, which may potentially have implications in terms of the risk for long-term complications.[31] There is evidence of a legacy effect in T1D with good glycemic control early in the course of the disease reducing or delaying the incidence of serious long-term complications.[32] This may, in turn, have economic implications in terms of the medical costs associated with long-term complications. The importance of optimizing treatment for patients with T1D is clear and it is hoped that the ADAPT study will provide valuable information regarding the use of AHCL systems in adult with T1D.

The ADAPT study will address the issue of whether the AHCL system can provide incremental benefits over a period of 6 months in terms of glycemic control relative to MDI plus IS-CGM in adults with T1D. The study will also provide an important evidence base for future cost-effectiveness analyses of the one of the most advanced AHCL systems currently available to support market access.

REFERENCES

[1] Brown SA, Kovatchev BP, Raghinaru D, et al. Six-Month Randomized, Multicenter Trial of Closed Loop in Type 1 Diabetes. N Engl J Med. 2019 Oct;381(18):1707-17

[2] Leelarathna L, Choudhary P, Wilmot EG, Lumb A, Street T, Kar P, Ng SM. Hybrid closed-loop therapy: Where are we in 2021? Diabetes Obes Metab. 2020 Dec; doi: 10.1111/dom.14273 (published online ahead of print)

[3] Collyns O, Meier R, Betts Z, et al. Improved Glycemic Outcomes with Medtronic MiniMed Advanced Hybrid Closed-Loop Delivery: Results from a Randomized Crossover Trial Comparing Automated Insulin Delivery with Predictive Low Glucose Suspend in People with Type 1 Diabetes. Diabetes Care. 2021. Online publication ahead of print; dc202250: https://doi.org/10.2337/dc20-2250

[4] McAuley SA, Lee MH, Paldus B, Vogrin S, de Bock MI, Abraham MB, Bach LA, Burt MG, Cohen ND, Colman PG, Davis EA, Hendrieckx C, Holmes-Walker DJ, Kaye J, Keech AC, Kumareswaran K, MacIsaac RJ, McCallum RW, Sims CM, Speight J, Stranks SN, Sundararajan V, Trawley S, Ward GM, Jenkins AJ, Jones TW, O'Neal DN; Australian JDRF Closed-Loop Research Group. Six Months of Hybrid Closed-Loop Versus Manual Insulin Delivery With Fingerprick Blood Glucose Monitoring in Adults With Type 1 Diabetes: A Randomized, Controlled Trial. Diabetes Care. 2020 Dec;43(12):3024-3033. doi: 10.2337/dc20-1447. Epub 2020 Oct 14. PMID: 33055139.

[5] Huo L, Harding JL, Peeters A, Shaw JE, Magliano DJ. Life expectancy of type 1 diabetic patients during 1997-2010: a national Australian registry-based cohort study. Diabetologia. 2016 Jun;59(6):1177-85

[6] Petrie D, Lung TW, Rawshani A, Palmer AJ, Svensson AM, Eliasson B, Clarke P. Recent trends in life expectancy for people with type 1 diabetes in Sweden. Diabetologia. 2016 Jun;59(6):1167-76

[7] Bjornstad P, Donaghue KC, Maahs DM. Macrovascular disease and risk factors in youth with type 1 diabetes: time to be more attentive to treatment? Lancet Diabetes Endocrinol. 2018 Oct;6(10):809-820

[8] Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, Maahs DM, Tamborlane WV, Bergenstal R, Smith E, Olson BA, Garg SK. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther. 2019 Feb;21(2):66-72

[9] NHS England 2019. Flash Glucose Monitoring: National Arrangements for Funding of Relevant Diabetes Patients. Available at: https://www.england.nhs.uk/wp-content/uploads/2020/02/national-arrangements-for-funding-of-relevant-diabetes-patients-v1.2.pdf [Last accessed August 11, 2020]

[10] Grunberger G, Handelsman Y, Bloomgarden ZT, Fonseca VA, Garber AJ, Haas RA, Roberts VL, Umpierrez GE. American Association of Clinical Endocrinologists and American College of Endocrinology 2018 Position Statement on Integration of Insulin Pumps and Continuous Glucose Monitoring in Patients with Diabetes Mellitus. Endocr Pract. 2018 Mar;24(3):302-30

[11] American Diabetes Association. 7. Diabetes Technology: *Standards of Medical Care in Diabetes-2019*. Diabetes Care. 2019 Jan;42(Suppl 1):S71-S80

[12] Jangam S, Dunn T, Xu Y, Hayter G, Ajjan RA. Flash glucose monitoring improves glycemia in higher risk patients: a longitudinal, observational study under real-life settings. BMJ Open Diabetes Res Care. 2019 Mar 25;7(1):e000611

[13] Landau Z, Abiri S, Gruber N, Levy-Shraga Y, Brener A, Lebenthal Y, Barash G, Pinhas-Hamiel O, Rachmiel M. Use of flash glucose-sensing technology (FreeStyle Libre) in youth with type 1 diabetes: AWeSoMe study group real-life observational experience. Acta Diabetol. 2018 Dec;55(12):1303-1310

[14] van den Boom L, Karges B, Auzanneau M, Rami-Merhar B, Lilienthal E, von Sengbusch S, Datz N, Schröder C, Kapellen T, Laimer M, Schmid SM, Müller H, Wolf J, Holl RW. Temporal Trends and Contemporary Use of Insulin Pump Therapy and Glucose Monitoring Among Children, Adolescents, and Adults With Type 1 Diabetes Between 1995 and 2017. Diabetes Care. 2019;42(11):2050-2056

[15] Reliability and validity of a diabetes quality-of-life measure for the diabetes control and complications trial (DCCT). The DCCT Research Group. Diabetes Care. 1988 Oct;11(9):725-32

[16] Renard E, Vague V, Hanaire H, Haardt MJ, Guerci B, Pinget M, Bringer pour le groupe Evadiac. Validation psychométrique d'une version française du questionnaire d'évaluation de la qualité de vie du diabétique élaboré par le DCCT Research Group (DQOL). Diabetes Metab. 1999;25:22.

[17] Bradley, 1994. The Diabetes Treatment Satisfaction Questionnaire: DTSQ. Handbook of Psychology and Diabetes.

[18] Health Psychology Research. Available at: https://www.healthpsychologyresearch.com/ [Last accessed September 14, 2021]

[19] Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia: quantification, validation, and utilization. Diabetes Care. 1987 Sep-Oct;10(5):617-21

[20] Hermanides J, Nørgaard K, Bruttomesso D, Mathieu C, Frid A, Dayan CM, Diem P, Fermon C, Wentholt IM, Hoekstra JB, DeVries JH. Sensor-augmented pump therapy lowers HbA(1c) in suboptimally controlled Type 1 diabetes; a randomized controlled trial. Diabet Med. 2011 Oct;28(10):1158-67

[21] Li G, Shih WJ, Xie T, Lu J. A sample size adjustment procedure for clinical trials based on conditional power. Biostatistics. 2002 Jun;3(2):277-87

[22] Chen YH, DeMets DL, Lan KK. Increasing the sample size when the unblinded interim result is promising. Stat Med. 2004 Apr 15;23(7):1023-38

[23] Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med. 2011 Dec 10;30(28):3267-84

[24] SPIRIT Statement Website. Available at: https://www.spirit-statement.org [Last accessed March 29, 2021]

[25] Borot S, Benhamou PY, Atlan C, Bismuth E, Bonnemaison E, Catargi B, Charpentier G, Farret A, Filhol N, Franc S, Gouet D, Guerci B, Guilhem I, Guillot C, Jeandidier N, Joubert M, Melki V, Merlen E, Penfornis A, Picard S, Renard E, Reznik Y, Riveline JP, Rudoni S, Schaepelynck P, Sola-Gazagnes A, Tubiana-Rufi N, Verier-Mine O, Hanaire H; Société francophone du diabète (SFD), Société française d'endocrinologie (SFE); Évaluation dans le diabète des implants actifs Group (EVADIAC). Practical implementation, education and interpretation guidelines for continuous glucose monitoring: A French position statement. Diabetes Metab. 2018 Feb;44(1):61-72

[26] American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019 Jan;42(Suppl 1):S61-S70.

[27] Graham C. Continuous Glucose Monitoring and Global Reimbursement: An Update. Diabetes Technol Ther. 2017 Jun;19(S3):S60-S66

[28] De Ridder F, den Brinker M, De Block C. The road from intermittently scanned continuous glucose monitoring to hybrid closed-loop systems. Part B: results from randomized controlled trials. Ther Adv Endocrinol Metab. 2019 Aug 30;10:2042018819871903

[29] Jendle J, Pöhlmann J, de Portu S, Smith-Palmer J, Roze S. Cost-Effectiveness Analysis of the MiniMed 670G Hybrid Closed-Loop System Versus Continuous Subcutaneous Insulin Infusion for Treatment of Type 1 Diabetes. Diabetes Technol Ther. 2019 Mar;21(3):110-118

[30] Brunton S. Therapeutic Inertia is a Problem for All of Us. Clin Diabetes. 2019 Apr;37(2):105-106

[31] Brož J, Janíčková Žďárská D, Urbanová J, Brabec M, Doničová V, Štěpánová R, Martinka E, Kvapil M. Current Level of Glycemic Control and Clinical Inertia in Subjects Using Insulin for the Treatment of Type 1 and Type 2 Diabetes in the Czech Republic and the Slovak Republic: Results of a Multinational, Multicenter, Observational Survey (DIAINFORM). Diabetes Ther. 2018 Oct;9(5):1897-1906

[32] Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. JAMA. 2003 Oct 22;290(16):2159-67

AUTHORS CONTRIBUTIONS

SdP, LV, RR, JS, JC, AH and OC contributed to the design of the study and critically reviewed the present manuscript. SdP, LV, RR, JS, JC, AH and OC approved the final version of the manuscript, and are accountable for all aspect of the work. The authors are grateful to Jayne Smith-Palmer at Ossian Health Economics and Communications for medical writing support in the preparation of the manuscript.

FUNDING STATEMENT

The ADAPT Study is sponsored and funded by Medtronic International Trading Sàrl. Award/Grant number is not applicable.

COMPETING INTEREST STATEMENT

SdP, LV, RR, JS, AH and OC are employees of Medtronic. JC is an employee of Bakken Research Center.

TABLES

Table 1 Inclusion and exclusion criteria for the ADAPT study

Inclusion criteria	Exclusion criteria
• Age ≥18 years at screening • Clinical diagnosis of T1D for ≥2 years prior to screening • On MDI therapy[a] for ≥2 years prior to screening • Subject has been followed and treated by investigator for at least ≥3 months prior to screening and has undergone local educational therapeutic programs • Subject is using: IS-CGM for ≥3 months with daily average of ≥5 scans with sensor readings > 70% of time over the previous month prior to screening Or, RT-CGM, ≥ 3 months with sensor use >70% of the time over the previous month • HbA1c of ≥8.0% (64 mmol/mol) at screening • Subject is willing to take or switch to Humalog™ (insulin lispro injection) or Novolog™ (insulin aspart) • Minimum daily insulin requirement of ≥8 units and maximum of 250 units per day • Subject is willing to upload data from the study pump and meter (subject must have internet access and computer system that meets the requirements for uploading study pump data at home) • Subject is willing and able to provide informed consent comply with all study procedures and wear all study devices, as required during the study	• Untreated Addison's disease, thyroid disorder, growth hormone deficiency, hypopituitarism or definite gastroparesis • Use of pramlintide, DPP-4 inhibitor, GLP-1 agonists/mimetics, metformin, SGLT2 inhibitors at screening • Renal failure, defined as creatinine clearance <30 mL/min • Subject is planning to switch from IS-CGM to RT-CGM during the 6-month study phase • History of hearing or vision impairment hindering perception of glucose display and alarms, or otherwise incapable of using the study devices • Women of child bearing potential who are pregnant at screening or plan to become pregnant during the study period • Females who are sexually active and able to conceive not using an effective method of contraception and not agreeing to continue using an effective method of contraception for the duration of the study • Unresolved adverse skin conditions in the area of sensor placement (e.g. psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection). • Active participation in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or device in the last 2 weeks before enrollment into the study • Current abuse of illicit drugs, marijuana, alcohol or prescription drugs (other than nicotine) • Subject has any other disease or condition that may preclude the patient from participating in the study • Subject is legally incompetent, illiterate or vulnerable person • Research staff involved with the study

a Defined as ≥3 insulin injections per day and/or a basal/bolus regimen

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; IS-CGM, intermittently scanned MDI, multiple daily injections; RT-CGM, real-time continuous glucose monitoring; SGLT-2, sodium-glucose co-transporter-2; T1D, type 1 diabetes

Table 2 Secondary endpoints to be assessed in Cohort A

Secondary endpoints
Percentage time spent in hyperglycemic range with SG >250 mg/dL (13.9 mmol/L)
Percentage time spent in hyperglycemic range with SG >180 mg/dL (>10.0 mmol/L)
Percentage time spent within range with SG between 70–180 mg/dL (3.9–10.0 mmol/L)
Percentage time spent in hypoglycemic range with SG <54 mg/dL (3.0 mmol/L)
Percentage time spent in hypoglycemic range with SG <70 mg/dL (3.9 mmol/L)

SG, sensor glucose

Table 3 Ancillary endpoints

Endpoint
• Percentage time spent in 70–140 mg/dL (3.9–7.8 mmol/L) range
• AUC in hypoglycemic range with SG <54 mg/dL (3.0 mmol/L), <70 mg/dL (3.9 mmol/L)
• Percentage time and AUC in hyperglycemic range with SG >140 mg/dL (7.8 mmol/L), >350 mg/dL (19.4 mmol/L) and AUC in hyperglycemic range with SG >180 mg/dL (10 mmol/L), >250 mg/dL (13.9 mmol/L)
• Number of biochemical hypoglycemic events with SG <54 mg/dL (3.0 mmol/L), <70 mg/dL (3.9 mmol/L) (defined as sensor values below the threshold per 15 and 20 consecutive minutes, respectively)
• Mean of SG values (mg/dL)
• Percentage time spent in closed loop and open loop
All above endpoints will be categorized by daytime (06:01 to 23:59) and night-time (00:00 to 06:00) and overall (24h)
• Percentage time spent in hyperglycemic range with SG >250 mg/dL (13.9 mmol/L)
• Percentage time spent in hyperglycemic range with SG >180 mg/dL (>10.0 mmol/L)
• Percentage time spent within range with SG between 70–180 mg/dL (3.9–10.0 mmol/L)
• Percentage time spent in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L)
• Percentage time spent in hypoglycemic range with SG <70 mg/dL (3.9 mmol/L)
The above five endpoints will be categorized by daytime (06:01 to 23:59) and night-time (00:00 to 06:00)
• Number of scans and percentage of sensor readings for MDI plus IS-CGM control arm
• Percentage of sensor readings for MDI plus RT-CGM control arm only
• Number of SMBG tests in the AHCL arm
• Percentage of sensor use
• Excursion amplitudes of the glucose values measured by MAGE
• Coefficient of variation of SG values
• Change in total daily dose of insulin from baseline to EOS
• Change in weight from baseline to EOS
• Change in BMI from baseline to EOS
• Mean HbA1c change (from baseline to 12 months)
• Mean HbA1c change (baseline to 6 month) by age groups and duration of diabetes
• Diabetes-related number and mean duration of hospitalizations, number and mean duration intensive care unit care, number of emergency room admissions, number of events requiring ambulance assistance, categorized by reason of diagnosis
• Number of lost days from school or work.
• Hypoglycemia Fear Survey score
• Diabetes Treatment Satisfaction Questionnaire score
• Diabetes Quality of Life questionnaire score

AHCL, advanced hybrid closed loop; AUC, area under the curve; BMI, body mass index; EOS, end of study; IS-CGM, intermittently scanned continuous glucose monitoring; MAGE, mean amplitude of glycemic excursions; MDI, multiple daily injections; RT-CGM, real time continuous glucose monitoring; SG, sensor glucose; SMBG, self-monitoring of blood glucose

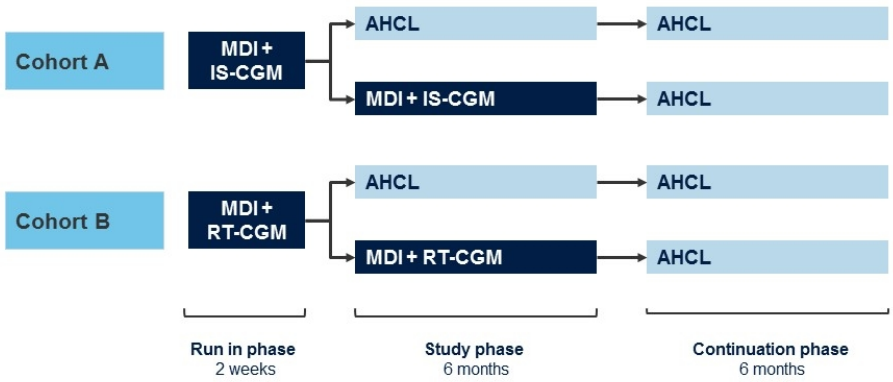
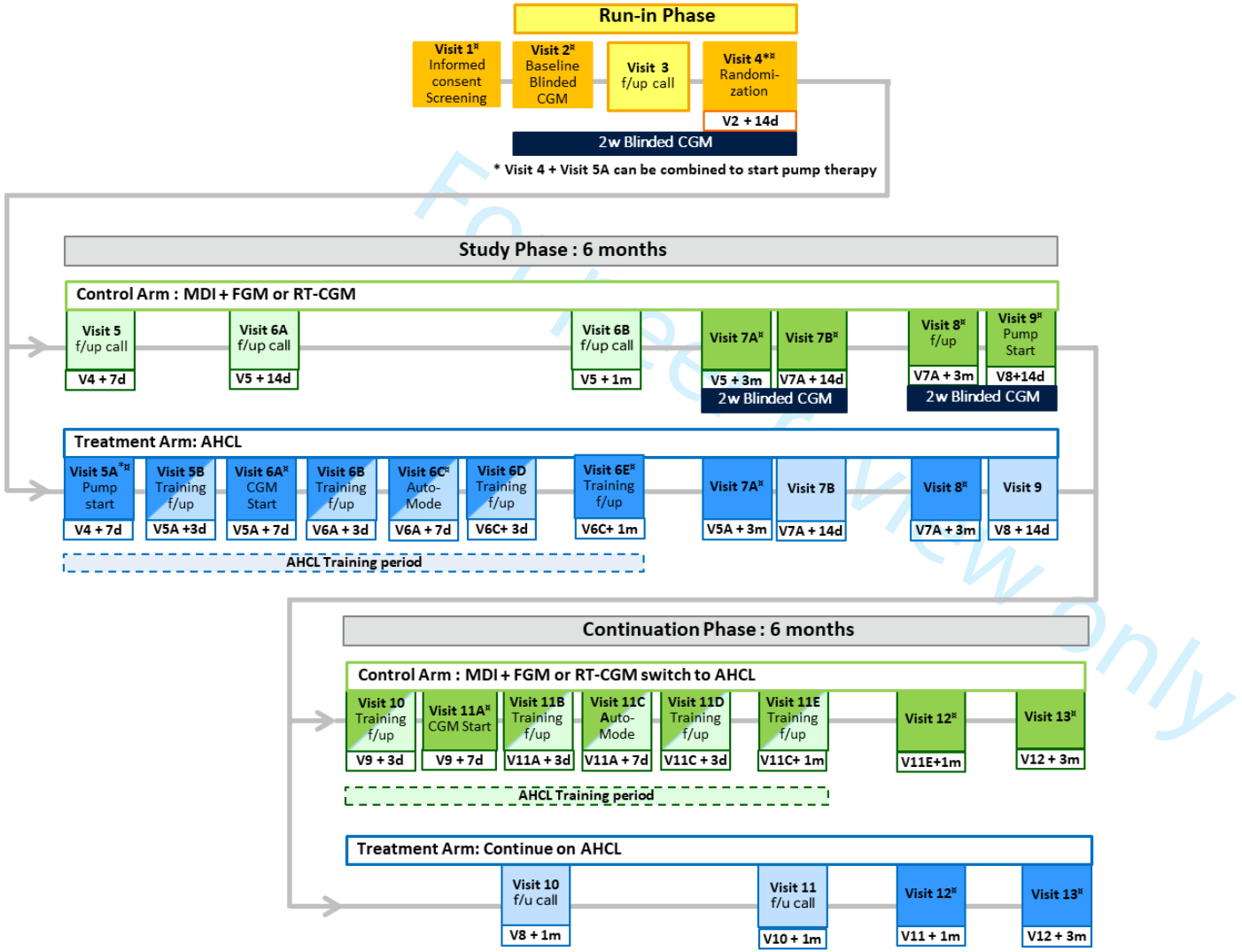


Figure 1 Study Design

AHCL, advanced hybrid closed loop; IS-CGM, intermittently scanned continuous glucose monitoring; MDI, multiple daily injections; RT-CGM, real-time continuous glucose monitoring

254x190mm (96 x 96 DPI)

Supplementary Figure 1 Visit schedule overview



¤ Visits allowed to be conducted remotely in pandemic period.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	CIP, page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Clinicaltrials.gov: NCT04235504
	2b	All items from the World Health Organization Trial Registration Data Set	1-3/6/8-10/19 Table 1
Protocol version	3	Date and version identifier	CIP, p.1, header
Funding	4	Sources and types of financial, material, and other support	Full sponsor /funding by MDT
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	N/A, MDT only__
	5b	Name and contact information for the trial sponsor	CIP 17.1.1. Appendix__
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Full sponsor /funding by MDT

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	No Steering committee CEC Charter DMC Charter Study roster
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	CIP p.20-21
	6b	Explanation for choice of comparators	CIP p.21 - 26_
Objectives	7	Specific objectives or hypotheses	CIP p.22
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	CIP p. 25_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	CIP 17.1.1 appendix_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p. 42-43_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	CIP Section 9 ___
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	CIP p 52 p. 109 _____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	CIP p.43, p 84__

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	CIP 23-24
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	CIP p. 25, 45__
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	CIP p. 101-102___
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	CIP p. 41, 102__

Methods: Assignment of interventions (for controlled trials)

Allocation:

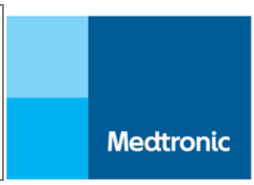
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Randomization Plan_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	In Oracle Database

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Randomization is performed by automatic assignment within eCRF Oracle Database, complete by Site staff, who are enrolling and following patients to intervention.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	CIP Section 9, Primary outcome p. 72 Questionnaires p. 73-74 CRFs___
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	CIP p.71___
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	DMP, DQP

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	CIP section 13 p 102-103, SAP___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	CIP p. 104-105, SAP_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	SAP_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	DMC Charter
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	DMC Charter, DMC SAP
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	CIP section 11, p. 89-99
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	CIP p.110____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	CIP p. 104-105__
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	CIP p.113_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	CIP p.75-76_____

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	CIP p 112_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	CTA_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	CTA_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	ICF_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	CIP p. 114 ICF, clinicaltrials.gov
	31b	Authorship eligibility guidelines and any intended use of professional writers	Publication Plan_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached___
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.



INFORMED CONSENT FOR THE MEDTRONIC

ADAPT CLINICAL STUDY

SUBJECT INFORMED CONSENT FORM SIGNATURE SHEET

- I have read the subject information for this study and the study doctor has answered all my questions regarding the study.
- I had sufficient time to consider my participation in this study, I am aware that participation in this study is completely voluntary, and I agree to follow the instructions of the study doctor.
- I realize that I may decide to refuse participation or stop participating at any time without penalty and without affecting the quality of my health care or the relationship with the study doctor.
- I understand and agree that personal information about me will be collected from my medical files, used and processed (manually and by computer) by the manufacturer of a product used in my treatment or any other designated party that is involved in the study (e.g., hospital, study doctor, regulatory authorities, ethics committees).
- I know what will happen if I leave the study and understand the details described in this form.
- I understand and agree that representatives from Medtronic, regulatory authorities and the Ethics Committee will be given direct access to my medical files.
- I understand and agree that the study doctor(s)/hospital will release the relevant personal information about me for the purpose of the study.
- I understand that my personal data may be provided to third-party vendor personnel for the purpose of carrying out home visits and/or supplies shipments and treated with strict confidentiality as detailed in the patient information sheet, if needed during pandemic.
- I understand that I am entitled to access the personal information collected about me and to have inaccuracies corrected.
- I agree to voluntarily be in and comply with this study.
- I understand that I will receive a dated and signed copy of the subject informed consent form.

- *This notification can be deleted for countries where personal physicians do not exist*
- *Use if EC requires a checkbox*

It is your choice if you would like your personal doctor to be informed of your participation in this study. Please check one of the boxes below to show your choice:

! must be checked by subject

☐ I agree to inform my personal doctor about my participation in this study

☐ I do not agree to inform my personal doctor about my participation in the study

Signature of the subject

I agree to be in this study and I have consented before the initiation of any study specific procedures.

Subject:

Name	Signature	Date (DD/MMM/YYYY)
	Must be written by subject!	*Must be written by subject!*

Study doctor or person designated by study doctor:

I have conducted the informed consent discussion.

Name	Signature	Date (DD/MMM/YYYY)
	Must be written by study doctor or delegate!	*Must be written by study doctor or delegate!*