# Comparing advanced hybrid closed loop therapy and standard insulin therapy in pregnant women with type 1 diabetes (CRISTAL): a parallel-group, open-label, randomised controlled trial

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## Summary

**Background** Advanced hybrid closed loop (AHCL) therapy can improve glycaemic control in pregnant women with type 1 diabetes. However, data are needed on the efficacy and safety of AHCL systems as these systems, such as the MiniMed 780G, are not currently approved for use in pregnant women. We aimed to investigate whether the MiniMed 780G can improve glycaemic control with less hypoglycaemia in pregnant women with type 1 diabetes.

**Methods** CRISTAL was a double-arm, parallel-group, open-label, randomised controlled trial conducted in secondary and tertiary care specialist endocrinology centres at 12 hospitals (11 in Belgium and one in the Netherlands). Pregnant women aged 18–45 years with type 1 diabetes were randomly assigned (1:1) to AHCL therapy (MiniMed 780G) or standard insulin therapy (standard of care) at a median of 10·1 (IQR 8·6–11·6) weeks of gestation. Randomisation was done centrally with minimisation dependent on baseline $HbA_{1c}$, insulin administration method, and centre. Participants and study teams were not masked to group allocation. The primary outcome was proportion of time spent in the pregnancy-specific target glucose range (3·5–7·8 mmol/L), measured by continuous glucose monitoring (CGM) at 14–17 weeks, 20–23 weeks, 26–29 weeks, and 33–36 weeks. Key secondary outcomes were overnight time in target range, and time below glucose range (<3·5 mmol/L) overall and overnight. Analyses were conducted on an intention-to-treat basis. This trial is registered with ClinicalTrials.gov (NCT04520971).

**Findings** Between Jan 15, 2021 and Sept 30, 2022, 101 participants were screened, and 95 were randomly assigned to AHCL therapy (n=46) or standard insulin therapy (n=49). 43 patients assigned to AHCL therapy and 46 assigned to standard insulin therapy completed the study. At baseline, 91 (95·8%) participants used insulin pumps, and the mean $HbA_{1c}$ was 6·5% (SD 0·6). The mean proportion of time spent in the target range (averaged over four time periods) was 66·5% (SD 10·0) in the AHCL therapy group compared with 63·2% (12·4) in the standard insulin therapy group (adjusted mean difference 1·88 percentage points [95% CI –0·82 to 4·58], p=0·17). Overnight time in the target range was higher (adjusted mean difference 6·58 percentage points [95% CI 2·31 to 10·85], p=0·0026), and time below range overall (adjusted mean difference –1·34 percentage points [95% CI, –2·19 to –0·49], p=0·0020) and overnight (adjusted mean difference –1·86 percentage points [95% CI –2·90 to –0·81], p=0·0005) were lower with AHCL therapy than with standard insulin therapy. Participants assigned to AHCL therapy reported higher treatment satisfaction. No unanticipated safety events occurred with AHCL therapy.

**Interpretation** In pregnant women starting with tighter glycaemic control, AHCL therapy did not improve overall time in target range but improved overnight time in target range, reduced time below range, and improved treatment satisfaction. These data suggest that the MiniMed 780G can be safely used in pregnancy and provides some additional benefits compared with standard insulin therapy; however, it will be important to refine the algorithm to better align with pregnancy requirements.

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## Introduction

Type 1 diabetes in pregnancy is associated with an increased risk of adverse perinatal and maternal outcomes such as congenital anomalies, neonatal death, preterm delivery, and pre-eclampsia.[1–5] Pregnancy outcomes can be improved by tight glycaemic control, with $HbA_{1c}$ less than 6·5% and a pregnancy-specific time in glucose target range of 70% or higher (of glucose values 3·5–7·8 mmol/L [63–140 mg/dL]) being advocated during pregnancy.[6–8] Achieving this tight control is an elusive goal in many pregnant women with type 1 diabetes. Moreover, tight

## Research in context

### Evidence before this study

We searched PubMed for reports of clinical trials published in English from database inception up to Jan 30, 2024, comparing advanced hybrid closed loop (AHCL) therapy and standard insulin therapy in pregnant women with type 1 diabetes. We used the search terms "closed-loop therapy", "closed-loop insulin delivery", "automated insulin delivery", and "advanced hybrid closed loop therapy", in combination with the terms "type 1 diabetes" and "pregnancy". We identified eight manuscripts of seven studies: two small phase 1 crossover randomised trials, two phase 2 crossover randomised trials plus a secondary analysis of these trials, a randomised controlled trial, and two observational studies. The CamAPS FX system is currently the only AHCL therapy licensed for use in pregnancy in Europe and Australia. However, since AHCL systems can facilitate achievement of optimal preconception glycaemic control, more women are becoming pregnant while using AHCL systems (such as the MiniMed 780G), which are not approved for use in pregnancy. Data are therefore needed on the safety and efficacy of off-label use of AHCL systems in pregnancy.

### Added value of this study

Since AHCL systems can facilitate achievement of optimal preconception glycaemic control, more women are becoming pregnant while using AHCL systems (such as the MiniMed 780G), which are not approved for use in pregnancy. The CRISTAL study is, to the best of our knowledge, the first large, parallel-group, open-label, multicentre randomised controlled trial comparing the widely used MiniMed 780G with standard insulin therapy in pregnant women with type 1 diabetes. Our results suggest that in women with overall tight glycaemic control in the first trimester, AHCL therapy resulted in a similar proportion of time spent in the target glucose range (3·5–7·8 mmol/L) compared with standard insulin therapy, with higher overnight time in target range, less time below glucose range <3·5 mmol/L overall and overnight, reduced hypoglycaemia unawareness, reduced glycaemic variability, and improved treatment satisfaction.

### Implications of all the available evidence

In pregnant women with type 1 diabetes starting with tighter glycaemic control in the first trimester, AHCL therapy did not improve overall time in the target glucose range but improved overnight time in glucose target (3·5–7·8 mmol/L), reduced time below range, and improved treatment satisfaction. Our findings suggest that the MiniMed 780G is safe for use in pregnancy and provides some additional benefits compared with standard insulin therapy.

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glycaemic control comes with increased risks of maternal hypoglycaemia.[1,9–12]

Insulin pumps and in particular continuous glucose monitoring (CGM) have allowed more women to achieve the proposed strict glycaemic targets,[13] but there is still a major unmet need for many pregnant women with type 1 diabetes. Advanced hybrid closed loop (AHCL) therapy, providing automated glucose-responsive insulin delivery with additional manually triggered premeal boluses, has improved glycaemic control in non-pregnant individuals with type 1 diabetes.[14–16] The AiDAPT trial, the first large trial evaluating AHCL therapy in pregnant women with type 1 diabetes, showed that, in women with a mean baseline $HbA_{1c}$ of 7·7% (SD 1·2), treatment with the CamAPS FX system (Cambridge model predictive control algorithm, University of Cambridge, Cambridge, UK) could increase the time in pregnancy range to 68%, close to the target of 70%.[17,18] The CamAPS FX system is currently the only AHCL therapy licensed for use in pregnancy in Europe and Australia.

Outside pregnancy, other AHCL systems, such as the MiniMed 780G system (Medtronic; Northridge, CA, USA), have shown the ability to achieve tight glycaemic control, improving time in range and reducing hypoglycaemia, measured as time below range.[14–16] The MiniMed 780G uses an algorithm that automatically adapts the basal insulin rate and also provides automated insulin boluses to correct for hyperglycaemia.[19] The MiniMed 780G has a lowest glucose concentration target setting of 5·5 mmol/L (100 mg/dL). Since AHCL systems can facilitate optimal preconception glycaemic control, more women are becoming pregnant while using AHCL systems such as the MiniMed 780G that are not approved for use in pregnancy.

We aimed to investigate whether the MiniMed 780G can safely improve glycaemic control with less hypoglycaemia in pregnant women with type 1 diabetes.

## Methods

### Study design and participants

The CRISTAL (Closed-loop insulin delivery in pregnant women with type 1 diabetes) study was a double-arm, parallel-group, open-label, randomised controlled trial comparing the MiniMed 780G AHCL system (the intervention group) with standard insulin therapy (control group with multiple daily injections, standalone insulin pumps, or sensor-augmented pump therapy with predictive suspension of insulin infusion before or at low sensor glucose concentration), with both treatment groups using CGM. The trial was conducted in secondary and tertiary care specialist endocrinology centres at 11 hospitals in Belgium and one hospital in the Netherlands.

The protocol (available in the appendix) was approved by the medical ethics review committees of participating centres, and Belgian and Dutch national competent authorities. The protocol has previously been published.[20] The trial was done in accordance with the Declaration of

See Online for appendix

Helsinki in its latest form. Since the Guardian 4 CGM (Medtronic; Northridge, CA, USA) became available during the trial, a protocol amendment was approved on Oct 20, 2021, to use the Guardian 4 CGM. Trial progress and safety were evaluated by a trial steering committee. The Leuven and Amsterdam Clinical Trials Units were responsible for data and safety monitoring. KBen, KBeu, PG, and CM drafted the manuscript and declare data integrity and compliance with the protocol.

We recruited pregnant women with type 1 diabetes, diagnosed at least 1 year before recruitment, aged 18–45 years, with a singleton pregnancy and treated with intensive insulin therapy (multiple daily injections or an insulin pump). Additional inclusion criteria were an $HbA_{1c}$ of 10% or lower (86 mmol/mol). Any type of CGM could be used. An AHCL system could be used as open loop or sensor-augmented pump therapy but not as a closed loop system. Women were recruited until 11 weeks and 6 days' gestation after confirmation of a viable pregnancy by ultrasonography or a hCG blood test. Key exclusion criteria were use of an AHCL system as closed loop, multiple pregnancies, medications known to interfere with glucose metabolism, total daily insulin dose of 1·5 units per kg or higher, known allergy to adhesives for infusion set or CGM (or both), and a physical or psychological disease likely to interfere with the conduct of the study according to evaluation by the treating physician. All participants gave written informed consent before the start of trial-related activities.

### Randomisation and masking

Participants were randomly assigned (1:1) to MiniMed 780G AHCL or the control group (standard insulin therapy with multiple daily injections or insulin pump therapy) based on an approach to deterministically minimise the imbalance between both groups in the following baseline characteristics:[21] $HbA_{1c}$ (local analysis, stratified as <7% or ≥7% [53 mmol/mol]), insulin delivery method (insulin injections or insulin pump), and centre. Participants were randomly assigned with the central software randomisation algorithm performed by I Biostat. Permuted block randomisation was performed on the first four participants. Subsequently, deterministic minimisation of variation was applied. The minimisation procedure and randomisation were done by the statistician (AL). The outcome of the randomisation was sent digitally to the study centres and communicated to each participant by the local study teams. Participants, investigators, and study teams were not masked to group allocation.

### Procedures

Local teams assessed eligibility of participants. Data were collected on demographics as well as medical and obstetric history. Results of a physical examination were recorded (with measurement of bodyweight, blood pressure, and height), several validated questionnaires were completed, and $HbA_{1c}$ was measured at each centre with a method in accordance with the International Federation of Clinical Chemistry and Laboratory Medicine.[22]

Up to 1 week after the screening visit, participants started a 10-day run-in phase for baseline glycaemic assessment with a CGM. A masked CGM (Guardian 3, Medtronic, Northridge, CA, USA; 7-day wear) was only requested from participants using a CGM method other than the Guardian 3 or 4 CGM. Self-monitoring of blood glucose was required at least twice daily for retrospective CGM calibration when a masked Guardian 3 was used.

Participants were randomly assigned within 1 week after the run-in phase and before 14 weeks' gestation. Differences in glycaemia between both groups were evaluated by similar CGM data collected during 21 days at different timepoints during pregnancy: at 9–12 weeks (if inclusion <8 weeks), 14–17 weeks, 20–23 weeks, 26–29 weeks, and 33–36 weeks of gestation. At each study visit (at 9 weeks [if inclusion <8 weeks], 14 weeks, 20 weeks, 26 weeks, and 33 weeks of gestation), a physical examination was done (with measurement of bodyweight and blood pressure) and blood was collected (for central analysis of $HbA_{1c}$ with high-performance liquid chromatography at the laboratory of UZ Leuven (Leuven, Belgium) and for long-term storage in the biobank to allow future analyses of new biomarkers and metabolomics). Glucose monitoring and insulin therapy data were collected at each study visit and reviewed to adjust the therapy. In addition to the study visits, in line with routine practice, participants were followed up every 2 weeks at the diabetes clinic (face to face or teleconsultation with a face-to-face visit at least every 4 weeks). The trial flow diagram is included in the appendix (p 6).

Within 1 week after randomisation, participants received structured education by the local teams on the use of the MiniMed 780G and switched to AHCL therapy. The MiniMed 780G includes a proportional-integral-derivative technology with insulin feedback (SmartGuard technology) consisting of the 780G insulin pump and Accu-Chek Guide Link glucometer with Guardian 3 or 4 CGM. As the Guardian 4 CGM became available during the trial, participants were switched from the Guardian 3 to the Guardian 4 CGM and new participants used the Guardian 4 from the start. The Guardian 4 sensor has a new advanced sensor calibration algorithm but is otherwise similar to the Guardian 3 sensor, and is intended to minimise or eliminate required calibrations, thereby reducing the glucose management burden for the user. The Guardian 4 sensor is physically identical to the Guardian 3 sensor, and the Guardian 4 transmitter is equivalent to the Guardian Connect Transmitter with the addition of the G Algorithm. Therefore, no major biases are expected when switching from the Guardian 3 CGM to the Guardian 4 CGM in the intervention group, nor when comparing data with the Guardian 3 CGM used during the run-in phase or in the standard of care group.[20]

Participants were recommended to set the glucose target at 5·5 mmol/L and active insulin time at 2 h throughout pregnancy, and to use the CGM and AHCL mode at least 80% of the time. Additionally, women were advised to limit their intake of carbohydrates with a high glycaemic index and to a bolus 15 min before meals (if needed, the time from bolus to meal could be increased to 30–45 min later in pregnancy).[7] If postprandial hyperglycaemia occurred despite optimisation of the insulin-to-carbohydrate ratios (and after optimisation of dietary intake and timing of bolus), participants were advised to provide assisted carbohydrate estimation (ie, add more carbohydrates than actually consumed; individualised advice was provided on what proportion of carbohydrates should be added according to need) between meals or with meals, or both, to assist the algorithm in increasing the bolus (appendix p 3).[23] Data on the need for assisted carbohydrate estimation (amount and frequency) were recorded prospectively.

Participants were offered the option to continue AHCL therapy during labour and delivery (data not reported).

Participants allocated to the standard insulin therapy group (the standard of care) continued with standard insulin therapy with multiple daily injections or insulin pump therapy (pump with standalone CGM or sensor-augmented pump therapy) with any type of CGM. For participants not using a Guardian 3 or 4 CGM, a masked Guardian 3 was used at the different time periods (14–17 weeks', 20–23 weeks', 26–29 weeks', and 33–36 weeks' gestation) for glycaemic assessment. Women were advised to limit their intake of carbohydrates with a high glycaemic index and to bolus 15 mins before meals in early pregnancy, and to increase the time from bolus to meal to 30–45 mins later in pregnancy.

After delivery, umbilical cord blood was collected for measurement of C-peptide. Neonatal skinfold thickness measurements were performed within 72 h after birth, by trained study staff by use of a Harpenden skinfold caliper. Skinfolds were measured twice consecutively at the triceps, subscapular, and flank. The mean measured value at each site was used to calculate the sum of skinfolds. Neonatal body fat mass was measured according to the formula of Catalano.[20]

## Outcomes

The primary outcome was the mean proportion of time spent in the pregnancy-specific target glucose range (3·5–7·8 mmol/L [63–140 mg/dL]) as measured by CGM over 14–17 weeks', 20–23 weeks', 26–29 weeks', and 33–36 weeks' gestation. Key secondary outcomes were overnight (between 2400 h and 0600 h) time in target range, and time below glucose range (<3·5 mmol/L) overall and overnight as measured by CGM over 14–17 weeks', 20–23 weeks', 26–29 weeks', and 33–36 weeks' gestation.

Additional exploratory secondary outcomes were the following glycaemic outcomes: the primary and key

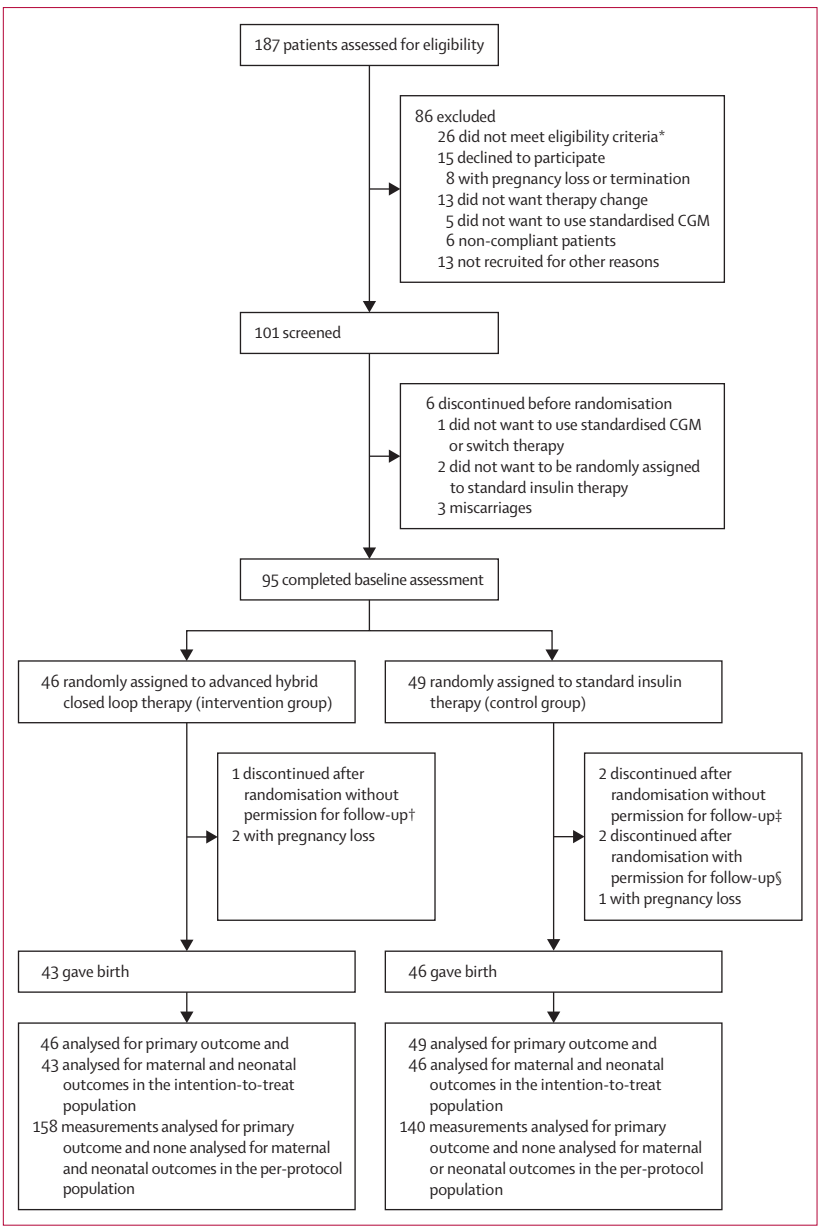


***Figure 1:*** **Trial profile**

CGM=continuous glucose monitoring. *Reasons for not meeting eligibility criteria were: type 1 diabetes diagnosis less than 1 year before pregnancy (n=2), $HbA_{1c}$ greater than 10% (n=1), outside of gestational age window (>11 weeks 6 days; n=8), no intensive insulin therapy (n=1), multiple pregnancies (n=1), use of advanced hybrid closed loop therapy and not willing to stop (n=11), allergy to adhesives (n=1), and language barrier (n=1). Without permission for follow-up indicates women who withdrew consent and did not give permission to collect data in the context of the study from their electronic medical records, or in other words, who withdrew from the study entirely. With permission for follow-up indicates women who withdrew consent but gave permission to collect data in the context of the study from their electronic medical records without performing any study-related procedures. †One participant withdrew from the advanced hybrid closed loop therapy group at 24 weeks of gestation due to the burden of trial participation but continued to use advanced hybrid closed loop therapy outside this trial. ‡One participant withdrew from the standard insulin therapy group at 4 weeks of gestation due to their wish of switching to advanced hybrid closed loop therapy and one withdrew at 15 weeks of gestation due to the burden of standardised CGM use and trial participation. §One participant withdrew from the standard insulin therapy group at 9 weeks of gestation due to the burden of standardised CGM use and trial participation and one withdrew at 11 weeks of gestation due to hyperemesis gravidarum and the burden of trial participation.

| | Advanced hybrid closed loop therapy (n=46) | Standard insulin therapy (n=49) |
|---|---|---|
| Age (years) | 30·8 (4·6) | 30·3 (3·8) |
| White ethnicity* | 41/46 (89·1%) | 43/49 (87·8%) |
| Duration of diabetes, years | 17·0 (9·2) | 30·3 (3·8) |
| BMI, kg/m² | 26·0 (3·6) | 26·9 (5·4) |
| Higher education*† | 31/45 (68·9%) | 32/47 (68·1%) |
| Gestational age at recruitment,weeks‡ | 8·2 (7·0–10·1) | 8·6 (6·9–10·0) |
| Gestational age at randomisation, weeks | 10·3 (8·9–11·9) | 10·1 (8·5–11·6) |
| Gestational age at start of advanced hybrid closed loop therapy, weeks§ | 10·7 (8·9–12·6) | .. |
| Medical history | | |
| Microvascular complications¶ | | |
| Retinopathy | 12/44 (27·3%) | 10/47 (21·3%) |
| Microalbuminuria pre-gestational | 6/44 (13·6%) | 8/40 (20·0%) |
| Neuropathy | 2/45 (4·4%) | 3/48 (6·2%) |
| Macrovascular diabetes complications | 1/46 (2·2%) | 0/49 (0·0%) |
| Severe hypoglycaemia (≥1) in 12 months before recruitment*‖ | 7/46 (15·2%) | 4/49 (8·2%) |
| Hospital admission for diabetic ketoacidosis (≥1) in 12 months before recruitment | 2/46 (4·3%) | 2/49 (4·1%) |
| Chronic hypertension | 1/46 (2·2%) | 1/49 (2·0%) |
| Systolic blood pressure, mm Hg | 120·5 (12·5) | 119·2 (11·7) |
| Diastolic blood pressure, mm Hg | 74·3 (9·9) | 73·2 (8·9) |
| Pregnancy history | | |
| Multiparity | 26/46 (56·5%) | 26/49 (53·1%) |
| Preconception diabetes care (≥1 consult) | 27/45 (60·0%) | 27/49 (55·1%) |
| Planned pregnancy* | 34/46 (73·9%) | 33/49 (67·3%) |
| Preconception | | |
| History of miscarriage (<20 weeks) | 16/46 (34·8%) | 15/49 (30·6%) |
| History of death in utero or stillbirth (≥20 weeks) | 1/46 (2·2%) | 1/49 (2·0%) |
| Folic acid 4–5 mg supplementation before pregnancy | 26/46 (56·5%) | 24/49 (50·0%) |
| Folic acid 4–5 mg supplementation during pregnancy | 40/46 (87·0%) | 43/49 (87·8%) |
| Alcohol consumption during pregnancy* | 4/45 (8·9%) | 5/47 (10·6%) |
| Smoking before pregnancy* | 7/42 (16·7%) | 10/43 (23·3%) |
| Smoking during pregnancy* | 3/45 (6·7%) | 4/47 (8·5%) |
| $HbA_{1c}$ (%) | 6·5% (0·6) | 6·5% (0·7) |
| <6·0% | 6/46 (13·0%) | 9/49 (18·4%) |
| 6·0 to <7·0% | 30/46 (65·2%) | 29/49 (59·2%) |
| 7·0 to <8·0% | 9/46 (19·6%) | 9/49 (18·4%) |
| ≥8·0% | 1/46 (2·2%) | 2/49 (4·1%) |
| $HbA_{1c}$ (mmol/mol) | 47·3 (7·0) | 47·5 (7·4) |
| (Continued from previous column) | | |
| Diabetes therapy | | |
| Continuous glucose monitor | 46/46 (100·0%) | 49/49 (100·0%) |
| Medtronic | 41/46 (89·1%) | 40/49 (81·6%) |
| Dexcom | 4/46 (8·7%) | 5/49 (10·2%) |
| Abbott FreeStyle Libre | 1/46 (2·2%) | 4/49 (8·2%) |
| Masked continuous glucose monitor** | 3/44 (6·8%) | 9/49 (18·4%) |
| Insulin delivery | | |
| Multiple daily injections†† | 2/46 (4·3%) | 2/49 (4·1%) |
| Insulin pump‡‡ | 44/46 (95·7%) | 47/49 (95·9%) |
| Continuous subcutaneous insulin infusion with standalone continuous glucose monitor | 3/44 (6·8%) | 7/47 (14·9%) |
| Sensor-augmented pump§§ | 37/44 (84·1%) | 38/47 (80·8%) |
| Advanced hybrid closed loop therapy | 4/44 (9·1%) | 2/47 (4·3%) |
| Total daily insulin (U/kg per day) | 0·6 (0·2) | 0·6 (0·2) |
| Daily basal insulin (U/kg per day) | 0·2 (0·1) | 0·2 (0·1) |
| Daily bolus insulin (U/kg per day) | 0·3 (0·1) | 0·4 (0·1) |
| Time spent in the pregnancy-specific glucose target range (%) | 60·5% (14·2) | 57·6% (13·7) |
| >70% time spent in the pregnancy-specific glucose target range | 10 (21·7%) | 7 (14·3%) |

(Table 1 continues in next column)

Data are n (%), mean (SD), or median (IQR). *Outcomes reported by participants. Ethnic minority background in the advanced hybrid closed loop therapy group: two of Asian origin and three of North African origin. Ethnic minority background in the standard insulin therapy group: one of Asian origin, four of North African origin, and one of Sub-Saharan African origin. †Higher education comprises higher education outside the university (short type or long type) or a university degree (bachelors or masters). ‡Recruitment corresponded with the screening visit and run-in with the 10-day baseline run-in phase started within 1 week after the screening visit. §Start of advanced hybrid closed loop therapy can be different from randomisation as it is defined as activation of advanced hybrid closed loop therapy within 1 week after the run-in phase and randomisation is defined as the first day after the run-in phase or startup of the MiniMed 780G insulin pump. ¶Presence of microvascular complications was collected from the electronic medical record. ‖Severe hypoglycaemia was defined as requiring third-party assistance. **Baseline continuous glucose monitor use data were collected during run-in with the standardised (masked or not) continuous glucose monitor. In two participants from the advanced hybrid closed loop therapy group, use of the masked continuous glucose monitor was not successful and no standardised continuous glucose monitor data were collected. Instead, data of their own continuous glucose monitor were collected. ††One participant in the standard insulin therapy group who used multiple daily injections switched to MiniMed 780G in manual mode after run-in. ‡‡Types of insulin pumps during run-in in the advanced hybrid closed loop therapy group: continuous subcutaneous insulin infusion with standalone continuous glucose monitor: one used MiniMed 640G and one used Accu-Chek Insight; sensor-augmented pump: 19 used MiniMed 780G in manual mode, 16 used MiniMed 640G, and two used MiniMed 670G in manual mode; advanced hybrid closed loop therapy: four used MiniMed 780G in auto mode. Types of insulin pumps during run-in in the standard of care group: continuous subcutaneous insulin infusion with standalone continuous glucose monitor: three used MiniMed 640G, two used Accu-Chek Insight, one used MiniMed Paradigm 715, and one used OmniPod; sensor-augmented pump: 20 used MiniMed 780G in manual mode, 15 MiniMed 640G, and three used MiniMed 670G in manual mode; advanced hybrid closed loop therapy: two used MiniMed 780G in auto mode. §§Sensor-augmented pump therapy was defined as systems with suspend-on-low, suspend-before-low or predictive low-glucose suspend features.

***Table 1:*** **Baseline characteristics of participants**

secondary outcomes at the different prespecified timepoints in pregnancy; time in target range during the day (0600 h to 2400 h); time below and above target range during the day; mean sensor glucose concentration; time above target range (>7·8 mmol/L) overall and overnight; time spent with glucose concentration higher than 10 mmol/L, lower than 3·9 mmol/, lower than 3·3 mmol/L, lower than 3·0 mmol/L, and lower than 2·8 mmol/L; time in non-pregnant target range (3·9–10·0 mmol/L); low blood glucose index; CGM compliance; self-monitoring of blood glucose; $HbA_{1c}$ during each trimester; insulin doses; and

| | Baseline | | Antenatal period (over four visits)* | | Adjusted mean difference (95% CI)† |
|---|---|---|---|---|---|
| | Advanced hybrid closed loop therapy (n=46) | Standard insulin therapy (n=49) | Advanced hybrid closed loop therapy (n=46) | Standard insulin therapy (n=49) | |
| **Primary outcome** | | | | | |
| Proportion of time with glucose concentration in range 3·5–7·8 mmol/L | 60·5% (14·2) | 57·6% (13·7) | 66·5% (10·0) | 63·2% (12·4) | 1·88% (–0·82 to 4·58) |
| **Key secondary outcomes** | | | | | |
| Proportion of overnight time with glucose concentration in range 3·5–7·8 mmol/L (2400 h to 0600 h)‡ | 64·8% (17·6) | 60·4% (21·9) | 75·1% (13·1) | 67·2% (14·6) | 6·58% (2·31 to 10·85)§ |
| Proportion of time with glucose concentration <3·5 mmol/L | 5·3% (4·9) | 5·1% (3·2) | 2·5% (2·8) | 4·1% (3·4) | –1·34% (–2·19 to –0·49)§ |
| Proportion of overnight time with glucose concentration <3·5 mmol/L (2400 h to 0600 h)‡ | 5·3% (6·8) | 4·0% (3·9) | 1·9% (3·2) | 4·2% (4·7) | –1·86% (–2·90 to –0·81)§ |
| **Exploratory secondary outcomes** | | | | | |
| Mean glucose concentration (mmol/L) | 7·1 (1·0) | 7·3 (1·1) | 7·1 (0·7) | 7·0 (0·8) | 0·14 (–0·04 to 0·33) |
| $HbA_{1c}$ (%) | 6·5% (0·6) | 6·5% (0·7) | 6·2% (0·6) | 6·1% (0·5) | 0·07 (–0·07 to 0·20) |
| $HbA_{1c}$ (mmol/mol) | 47·3 (7·0) | 47·5 (7·4) | 44·1 (6·4) | 42·7 (6·1) | 0·77 (–0·73 to 2·26) |
| Glucose management indicator (%) | 6·4% (0·4) | 6·5% (0·5) | 6·3% (0·3) | 6·3% (0·4) | 0·06 (–0·02 to 0·14) |
| Glucose management indicator (mmol/mol) | 46·3 (4·9) | 47·3 (5·4) | 45·9 (3·1) | 45·9 (4·0) | 0·68 (–0·18 to 1·54) |
| Glucose standard deviation (mmol/L) | 2·6 (0·6) | 2·7 (0·6) | 2·2 (0·4) | 2·4 (0·5) | –0·11 (–0·23 to 0·01) |
| Glucose coefficient of variation (%) | 35·6% (6·3) | 36·2% (5·2) | 31·4% (4·9) | 33·3% (5·5) | –2·24 (–3·70 to –0·79)§ |
| Mean amplitude of glycaemic excursions (mmol/L) | 5·8 (1·4) | 6·0 (1·2) | 5·1 (1·1) | 5·4 (1·3) | –0·23 (–0·53 to 0·08) |
| Proportion of time with glucose concentration >7·8 mmol/L | 34·2% (15·5) | 37·3% (14·7) | 30·9% (10·6) | 32·8% (13·1) | 0·49% (–2·43 to 3·42) |
| Proportion of time with glucose concentration >10·0 mmol/L | 14·8% (10·7) | 16·8% (11·7) | 11·3% (6·9) | 12·3% (9·0) | 0·33% (–1·69 to 2·36) |
| Proportion of time with glucose concentration in range 3·9–10·0 mmol/L | 76·8% (10·1) | 74·8% (11·1) | 84·2% (7·0) | 80·7% (9·1) | 3·26% (0·95 to 5·57)§ |
| Proportion of overnight time with glucose concentration >7·8 mmol/L (2400 h to 0600 h)‡ | 29·9% (18·2) | 35·6% (22·8) | 23·0% (13·2) | 28·6% (15·1) | –4·46% (–8·68 to –0·25)§ |
| Proportion of time during the day with glucose concentration in range 3·5–7·8 mmol/L (0600 h to 2400 h)‡ | 59·0% (14·5) | 56·6% (13·4) | 63·7% (11·0) | 61·6% (13·2) | 0·51% (–2·48 to 3·49) |
| Proportion of time during the day with glucose concentration <3·5 mmol/L (0600 h to 2400 h)‡ | 5·3% (4·8) | 5·5% (3·7) | 2·8% (2·9) | 4·0% (3·5) | –1·08% (–1·86 to –0·29)§ |
| Proportion of time during the day with glucose concentration >7·8 mmol/L (0600 h to 2400 h)‡ | 35·7% (16·0) | 37·9% (15·0) | 33·6% (11·6) | 34·4% (14·0) | 1·28% (–1·95 to 4·50) |

(Table 2 continues on next page)

measures of glycaemic variability (SD, coefficient of variation, and mean amplitude of glucose excursions). Further exploratory endpoints were the following participant-reported outcomes: fear of hypoglycaemia (assessed by the Hypoglycaemia Fear Survey II [HFS-II]); hypoglycaemia awareness status as evaluated by the Gold questionnaire, in which an individual's experience in detecting hypoglycaemic events is scored from 1 (always aware) to 7 (never aware) in a Likert-type scale; the Problem Areas in Diabetes-short form (PAID-5) questionnaire assessing fear, depressed mood, and the demands of living with diabetes; overall health status assessed by the 36-Item Short Form Health Survey (SF-36); symptoms of depression assessed by the 20-item Centre for Epidemiologic Studies-Depression (CES-D) questionnaire; and treatment satisfaction assessed by the Diabetes Treatment Satisfaction Questionnaire (DTSQ) status and the DTSQ change, which has been developed to overcome potential ceiling effects (where respondents score maximum or near-maximum satisfaction at baseline and can show little or no improvement at follow-up).[20]

Pregnancy outcomes were exploratory obstetric and neonatal outcomes.

Obstetric outcomes were gestational weight gain; maternal hypertensive disorders including worsening of pre-existing hypertension, gestational hypertension, and pre-eclampsia; other pregnancy complications (including haemolysis, elevated liver enzymes and low platelets [HELLP] syndrome, polyhydramnios, and oligohydramnios); hospital admissions and duration of hospital stay; pregnancy duration; preterm delivery (<37 weeks); type of labour; mode of delivery; miscarriage (<20 weeks); stillbirth (fetal demise ≥20 weeks); neonatal death (<1 month after delivery); and umbilical cord blood C-peptide.[20]

Neonatal outcomes were sex; birthweight and percentile; macrosomia (>4 kg); incidence of large-for-gestational age infants; gestational age-adjusted birthweight greater than the 97th percentile; and small for gestational age, all adjusted for infant's sex and parity; 10 min Apgar score;

| | Baseline | | Antenatal period (over four visits)* | | Adjusted mean difference (95% CI)† |
|---|---|---|---|---|---|
| | Advanced hybrid closed loop therapy (n=46) | Standard insulin therapy (n=49) | Advanced hybrid closed loop therapy (n=46) | Standard insulin therapy (n=49) | |
| (Continued from previous page) | | | | | |
| **Hypoglycaemia** | | | | | |
| Low blood glucose index | 2·1 (1·5) | 2·1 (1·0) | 1·3 (0·9) | 1·8 (1·1) | −0·49 (−0·76 to −0·23)§ |
| Proportion of time with glucose concentration <3·9 mmol/L | 8·4% (6·3) | 8·3% (4·7) | 4·5% (3·9) | 7·0% (4·9) | −2·15% (−3·37 to −0·92)§ |
| Proportion of time with glucose concentration <3·3 mmol/L | 4·2% (4·3) | 4·0% (2·6) | 1·9% (2·3) | 3·1% (2·9) | −1·01% (−1·70 to −0·31)§ |
| Proportion of time with glucose concentration <3·0 mmol/L | 2·5% (3·2) | 2·3% (1·8) | 1·0% (1·5) | 1·7% (2·0) | −0·58% (−1·06 to −0·09)§ |
| Proportion of time with glucose concentration <2·8 mmol/L | 1·7% (2·5) | 1·5% (1·4) | 0·5% (1·0) | 1·0% (1·6) | −0·44% (−0·81 to −0·07)§ |
| **Participant-reported outcomes** | | | | | |
| DTSQ status satisfaction (points) | 28·0 (5·5) | 28·6 (5·0) | 30·1 (5·0) | 27·4 (6·3) | 2·69 (0·56 to 4·82)§ |
| DTSQ change satisfaction (points) | NA | NA | 10·1 (7·3) | 4·9 (7·3) | 4·98 (2·37 to 7·58)§ |
| Hypoglycaemia unawareness based on the Gold score (points) | 2·1 (1·1) | 2·5 (1·5) | 2·1 (1·4) | 2·6 (1·5) | −0·57 (−1·09 to −0·05)§ |

Descriptive data are observed means (SDs at baseline and over the four prespecified timepoints; corresponds with average over periods 14–17 weeks', 20–23 weeks', 26–29 weeks', and 33–36 weeks' gestation), unless otherwise stated. The median proportion of time participants used continuous glucose monitoring was 93·2% (IQR 89·0–97·1) at baseline and 95·8% (92·8–97·3) in the antenatal period in the advanced hybrid closed loop therapy group, and 92·4% (82·0–95·6) at baseline and 92·8% (84·6–95·7) in the antenatal period in the standard insulin therapy group. The median total number of hours participants used continuous glucose monitoring was 221·7 (IQR 213·1–233·0) at baseline and 480·1 (458·7–489·0) in the antenatal period in the advanced hybrid closed loop therapy group, and 221·8 (196·7–229·4) at baseline and 465·1 (420·3–482·2) in the antenatal period in the standard insulin therapy group. DTSQ=Diabetes Treatment Satisfaction Questionnaire. *For the primary outcome and key secondary outcomes, data were analysed according to the intention-to-treat principle with multiple imputation to deal with missing data. For the exploratory secondary outcomes, intention-to-treat analyses were performed with inclusion of participants with incomplete follow-up data (eg, missing study visits); nevertheless, two participants (one in each group), for whom no follow-up data were collected (all study visits missing), were excluded. †Data are mean (95% CI). Analysis was corrected for baseline time spent in the pregnancy-specific glucose target range (3·5–7·8 mmol/L), $HbA_{1c}$ concentration, insulin delivery method, and clinical centre. A difference greater than zero corresponds to a higher value in the advanced hybrid closed loop therapy group compared to standard insulin therapy group; a difference lower than zero corresponds to a lower value in the advanced hybrid closed loop therapy group compared to standard insulin therapy group. ‡Overnight time was defined as from 2400 h to 0600 h. Daytime was defined as from 0600 h to 2400 h. §These outcomes are significantly different between both groups: proportion of overnight time with glucose concentration in range 3·5–7·8 mmol/L (2400 h to 0600 h; p=0·0026), proportion of time with glucose concentration less than 3·5 mmol/L (p=0·0020), proportion of overnight time with glucose concentration less than 3·5 mmol/L (2400 h to 0600 h; p=0·00050), glucose coefficient of variation (p=0·0028), proportion of time with glucose concentration in range 3·9–10·0 mmol/L (p=0·0062), proportion of overnight time with glucose concentration higher than 7·8 mmol/L (2400 h to 0600 h; p=0·038), proportion of time during the day with glucose concentration less than 3·5 mmol/L (0600 h to 2400 h; p=0·0078), low blood glucose index (p=0·00040), proportion of time with glucose concentration less than 3·9 mmol/L (p=0·00080), proportion of time with glucose concentration less than 3·3 mmol/L (p=0·0052), proportion of time with glucose concentration less than 3·0 mmol/L (p=0·021), proportion of time with glucose concentration less than 2·8 mmol/L (p=0·020), DTSQ status satisfaction (points; p=0·013), DTSQ change satisfaction (points; p=0·00020), and hypoglycaemia unawareness based on the Gold score (points; p=0·032). Differences in the primary and key secondary outcomes are considered significant at p values less than 0·0125. Differences in exploratory secondary outcomes are considered significant at p values less than 0·05.

***Table 2*: Primary and secondary glycaemic and participant-reported outcomes**

shoulder dystocia; birth trauma; congenital malformations; neonatal respiratory distress syndrome (at least 4 h of respiratory support with supplemental oxygen, continuous positive airway pressure, or intermittent positive-pressure ventilation during the first 24 h after delivery); neonatal hypoglycaemia (glycaemia <2·2 mmol/L or need for intravenous glucose); neonatal jaundice (hyperbilirubinaemia; need for phototherapy); duration of and indication for admission on the neonatal intensive care unit (NICU; NICU admission defined as >24 h); sum of skinfolds; neonatal fat mass; and breastfeeding.[20]

The following safety outcomes were reported: number and duration of hypoglycaemic episodes (time spent with glucose <3·5 mmol/L and <2·8 mmol/L), nocturnal or severe hypoglycaemic episodes, or both (defined as requiring third-party assistance), and diabetic ketoacidosis (defined as pH ≤7·30, bicarbonate ≤18 mmol/L, anion gap >10, and ketones positive in urine or serum). Device-related or diabetes-related adverse events were reported, along with any other serious adverse event.

## Statistical analysis

We estimated that a sample size of 92 participants would have about 90% power for the primary and key secondary outcomes, adopting a 5% two-sided family-wise type I error rate, anticipating 20% dropout. Calculations for the primary outcome assumed an absolute between-group difference in time in range of 10 percentage points, with an SD of 13%.[24] The calculations further included the following key prespecified secondary outcome: for time spent below the pregnancy-specific target glucose range overall (both day and night; <3·5 mmol/L), the power to show a difference of 1·1 percentage points between both groups,[24] assuming an SD of 1·6%, equals 91%. The SD for change rather than for a single measurement was reported by Stewart and colleagues.[24] As the correlation between both measurements was not reported, we assumed a correlation of 0·20 to estimate the SD of a single measurement. The same approach was followed for the other prespecified secondary outcomes. For overnight time lower than 3·5 mmol/L, the power to

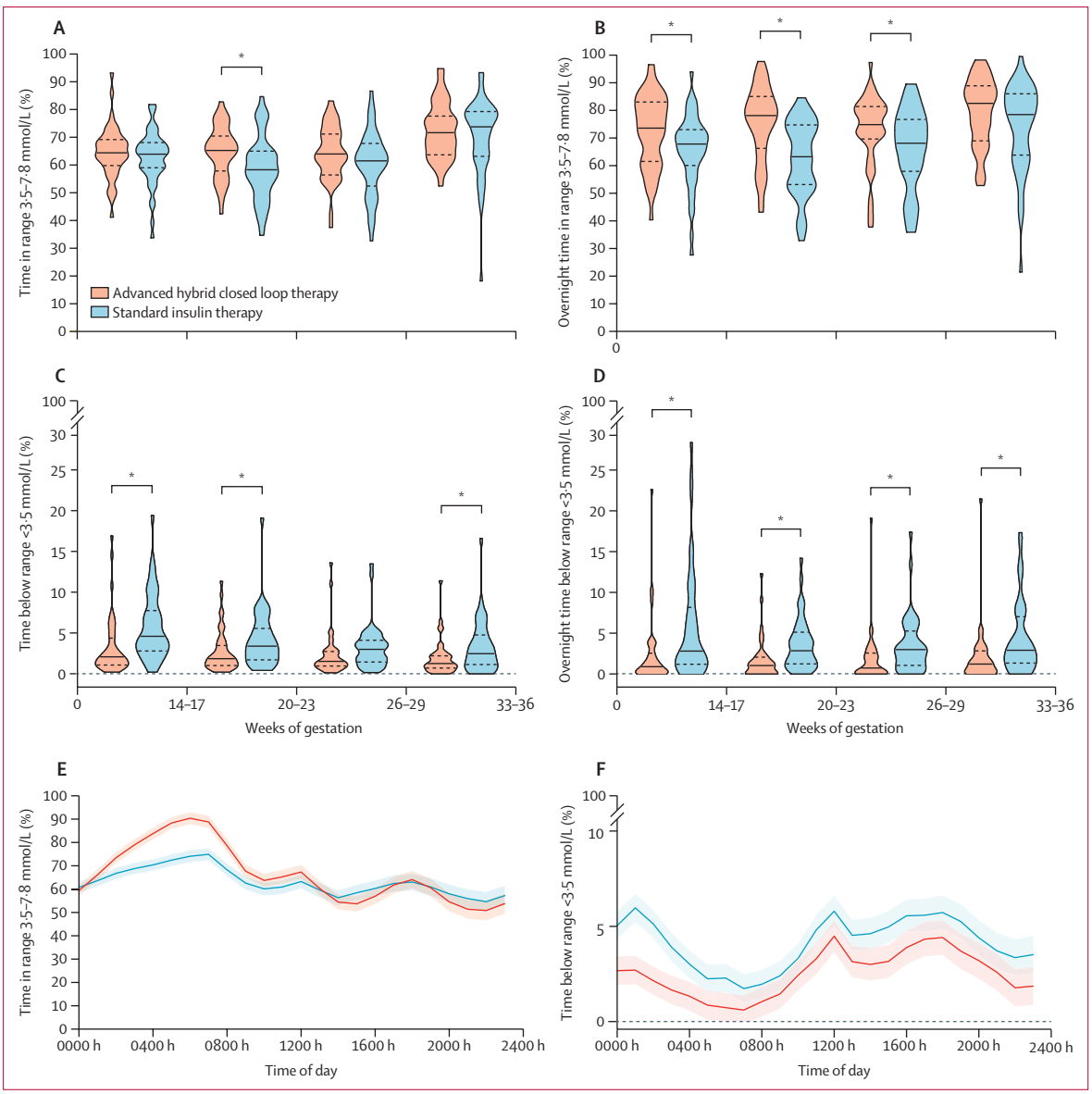


***Figure 2*: Proportion of time in and below the pregnancy-specific target glucose range, overall and overnight, according to weeks of gestation and time of day**
Violin plots indicate the distribution of time spent in and below the pregnancy-specific target range overall (panels A and C) and overnight (panels B and D) by randomisation group at 14–17 weeks', 20–23 weeks', 26–29 weeks', and 33–36 weeks' gestation. The violin width represents the number of participants at a certain value. Solid lines indicate the median value and dotted lines indicate the IQR. Significant differences between both groups are denoted by asterisks. Envelope plots are shown for time spent in the pregnancy-specific target range (panel E) and time spent below the pregnancy-specific target range (panel F), measured with continuous glucose monitoring, per randomisation group, according to time of the day over the four prespecified timepoints (ie, corresponds with averaged over trial periods 14–17 weeks', 20–23 weeks', 26–29 weeks', and 33–36 weeks' gestation). Shaded areas represent IQRs.

show a difference of 1·6 percentage points between both groups for overnight time lower than 3·5 mmol/L, assuming an SD of 2·5%, equals 87%. For overnight time spent in the pregnancy-specific target glucose range (3·5–7·8 mmol/L), the power to show a difference of 15·2 percentage points between both groups,[25] assuming an SD of 18·4%, equals 97%. A blinded sample size recalculation was performed after inclusion of 50% of patients. This subsample was used to re-estimate variances and correlations without unblinding the study.[26] The aim of this recalculation was to increase the sample size if needed to achieve the anticipated power. No decrease in sample size was intended. The sample size re-estimation was performed with the observed pooled SDs and the intraclass correlations of the four outcome measures, as calculated from the interim data. The interim data contained 108 observations from 34 patients. All other parameters for the sample size recalculation were the same as in the initial sample size calculation. As no sample size adaptation was required

| | Advanced hybrid closed loop therapy (n=46) | Standard insulin therapy (n=49) |
|---|---|---|
| **Severe hypoglycaemia*** | | |
| Number of events | 8 | 7 |
| Participants with one or more events | 6 (13·0%) | 5 (10·2%) |
| Incidence per 100 person-years | 35·2 | 28·7 |
| Number of hospital admissions | 0 | 5 |
| Participants with one or more hospital admissions | 0 (0·0%) | 3 (6·1%) |
| Incidence of hospital admission per 100 person-years | 0·0 | 20·5 |
| **Ketosis or diabetic ketoacidosis†** | | |
| Number of hospital admissions for or with ketosis | 4 | 2 |
| Participants with one or more hospital admissions | 3 (6·5%) | 2 (4·1%) |
| Incidence of hospital admission for or with ketosis per 100 person-years | 17·6 | 8·2 |
| Number of hospital admissions for diabetic ketoacidosis | 1 | 1 |
| Incidence of hospital admission for diabetic ketoacidosis per 100 person-years | 4·4 | 4·1 |
| **Serious adverse events‡** | | |
| Number of serious adverse events | 24 | 24 |
| Participants with one or more events | 19 (41·3%) | 15 (30·6%) |
| Incidence per 100 person-years | 105·7 | 98·5 |
| **Device deficiencies§** | | |
| Number of device deficiencies | 40 | 39 |
| Number of device-related adverse events¶ | 2 | 3 |
| Advanced hybrid closed loop therapy | 1 | NA |
| Continuous glucose monitor | 1 | 3 |
| Participants with one or more events | 2 (4·3%) | 3 (6·1%) |
| Incidence per 100 person-years | 8·8 | 12·3 |

Data are n (%), unless otherwise stated. NA=not applicable. *Severe hypoglycaemia was defined as requiring third-party assistance and was participant-reported. †Diabetic ketoacidosis was diagnosed at the clinic and defined as follows: pH 7·30 or lower, bicarbonate 18 mmol/L or lower, anion gap higher than 10, and ketones positive in urine or serum. ‡Serious adverse events were defined as any adverse event that resulted in death; a serious deterioration in the health of the participant that led to a life-threatening illness or injury, permanent impairment of a body structure or function, in-patient or prolonged hospital admission, medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or function, chronic disease; fetal distress, fetal death, or fetal congenital anomaly. §Device deficiencies were defined as any in the identity, quality, durability, reliability, safety, or performance of an investigational device, including malfunction, use errors, or inadequacy in information supplied by the manufacturer. ¶In the advanced hybrid closed loop therapy group, the adverse event related to use of the advanced hybrid closed loop system was attributed to blockage of the insulin infusion set (causing hyperglycaemia with symptoms) and the adverse event related to use of the continuous glucose monitor was attributed to difficulties in warming up of different sensors with no connection between the sensor and pump (no advanced hybrid closed loop therapy) and also no alarms (causing severe hypoglycaemia). In the standard of care group, two adverse events related to use of the continuous glucose monitor were attributed to a discrepancy between the sensor and self-monitoring of blood glucose (one causing headache and the other causing hyperglycaemia with ketones) and one adverse event related to use of the continuous glucose monitor was attributed to loss of connection between the sensor and pump (causing severe hypoglycaemia).

*Table 3:* **Safety outcomes**

for the primary endpoint, the initial sample size was not changed. Details are outlined in the statistical analysis plan (appendix pp 4–5).

Analyses were performed on an intention-to-treat basis. For the analysis of the primary outcome and key secondary outcomes, linear mixed-effects regression models were used, with baseline outcome, baseline $HbA_{1c}$, and insulin delivery method and study visit as covariates, and centre as random effect. The estimated treatment effect represents a difference between study groups, averaged over the four observation periods (14–17 weeks', 20–23 weeks', 26–29 weeks', and 33–36 weeks' gestation). The time-averaged mean difference between the groups was presented with a 95% CI. Multiple imputation was applied to deal with missing data. Fully conditional specification was adopted where randomisation group, stratification variables, and baseline or previous observations were used as variables in the prediction model. Ten complete data sets were constructed, analysed, and summarised into a final result. All p values are two-sided and a 1·25% significance level was adopted for the primary and key secondary outcomes to deal with multiple testing. Analyses were performed with SAS software (version 9.4).

As a prespecified sub-analysis, we analysed the primary outcome and the three key secondary outcomes between women who started the intervention at less than 10 weeks' gestation (early start) and women who started the intervention at 10 weeks' gestation or later (late start). Data were analysed analogous to the primary analysis, by use of a multivariate linear mixed model, with early versus late start, study visits, baseline $HbA_{1c}$, method of insulin delivery, and baseline outcome value as main effects, and a random effect of centre.

All analyses were repeated on the per-protocol analysis set. The per-protocol analysis set included the same data as the intention-to-treat analysis set. Nevertheless, follow-up outcome data were excluded if they were collected during trial periods while violating the following required conditions: use of Guardian sensor and CGM 80% or higher for all participants, use of AHCL therapy 80% or higher for the intervention group, and no use of AHCL therapy in the control group.

### Role of the funding source

UZ Leuven was the sponsor of this investigator-initiated study. Trial funding was provided by the Diabetes Liga Research Fund, and Medtronic provided devices and an unrestricted grant for academic research. Representatives from the Diabetes Liga (representing people living with diabetes and health-care professionals in diabetes care) and Medtronic received a copy of the manuscript before submission. The funders had no role in trial design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit the manuscript for publication.

## Results

Between Jan 15, 2021, and Sept 30, 2022, 187 women with type 1 diabetes who were followed up in the participating centres became pregnant during the recruitment period; of these, 101 women with type 1 diabetes were screened, of whom 95 were randomly assigned at a median of 10·1 (IQR 8·6–11·6) weeks' gestation (figure 1). 46 women were allocated to the intervention (AHCL therapy) and 49 to the standard insulin therapy group; 43 women in the AHCL therapy group and 46 in the standard insulin therapy

group completed the study (figure 1; appendix p 11). Two participants in each group discontinued their assigned therapy (figure 1; appendix p 12). Baseline characteristics were similar between both treatment groups and representative of the Belgian-Dutch pregnant population with type 1 diabetes (table 1, appendix pp 13–15).[27] Mean baseline $HbA_{1c}$ was 6·5% (SD 0·6), with a mean baseline time spent in pregnancy-specific range of 59·0% (SD 13·9). At baseline, all participants used CGM and 91 (95·8%) used an insulin pump (of whom 75 [82·4%] used sensor-augmented pump therapy). The intervention was started at a median of 10·7 (IQR 8·9–12·6) weeks of gestation. The proportion of completed trial visits was 98·5% (appendix p 7). Across both groups, CGM was used 93·7% of the time between randomisation and delivery (appendix pp 8, 16). AHCL therapy was used 95·3% of the time, participants used the glucose target of 5·5 mmol/L 98·0% of the time and used active insulin time at 2 h 92·4% of the time, and assisted carbohydrate estimation was used by 28 (60·9%) of 46 participants in the AHCL therapy group, starting on average at 19 weeks, with a progressive increase in the amount of carbohydrates added (appendix pp 17–18).

The proportion of time spent in the pregnancy-specific target glucose range increased from baseline to the antenatal period (averaged over the four prespecified timepoints: 14–17 weeks', 20–23 weeks', 26–29 weeks', and 33–36 weeks' gestation) in both groups: from 60·5% (SD 14·2) to 66·5% (10·0) in the AHCL therapy group and from 57·6% (13·7) to 63·2% (12·4) in the standard insulin therapy group (adjusted mean difference, 1·88 percentage points [95% CI –0·82 to 4·58]; p=0·17; (table 2). Overnight time in target range was higher (adjusted mean difference 6·58 percentage points [95% CI 2·31 to 10·85], p=0·0026), and time below glucose range overall (adjusted mean difference –1·34 percentage points [–2·19 to –0·49], p=0·0020) and overnight (adjusted mean difference –1·86 percentage points [–2·90 to –0·81], p=0·0005) were lower in women in the AHCL therapy group than in the standard insulin therapy group. The results of the per-protocol analyses were consistent with those of the intention-to-treat analyses (appendix p 19). The prespecified subgroup analysis showed similar results between women who started the intervention at less than 10 weeks of gestation and those who started at 10 weeks of gestation or later (appendix pp 9, 19–22).

Participants allocated to AHCL therapy spent less time with glucose lower than 3·9 mmol/L, lower than 3·5 mmol/L, lower than 3·0 mmol/L, and lower than 2·8 mmol/L, and the low blood glucose index was also significantly lower in this group compared with the standard insulin therapy group (table 2). Overnight time above target range (>7·8 mmol/L) was lower in women using AHCL therapy than those using standard insulin therapy (adjusted mean difference –4·46 percentage points [95% CI –8·68 to –0·25], p=0·038). The coefficient of variation was lower in the AHCL therapy group than in the standard insulin therapy group (adjusted mean difference –2·24 percentage points [95% CI –3·70 to –0·79], p=0·0028). Mean glucose, $HbA_{1c}$ concentrations, total insulin doses, and time above target range (>7·8 mmol/L) were similar in both groups (table 2, appendix pp 23–24). Time spent in the non-pregnant target range (3·9–10·0 mmol/L) was higher in the AHCL therapy group than in the standard insulin therapy group (adjusted mean difference 3·26 percentage points [95% CI 0·95 to 5·57], p=0·0062). Time spent in the target glucose range was higher during 20–23 weeks' gestation in the AHCL therapy group than in the standard insulin therapy group (adjusted mean difference 6·14 percentage points

| | Advanced hybrid closed loop therapy (n=43) | Standard insulin therapy (n=46) |
|---|---|---|
| **Obstetric and maternal outcomes** | | |
| Gestational hypertension | 4/43 (9·3%) | 6/46 (13·0%) |
| Pre-eclampsia | 4/42 (9·5%) | 2/46 (4·3%) |
| HELLP syndrome | 1/42 (2·4%) | 0/46 (0·0%) |
| Mode of delivery | | |
| Vaginal | 16/43 (37·2%) | 14/45 (31·1%) |
| Vacuum pump (instrumental) | 6/43 (13·9%) | 2/45 (4·4%) |
| Caesarean section (total) | 21/43 (48·8%) | 29/45 (64·4%) |
| Planned or elective caesarean section | 14/21 (66·7%) | 19/29 (65·5%) |
| Unplanned or emergency caesarean section | 7/21 (33·3%) | 10/29 (34·5%) |
| Repeat caesarean section | 10/21 (47·6%) | 9/29 (31·0%) |
| Total gestational weight gain (kg)* | 11·8 (4·2) | 13·9 (5·7) |
| Excessive gestational weight gain† | 14/43 (32·6%) | 26/46 (56·5%) |
| Median duration of postpartum hospital stay (days) | 4·0 (3·0–5·0) | 4·0 (3·0–4·0) |
| Breastfeeding‡ | 33/41 (80·5%) | 37/45 (82·2%) |
| **Fetal and neonatal outcomes** | | |
| Miscarriage (<20 weeks)§ | 2/45 (4·4%) | 1/47 (2·1%) |
| Death in utero or stillbirth (≥20 weeks)¶ | 1/45 (2·2%) | 0/47 (0·0%) |
| Neonatal death | 0/42 (0·0%) | 0/46 (0·0%) |
| Gestational age at delivery (weeks and days) | 37 weeks and 2 days (1 week and 1 day) | 37 weeks and 5 days (1 week and 1 day) |
| Preterm birth (<37 weeks)‖ | 12/43 (27·9%) | 9/46 (19·6%) |
| Birthweight outcomes** | | |
| Birthweight (kg) | 3·6 (0·6) | 3·7 (0·5) |
| Small for gestational age | 0/43 (0·0%) | 0/46 (0·0%) |
| Large for gestational age | 24/43 (55·8%) | 31/46 (67·4%) |
| Extremely large for gestational age (>P97) | 16/43 (37·2%) | 20/46 (43·5%) |
| Macrosomia (>4 kg) | 13/43 (30·2%) | 15/46 (32·6%) |
| Birthweight >4·5 kg | 2/43 (4·7%) | 4/46 (8·7%) |
| Median sum of skinfolds (mm) | 18·8 (15·1–19·8) | 18·4 (15·8–21·8) |
| Median neonatal body fat mass (g) | 1514·4 (1381·7–1619·6) | 1436·4 (1262·5–577·0) |
| Median neonatal body fat mass (%) | 39·0 (39·0–39·0) | 39·0 (39·0–39·0) |

(Table 4 continues on next page)

| | Advanced hybrid closed loop therapy (n=43) | Standard insulin therapy (n=46) |
|---|---|---|
| (Continued from previous page) | | |
| Neonatal complications | | |
| Congenital malformation†† | 2/41 (4·9%) | 4/46 (8·7%) |
| Birth trauma‡‡ | 1/41 (2·4%) | 0/45 (0·0%) |
| Shoulder dystocia | 3/40 (7·5%) | 3/44 (6·8%) |
| Respiratory distress§§ | 6/41 (14·6%) | 5/46 (10·9%) |
| Hypoglycaemia (<40 mg/dL) | 12/38 (31·6%) | 19/42 (45·2%) |
| Hypoglycaemia treated with intravenous glucose | 2/11 (18·2%) | 5/18 (27·8%) |
| Hyperbilirubinaemia with need for phototherapy | 9/34 (26·5%) | 5/39 (12·8%) |
| Neonatal (intensive) care hospital admission (≥1 day)¶¶ | 14/42 (33·3%) | 11/45 (24·4%) |
| Neonatal (intensive) care hospital admission for neonatal hypoglycaemia‖‖ | 2/14 (14·3%) | 7/11 (63·6%) |
| Median duration of hospital stay (days) | 4·0 (3·0–5·0) | 4·0 (3·0–4·0) |
| Median duration of neonatal (intensive) care hospital admission (days) | 4·5 (2·0–11·0) | 6·5 (3·0–9·0) |

Data are n or n/N (%), mean (SD), or median (IQR). HELLP=haemolysis, elevated liver enzymes and low platelets. *Total gestational weight gain was calculated as the difference in weight between the last clinic visit before delivery and the screening visit. †Excessive gestational weight gain was assessed according to guidelines of the National Academy of Medicine (NAM; previously known as the Institute of Medicine) for weight gain during pregnancy. Excessive gestational weight gain is significantly different between both groups (p=0·033). ‡Breastfeeding refers to breastfeeding in the postpartum hospital admission period. §In the advanced hybrid closed loop therapy group, one miscarriage occurred at 12 weeks' gestation for no apparent reason and another occurred at 17 weeks' gestation, which was related to cervical insufficiency. In the standard insulin therapy group, one miscarriage occurred at 11 weeks' gestation for no apparent reason. ¶One stillbirth occurred in the advanced hybrid closed loop therapy group at 36 weeks' gestation and was related to a primary cytomegalovirus infection. ‖Percentages for preterm birth do not include pregnancy losses before 20 weeks' gestation. **Birth centiles were calculated with Flemish birth charts adjusted for gestational age, infant's sex, and parity. ††Congenital malformations were congenital heart defects (n=2) in the advanced hybrid closed loop therapy group and congenital heart defect (n=1), congenital bilateral sensorineural hearing loss (n=1), cryptorchidism (n=1), and congenital anomaly of the musculoskeletal system (n=1) in the standard insulin therapy group. ‡‡The birth trauma in the advanced hybrid closed loop therapy group was a clavicula or humerus fracture. §§Respiratory distress was treated with continuous positive airway pressure (CPAP; n=2), CPAP with oxygen (n=2), and CPAP with intermittent positive-pressure ventilation (n=2) in the advanced hybrid closed loop therapy group and with CPAP (n=2) and oxygen (n=3) in the standard insulin therapy group. ¶¶Reasons for neonatal (intensive) care hospital admission (≥1 day, neonatal intensive and non-intensive care unit admission included) in the advanced hybrid closed loop therapy group: prematurity (n=3), respiratory problems (n=2), hypoglycaemia (n=1), hyperbilirubinemia (n=2), standard procedure in infant of mother with type 1 diabetes (n=3), prematurity with macrosomia (n=1), respiratory problems with hypoglycaemia (n=1), and respiratory problems with macrosomia and congenital malformation (n=1). In the standard insulin therapy group: prematurity (n=1), respiratory problems (n=1), hypoglycaemia (n=5), standard procedure in infant of mother with type 1 diabetes (n=1), prematurity with respiratory problems and hypoglycaemia (n=1), prematurity with hyperbilirubinemia (n=1), and hypoglycaemia with polycythaemia (n=1). ‖‖Neonatal (intensive) care hospital admission for neonatal hypoglycaemia is significantly different between both groups (p=0·017). Both neonatal intensive and non-intensive care unit admission were included.

*Table 4:* **Maternal and neonatal outcomes**

[95% CI 1·66 to 10·63], p=0·0077; figure 2, appendix pp 25–29). The glycaemic improvements in both groups only occurred in the final weeks of pregnancy, with a mean time in target range of 72·5% (95% CI 68·9 to 76·2) in the AHCL therapy group and 70·6% (67·1 to 74·1) in the standard insulin therapy group (appendix pp 25–29). The consensus target (>70% time in target glucose range) was attained throughout pregnancy by 59 (33·7%) of 175 measurements in the antenatal period in the AHCL group and 53 (28·8%) of 184 measurements in the antenatal period in the standard insulin therapy group (appendix pp 10, 30).

Women using AHCL therapy had significantly higher treatment satisfaction and less hypoglycaemia unawareness (table 2). There were no significant differences between both treatment groups for the other participant-reported outcomes (appendix pp 31–33).

Eight events of severe hypoglycaemia were reported by participants using AHCL therapy and seven events were reported by participants in the standard insulin therapy group (table 3). No hospital admissions for severe hypoglycaemia occurred in the AHCL therapy group, while five hospital admissions for severe hypoglycaemia occurred in the standard insulin therapy group. In each group, one woman was admitted to hospital for diabetic ketoacidosis. Two women in the intervention group had a device-related adverse event, of which one event was attributed to AHCL therapy, compared with three in the control group (appendix pp 34–35).

There were two miscarriages and one stillbirth at 36 weeks' gestation (related to a primary cytomegalovirus infection) in the AHCL therapy group and one miscarriage in the standard insulin therapy group. Shoulder dystocia occurred in three babies in each group and there was one birth trauma in the AHCL therapy group (table 4, appendix pp 36–38).

Excessive gestational weight gain was lower in women using AHCL therapy than in those on standard insulin therapy. There were no differences in preterm birth rates, caesarean sections, or neonatal complications between both treatment groups. NICU admissions due to neonatal hypoglycaemia occurred less frequently in the AHCL therapy group than in the standard insulin therapy group (table 4).

## Discussion

We show that in women with a mean baseline $HbA_{1c}$ of 6·5% and mean time in pregnancy-specific range of 59·0%, using AHCL therapy resulted in a similar proportion of time spent in the target glucose range compared with standard insulin therapy, with 6·58% higher overnight time in target range (corresponding to an additional 24 mins per night) and lower time below glucose range overall (–1·34 percentage points; –19 mins per day) and overnight (–1·86 percentage points; –7 mins per night). There were no differences between both groups in other glycaemic control markers such as mean $HbA_{1c}$, mean glucose, or time above target range. A mean target glucose range greater than 70% was only reached between 33–36 weeks of pregnancy, in line with other studies showing that attainment of the target glucose range is often only achieved in the last 4 weeks of pregnancy.[7,13] However, in the AiDAPT trial, a significant increase in the target glucose range of 10·5%, without increased time below range was observed when using AHCL therapy compared to standard insulin therapy from 16 weeks of pregnancy onwards.[17]

Our study is, to the best of our knowledge, the first large randomised controlled trial evaluating the off-label

use in pregnancy of MiniMed 780G, a frequently used AHCL system. Although the AHCL system did not improve time in glucose target range, our results show that AHCL therapy improved overnight time in target range, reduced the risk of hypoglycaemia, and was associated with reduced hypoglycaemia unawareness, reduced glycaemic variability, and improved treatment satisfaction. Limiting the risk of hypoglycaemia in pregnancy is important since previous studies have shown that hypoglycaemia occurs frequently and limits the ability of women to achieve and maintain strict glycaemic control throughout pregnancy.[9–11]

Our findings suggest that the MiniMed 780G is safe for use in pregnancy, as no unanticipated safety events occurred. The number of severe adverse events was similar between both groups. Despite the fact that a glucose target of 5·5 mmol/L is still higher than recommended in the fasting state of pregnancy,[7] our results indicate that the MiniMed 780G performed well overnight but that the algorithm lacked flexibility with the meals to adapt fast enough to the increased insulin requirements later in pregnancy, necessitating assisted carbohydrate administration. This might explain why only 33·7% of women reached the glucose target range of greater than 70% throughout pregnancy. As every increase of 5 percentage points in time in target range is associated with improved pregnancy outcomes, it will be important to refine the algorithm to better align with pregnancy requirements.[28,29] Two observational studies by the LOIS-P Diabetes and Pregnancy Consortium in ten pregnant women with similar baseline glycaemic control to that of our study, showed a substantial increase in time in range (14–17%) with a zone model predictive control algorithm specifically adapted to pregnancy compared with SAP therapy in a supervised and at-home setting between 14 and 32 weeks until delivery, suggesting the potential benefits of a more customised system.[30,31]

Our study has similarities with the AiDAPT study, which compared AHCL therapy with standard insulin therapy in 124 pregnant women with type 1 diabetes.[17] However, important differences must be noted. First, women in the AiDAPT trial had a higher mean $HbA_{1c}$ at baseline (7·7% *vs* 6·5%), a lower time in pregnancy-specific range (46·1% *vs* 59·0%) and less time below range compared with our participants. Second, more than half of all participants in the standard insulin therapy group of the AiDAPT trial used multiple daily injections, while 38 (77·5%) of 49 women in the standard insulin therapy group in our trial used sensor-augmented pump therapy, achieving a time in range of 63·2% compared with 55·6% in the AiDAPT trial. The high use of insulin pump therapy at baseline in our study is in line with the standard of care for pregnant women with type 1 diabetes in Belgium and the Netherlands.[27] Another difference between the current study and AiDAPT trial is that the CamAPS system offers fully customisable glucose targets that can be lowered up to 4·4 mmol/L, while the glucose target cannot be lowered to less than 5·5 mmol/L with the MiniMed 780G. Of interest, similar proportions of time in range are achieved by both AHCL systems (68·2% with CamAPS FX and 66·5% with MiniMed 780G in the current study).[17] We believe the differences in population characteristics, and especially the different types of AHCL system used, might explain why we observed no significant difference between both groups in time spent in pregnancy-specific range and in time above target, while the time below range was significantly lower in the AHCL therapy group. By contrast, in the AiDAPT trial, both a higher time in pregnancy-specific range and less time above range was observed with AHCL therapy. Although women with a baseline $HbA_{1c}$ less than 6·5% were excluded from the AiDAPT trial, leading to a higher mean $HbA_{1c}$ at the start, prespecified subgroup analyses showed comparable treatment efficacy in all women, even the group with first trimester $HbA_{1c}$ less than 7% (39% of the total population), with a 7·5% increase in the time in range (72·2% of time spent in the pregnancy glycaemic target range).[17]

Similarly to the AiDAPT trial, our study was not powered for pregnancy outcomes. In general, outcomes were similar between both groups. NICU admissions due to neonatal hypoglycaemia occurred significantly less frequently in the AHCL therapy group than in the standard insulin therapy group. We also observed significantly less excessive gestational weight gain in the AHCL therapy group. Limiting excessive gestational weight gain is important since this is associated with fetal overgrowth and more postpartum weight retention.[32–35] Since the individual studies of AHCL therapy in pregnancy are not powered for obstetric and neonatal outcomes, a meta-analysis might help to increase the power for pregnancy outcomes and could also help to evaluate who can benefit most from AHCL therapy in pregnancy.[7]

Strengths of our study are the randomised controlled design of the trial and the inclusion of a tightly controlled population due to the absence of a lower $HbA_{1c}$ limit for inclusion. All forms of insulin therapy and all types of CGM could be used in the standard insulin therapy group to allow for a representative population.[20] To avoid bias by measuring glycaemic outcomes with different types of CGM, we used the same CGM in both groups at prespecified timepoints.

As this was an open-label trial, the treatment allocation could not be masked from participants and the research team. Other limitations of the study include the absence of power to detect differences in perinatal outcomes and absence of diversity in the population of women (only a few women on multiple daily injections could be included, almost 90% of women were White, and more than two-thirds were highly educated). The results might therefore not be generalisable to other populations. Additionally, the study was not powered for outcomes such as treatment satisfaction and risk of hypoglycaemia

(as these were all exploratory outcomes). Moreover, as randomisation occurred on average at 10 weeks, data in early pregnancy were scarce.

In conclusion, this trial showed that, in pregnant women with type 1 diabetes with a mean baseline $HbA_{1c}$ of 6·5%, AHCL therapy did not improve overall time in target range but improved overnight time in target, reduced time below range, and improved treatment satisfaction. Our findings suggest that the MiniMed 780G is safe for use in pregnancy and provides some additional benefits compared with standard insulin therapy.

#### Contributors

All authors (KBen, KBeu, NVW, DB, GV, YT, X-PA, FN, JM, DL, JC, VP, SES, RCP, AL, PG, and CM) contributed to the conception or development, or both, of the study and to data collection. KBen, KBeu, and AL contributed to data or statistical analyses, or both. KBen, KBeu, PG, and CM co-wrote the original draft of the manuscript, and declare data integrity and compliance with the protocol. KBeu contributed to the figures and tables. NVW, DB, GV, YT, X-PA, FN, JM, DL, JC, VP, SES, RCP, and AL contributed to editing of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

#### Declaration of interests

UZ Leuven received research support for KBen from the Diabetes Liga Research Fund (financial) and Medtronic (financial and non-financial). KU Leuven received research support for KBen from AstraZeneca (financial), Dexcom (non-financial), Eli Lilly (financial), Metagenics (financial), and Novo Nordisk (financial and non-financial). KBen reports consulting fees from AstraZeneca and Eli Lilly, and honoraria for speaking from AstraZeneca, Mundipharma, and Novo Nordisk. KBen received support for attending virtual conferences and meetings from AstraZeneca and Novo Nordisk. KBen is the recipient of a senior clinical research fellowship from FWO, the Flemish Research Council. KBeu is the recipient of a PhD fellowship strategic basic research (FWO-SB) from FWO. GV has served on the advisory board for Eli Lilly. GV reports honoraria for speaking and received support for attending (virtual) conferences and meetings from Boehringer-Ingelheim, Eli Lilly, and Novo Nordisk. YT had a fiduciary role in the Diabetes Liga (no financial compensation). YT reports consulting fees from Bayer and Eli Lilly, and honoraria for speaking from Boehringer-Ingelheim and Eli Lilly. YT received support for attending conferences and meetings from Bayer. X-PA reports honoraria for speaking from AstraZeneca, Menarini, and Novo Nordisk, and received support for attending (virtual) conferences and meetings from Novo Nordisk and Sanofi. FN is president of the Belgian Diabetes Forum, has served on advisory boards for Eli Lilly and Novo Nordisk, and received a grant from AstraZeneca to organise a symposium. FN reports honoraria for speaking from AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi. JM reports honoraria for speaking from Novo Nordisk and Sanofi; and received support for attending conferences and meetings from Novo Nordisk. DL reports honoraria for speaking from AstraZeneca, Novo Nordisk, and Sanofi. VP reports consulting fees from Abbott, Novartis, and Sanofi, and has served on the advisory board for Sanofi. SES reports honoraria for speaking from Eli Lilly and Medtronic; and has served on the advisory board for Roche (all financial compensation received by their institution and used for investigator-initiated research). RCP received governmental funding from ZonMw for research and establishing a network in the Netherlands. RCP has served on the advisory board for the stichting ZEHG and NVOG (College of Obstetrics). PG has served on the advisory board for Insulet and Ypsomed. KU Leuven received research grants for PG from Dexcom (financial and non-financial support), Medtronic, Novo Nordisk, Roche, Sanofi, and Tandem. PG reports consulting fees from Abbott, Bayer, and Medtronic, and honoraria for speaking from Abbott, Bayer, Dexcom, Insulet, Medtronic, Novo Nordisk, Vitalaire, and Ypsomed (financial compensation received by KU Leuven). PG received support for attending (virtual) conferences and meetings from Medtronic, Novo Nordisk, Roche, and Sanofi (financial compensation received by KU Leuven). PG is the recipient of a senior clinical research fellowship from FWO, the Flemish Research Council. CM has served on the advisory board for ActoBio, AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Imcyse, Insulet, Medtronic, Merck Sharp and Dohme, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Therapeutics, Vertex, and Zealand Pharma (financial compensation received by KU Leuven); and has served on the speakers' bureau for AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Novartis, Novo Nordisk, and Sanofi (financial compensation received by KU Leuven). All disclosures are unrelated to the present work. All other authors declare no competing interests.

#### Data sharing

Selected anonymous data and samples collected in the study and additional documents can be made available to others not involved in the CRISTAL study, on the basis of a reasonable request, beginning 6 months following Article publication. All inquiries should be made via email to Katrien Benhalima: katrien.benhalima@uzleuven.be.

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