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Subcutaneous weekly semaglutide with automated insulin delivery in type 1 diabetes: a double-blind, randomized, crossover trial

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Efforts to improve glycemic control in type 1 diabetes are ongoing. We performed a randomized, double-blind, crossover trial to assess semaglutide as adjunct to automated insulin delivery therapy in adults with type 1 diabetes. At each intervention, participants were titrated up to 1 mg or the maximum tolerated dose of semaglutide or placebo over 11 weeks, followed by the use of an automated insulin delivery system for 4 weeks. The primary outcome was the percentage of time spent in the target glucose range of 3.9–10.0 mmol l^{-1} during the last 4 weeks of each intervention. Twenty-eight participants were randomized and 24 completed the trial. The primary endpoint was met. Compared to placebo, semaglutide increased time in the target range by a mean 4.8 (s.d. = 7.6) percentage points ($P = 0.006$), without increasing the time spent below 3.9 mmol l^{-1} ($P = 0.19$) or below 3.0 mmol l^{-1} ($P = 0.65$). While no diabetic ketoacidosis or severe hypoglycemia occurred during any of the interventions, there were two episodes of recurrent euglycemic ketosis without acidosis during semaglutide use. We conclude that semaglutide improves glycemic control with automated insulin delivery compared to placebo. ClinicalTrials.gov registration: NCT05205928

The most advanced form of insulin therapy for type 1 diabetes (T1D) is automated insulin delivery (AID), which consists of continuous glucose monitoring (CGM), an insulin pump and an algorithm that adjusts insulin doses based on glucose levels. AID reduces glycated hemoglobin (HbA1c) and improves time spent in the target glucose range of 3.9–10.0 mmol l^{-1} (ref. 1). A goal of an HbA1c less than 7% is incorporated in diabetes guidelines to reduce the risk of microvascular and macrovascular diabetes complications[2–5], with 70% or more time spent in the target glucose range (3.9–10.0 mmol l^{-1}), which is considered the goal threshold according to the CGM guidelines as it is associated with an HbA1c of 7% or less[6].

However, in large randomized trials assessing AID use, 34–53% of participants were still not able to achieve an HbA1c of less than 7%[7–9], primarily because of suboptimal postprandial glucose control[10,11]. Moreover, these systems did not address the raising prevalence of obesity in T1D, which is associated with vascular risk and complications[12–14]. Obesity rates in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study cohort rose from 1% in 1983–1985 to 31% by 2005 (ref. 15).

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP1-RA) that is administered subcutaneously once weekly. Semaglutide has demonstrated glycemic, weight and cardiac benefits

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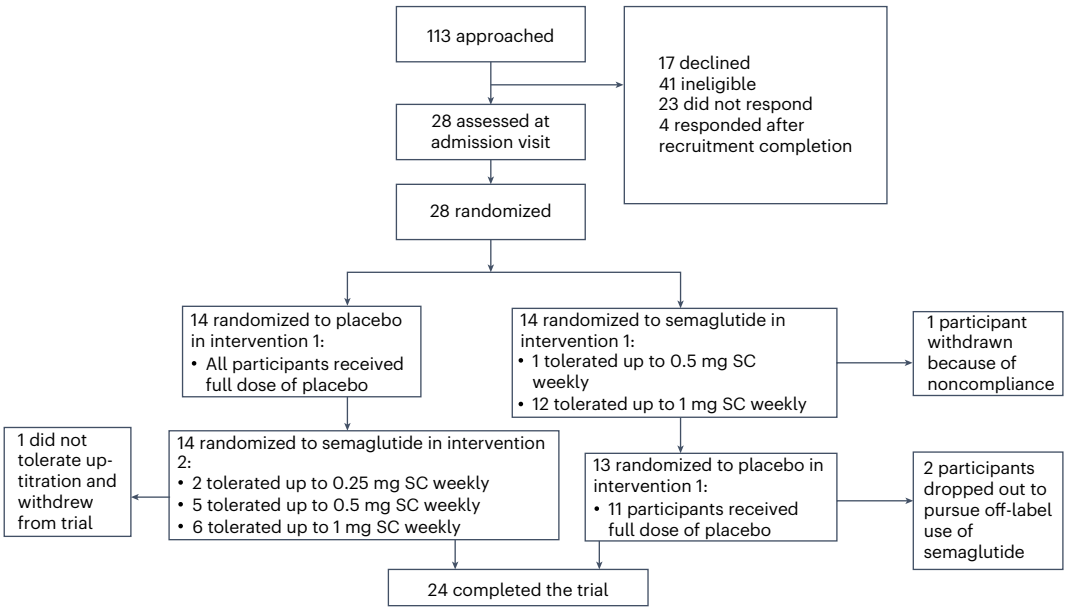

Fig. 1 | Participant recruitment and retention. CONSORT flow chart describing participant recruitment and retention. SC, subcutaneously.

in those with and without type 2 diabetes (T2D)[16–18]. Although semaglutide has not yet been assessed in T1D in clinical trials, retrospective data of off-label use has suggested benefits in reducing HbA1c, weight and insulin requirements[19,20].

The aim of this study was to assess whether semaglutide, versus placebo, improves glycemic control and other nonglycemic outcomes in those with T1D while using AID.

Results

Participant disposition

The Consolidated Standards of Reporting Trials (CONSORT) flow chart is depicted in Fig. 1. One hundred and thirteen adults with T1D were screened; 28 participants (61% female, aged 45 (s.d. = 14) years, with an HbA1c of 7.4% (0.8%); Table 1) were recruited and randomized between 18 October 2022 and 22 August 2023. Less than a third of participants met the HbA1c target (<7%) at baseline, similar to recent Canadian data in the general population with T1D[21,22]. Twenty-two (79%) participants were using commercial AID systems. Seven (25%) participants were overweight and 18 (64%) were obese.

Four participants did not complete the trial: two because of their desire to use semaglutide after the first intervention rather than continue the study, one because of difficulty complying with the study procedures and one because of the side effects of 0.5 mg semaglutide (Fig. 1). The two participants who withdrew from the study to pursue semaglutide use had assumed they were on semaglutide in the first intervention because of its effects; no formal unblinding occurred at any stage in the study for any participant. Of the 24 participants who completed the trial, the maximum tolerated dose of semaglutide was 0.25 mg in two (8.3%) participants, 0.5 mg in six (25.0%) participants and 1 mg in 16 (66.7%) participants. Of those 16 participants who completed the trial and tolerated the 1 mg dose, six completed the placebo intervention first and ten completed the semaglutide intervention first; however, four more participants with a body mass index (BMI) < 27 kg m^{-2} were randomized (by chance) to placebo first (Supplementary Table 1). The BMI of those who tolerated 1 mg until the end of the study was 34.0 (4.4) kg m^{-2} compared to 28.6 (5.3) kg m^{-2} ($P = 0.03$) for those who did not.

Changes during the titration period in participants' insulin therapy parameters are displayed in Supplementary Table 2. Extended Data Fig. 1 depicts the early and persistent reduction in insulin and carbohydrate intake with semaglutide. During the preceding titration phase, there were more additional follow-ups during semaglutide use because of several reasons, such as increased adverse events and the need for additional glycemic reviews for safety, although these additional follow-ups were predominantly accounted for by a minority of participants who were using open-loop pump therapy (Supplementary Table 3). During the last 4 weeks of each intervention, on the study's AID system, the number of additional follow-ups during semaglutide use was comparable to placebo (Supplementary Table 3).

Primary outcome

For the last 4 weeks of each intervention, on the study's AID system, the percentage of time in range was 74.2 (9.7) percentage points for semaglutide versus 69.4 (10.4) percentage points for placebo, a difference of 4.8 (7.6) percentage points ($P = 0.006$; Table 2). There was no evidence of carry-over effect for the primary endpoint ($P = 0.15$ for the treatment-intervention interaction term) or any secondary outcome.

Secondary outcomes

In the last 4 weeks of AID use, there was no difference in time spent in hypoglycemia ($P = 0.19$) between the interventions; therefore, the gain in time in-range was entirely due to a reduction in hyperglycemia. The mean glucose level and the s.d. of glucose levels were significantly reduced with semaglutide use compared to placebo, but the coefficient of variance was not (Table 2). Daytime and nighttime outcomes are reported in Supplementary Table 4.

Laboratory assessment (Supplementary Tables 3 and 5) demonstrated a reduction with semaglutide compared to placebo in HbA1c of 0.5% (interquartile range (IQR)[−0.7, −0.2]) ($P < 0.001$) and fructosamine of −15 µmol l^{-1} [−39, 2] ($P < 0.001$). High-density lipoprotein (HDL) cholesterol was lower with semaglutide than placebo ($P = 0.01$), whereas other lipid levels were unchanged. Ferritin level was lower after placebo compared to semaglutide, but three participants had iron deficiency early in the trial; they were randomized to placebo first, then treated with iron supplementation by semaglutide use. When these participants' data were removed, HbA1c remained significant (Supplementary Table 6). Alkaline phosphatase decreased more with semaglutide compared to placebo ($P = 0.002$), whereas bilirubin increased ($P = 0.02$). There were no differences in other laboratory measurements between interventions.

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Table 1 | Baseline characteristics of participants (*n*=28)

Characteristic	
Female sex (*n* (%))[a]	17 (61)
Age in years (mean (s.d.))	45 (14)
Duration of diabetes in years (mean (s.d.))	28 (13)
HbA1c in % (mean (s.d.))	7.4 (0.8)
HbA1c < 7% (*n* (%))	8 (29)
Use of CGM (*n* (%))	28 (100)
Freestyle Libre 2[b]	4
Guardian sensor	6
Dexcom G6	18
Insulin pump use (*n* (%))	
Open-loop systems	6 (21)
Medtronic	6
Closed-loop systems	22 (79)
MiniMed 670/770G[c]	6
Control-IQ	14
OmniPod with DIY Looping	2
Insulin use (*n* (%))[d]	
Lispro (Humalog)	17 (61)
Aspart (Novorapid)	4 (14)
Faster aspart (Fiasp)	5 (18)
Biosimilar insulins	2 (7)
BMI (kg m^{-2})	32.2 (5.1)
Categories of BMI in kg m^{-2} (*n* (%))	
Less than 25.0	3 (11)
25–29.9	7 (25)
30–34.9	11 (39)
35–39.9	5 (18)
≥40	2 (7)
Daily insulin requirements (U kg^{-1})	0.70 (0.27)
C-peptide[e]	
Random C-peptide level, median (IQR) (nmol l^{-1})	0 (0–0.0055)
Number of participants with detectable levels of C-peptide (*n* (%))	8 (29)

[a]There was no discrepancy between gender and biological sex at the admission visit, that is, all participants were *cis*-gendered. [b]One participant occasionally used the Guardian 3 sensor. Two participants switched from Freestyle Libre 2 to Dexcom G6 during the titration period of intervention 2. [c]The MiniMed 780G upgrade arrived in Canada in Spring 2023. One participant upgraded to 780G soon after randomization, whereas two participants upgraded at approximately day 56 of intervention 2. [d]Those on biosimilar insulins and Fiasp were switched to a similar insulin compatible with the Ypsomed pump for the duration of the research-based AID portion. [e]Less than the detectable limit (<0.003 nmol l^{-1}) was rounded to 0. Twenty-seven participants had available baseline C-peptide levels (one missing because of a laboratory error).

Table 2 | Comparison of CGM and pump data between placebo and semaglutide (at the maximum tolerated dose) as adjunct to hybrid closed-loop therapy (*n*=24)

Outcome	Placebo	Semaglutide	Paired difference (semaglutide versus placebo)	*P*
Time in range (%) of glucose (mmol l^{-1})				
Target 3.9–10.0	69.4 (10.4)	74.2 (9.7)	4.8 (7.6)	0.006
Target 3.9–7.8	46.0 (10.8)	49.6 (10.2)	3.6 (9.2)	0.07
Below 3.9	1.1 [0.7, 2.0]	1.2 [0.9, 2.4]	0.3 [−0.1, 0.6]	0.19
Below 3.0	0.3 [0.1, 0.3]	0.3 [0.1, 0.4]	0 [−0.1, 0.1]	0.65
Above 7.8	53.9 (11.0)	50.2 (10.9)	−3.7 (9.8)	0.09
Above 10.0	29.1 (10.6)	24.1 (10.1)	−5.0 (8.0)	0.006
Above 13.9	8.4 [4.0, 12.0]	5.4 [2.7, 8.9]	−1.7 [−4.2, 0]	0.008
Mean glucose (mmol l^{-1})	8.8 (1.0)	8.4 (0.9)	−0.4 (0.7)	0.02
s.d. (mmol l^{-1})	3.2 (0.7)	3.0 (0.6)	−0.3 (0.5)	0.01
Coefficient of variation (%)	36.4 (4.5)	35.1 (4.7)	−1.4 (3.8)	0.10
Time in 3.9–10.0 ≥ 70% (*n* (%))	10 (42)	13 (54)	–	0.39
Total insulin (U day^{-1})	62.1 [38.8, 85.1]	46.1 [32.7, 62.7]	−11.3 [−23.6, −4.9]	<0.001
Total insulin (U kg day^{-1})	0.77 (0.35)	0.64 (0.28)	−0.13 (0.16)	0.002
Change in total insulin per day from baseline (%)	+7.7 (25.6)	−14.6 (23.2)	−22.3 (18.4)	<0.001
Basal insulin (U day^{-1})	35.0 [22.8, 49.1]	30.6 [21.0, 40.6]	−3.5 [−9.7, −0.3]	0.003
Basal insulin as percentage of total insulin (%)	57.7 (8.6)	64.0 (9.5)	6.3 (7.4)	<0.001
Bolus insulin (U day^{-1})	23.5 [16.9, 33.1]	15.2 [10.8, 22.9]	−6.2 [−14.1, −3.5]	<0.001
Bolus insulin as percentage of total insulin (%)	42.3 (8.6)	36.0 (9.5)	−6.0 (7.4)	<0.001
Total carbohydrates (g day^{-1})	142 [100, 172]	95 [75, 141]	−36 [−55, −15]	<0.001

Data are shown as the mean (s.d.) or median [IQR]. A two-sided linear mixed model was used for the parametric analyses, while a Wilcoxon signed-ranked test was used for the nonparametric analysis. A chi-squared test was used for the categorical analysis.

Weight was reduced by 5.3 (2.9) kg with semaglutide compared to placebo ($P < 0.001$; Table 3), constituting a −5.1% (3.0) relative change from baseline. Waist circumference and hip circumference were also all reduced with semaglutide (Table 3). There were no differences in other anthropometric measurements between interventions (Supplementary Table 7).

Daily insulin use was reduced by 11.3 units [−23.6, −4.9] with semaglutide compared to placebo ($P < 0.001$; Table 2). This reduction was driven by reductions in both bolus (−6.2 U [−14.1, −3.5]) and basal insulin (−3.5 U [−9.7, −0.3]). Moreover, weight-based daily insulin requirements (a marker of insulin sensitivity) were also reduced with semaglutide (0.77 (0.35) U kg day^{-1}) compared to placebo (0.64 (0.28) U kg day^{-1}, $P = 0.002$). Daily carbohydrate intake (as entered into the participants' bolus calculator) was also reduced by 36 g [−55, −15] with semaglutide compared to placebo ($P < 0.001$).

Safety

Adverse events (AEs) for all 28 participants are described in Table 4. The most common AEs were gastrointestinal; 72 AEs were reported in 23 (82%) participants with semaglutide and 14 AEs were reported in 7 (25%) participants with placebo. Diabetic ketoacidosis did not occur; however, there were two episodes of euglycemic ketosis during semaglutide use, both leading to participant-initiated emergency visits to rule out ketoacidosis and other causes (Supplementary Text 1). One of the cases was thought to be related to semaglutide use, whereas the other was suspected to be unrelated because of a coinciding

Table 3 | Anthropometric and laboratory outcomes at baseline and at the end of each intervention (*n*=23* for anthropometrics outcomes, *n*=24 for laboratory outcomes)

Outcome	Baseline	Placebo	Semaglutide	Placebo-adjusted change	*P*
Anthropometric outcome					
Weight (kg)	91.3 (17.4)	89.7 (17.8)	84.3 (17.1)	−5.3 (2.9)	<0.001
Weight (%) from baseline	–	−2.1 (3.7)	−6.7 (5.1)	−5.1 (3.0)	<0.001
BMI (kg m^{-2})	32.3 (5.5)	31.8 (5.8)	29.8 (5.3)	−1.9 (1.1)	<0.001
Waist circumference (cm)	101.1 (14.3)	99.2 (15.3)	93.8 (15.8)	−5.2 (4.6)	<0.001
Hip circumference (cm)	111.8 (10.8)	112.1 (11.1)	107.6 (10.9)	−4.5 (3.1)	<0.001
Laboratory outcome					
HbA1c (%)	7.5 [7.1, 7.9]	7.1 [6.5, 7.5]	6.8 [6.2, 7.1]	−0.5 [−0.7, −0.2]	<0.001
HbA1c < 7% (*n* (%))	5 (21)	10 (42)	17 (71)	–	0.002
Fructosamine (μmol l^{-1})	–	330 [300, 351]	304 [280, 341]	−15 [−39, 2]	<0.001
Total cholesterol (mmol l^{-1})	4.18 [3.61, 4.86]	4.02 [3.29, 4.72]	3.38 [2.98, 4.46]	−0.22 [−0.73, 0.05]	0.37
Triglycerides (mmol l^{-1})	1.69 [0.80, 1.78]	0.89 [0.66, 1.09]	1.17 [−0.63, 1.33]	0.08 [−0.3, 0.32]	0.07
HDL cholesterol (mmol l^{-1})	1.46 (0.42)	1.47 (0.36)	1.29 (0.34)	−0.17 (0.29)	0.01
LDL cholesterol (mmol l^{-1})	2.24 (1.03)[b]	2.09 (0.81)	2.01 (0.79)	−0.28 (0.77)	0.19
Non-HDL cholesterol (mmol l^{-1})	2.90 (1.12)	2.63 (0.92)	1.35 (0.96)	−0.17 (0.47)	0.11

Data are shown as the mean (SD) or median [IQR]. A two-sided linear mixed model was used for the parametric analyses. A Wilcoxon signed-ranked test was used for the nonparametric analysis. A chi-squared test was used for the categorical analysis. [a]One participant could not be present for the final anthropometric measurements because of an injury. [b]Hypertriglyceridemia in two participants, therefore *n*=22 for the baseline outcome.

food-borne illness and pump malfunction. There was one episode of severe hypoglycemia with placebo during the titration period, related to CGM malfunction. In two participants, there was incidentally found progression of clinically stable or regressed retinopathy (one episode of proliferative retinopathy during placebo use and one nonproliferative sequela during semaglutide use); neither event was sight-threatening as per ophthalmology consultation. There was one serious AE during semaglutide, which was deemed to be unrelated to the study (a recurrent tibial fracture after a prior surgery; Supplementary Text 2).

Exploratory outcomes

The reduction in weight was correlated with the improvements in time in range (Pearson $\rho = 0.50$, $P = 0.015$) and HbA1c (Pearson $\rho = 0.43$, $P = 0.04$; Supplementary Table 8 and Extended Data Fig. 2), that is, those who had the highest weight reduction tended to have the most glycemic benefits. Stratified effect sizes for changes in time in range, HbA1c and weight loss are listed according to category of baseline BMI; weight reduction also supported that improvements were more pronounced for those with higher BMI and more weight loss (Supplementary Table 9). This was more pronounced than the stratified effect size for time in range according to baseline HbA1c (Supplementary Table 10).

Of the 24 participants who completed the trial, six (25%) participants had detectable random plasma C-peptide levels at baseline (defined as greater than 0.003 nmol l^{-1}). Placebo-adjusted changes in time in range, weight and HbA1c were 6.2 (9.7) percentage points, −6.3 (5.7) kg and −0.7% (0.3) in those with detectable C-peptide levels compared to 4.4 (7.1) percentage points, −6.4 (3.4) kg and −0.4% (0.3) in those with undetectable levels (Supplementary Table 11).

Post hoc analyses

Fourteen participants used the commercial Control-IQ technology at baseline, with 12 completing the trial. During the last 2 weeks of the titration periods in those 12 participants, semaglutide led to a higher time in range by 4.3 percentage points (5.5, $P = 0.02$), lower insulin usage by 12.2 U [−16.2, −5.4] ($P = 0.008$) and lower carbohydrate intake by 50 g (35; $P = 0.0004$) compared to placebo, without increasing time spent in hypoglycemia (Supplementary Table 12).

Discussion

In this trial, semaglutide improved glycemic control, with lower insulin requirements, in adults with T1D when used with AID. Semaglutide also reduced carbohydrate intake, body weight, BMI and waist and hip circumferences compared to placebo. Those who had the highest weight reduction had the most glycemic benefits.

Shorter-acting GLP1-RAs have been studied previously in T1D, in particular liraglutide[23,24]. The reduction in HbA1c in our study was larger than what has been reported with liraglutide[23,24]. However, the reduction was less than what has been reported with semaglutide in T2D[25], even in those with similar baseline HbA1c. In T2D, semaglutide promotes beta cell function and insulin secretion via the incretin effect[26,27], mechanisms that are absent in T1D. In our study, HbA1c reductions in those with detectable C-peptide levels tended to be higher than those with undetectable levels, a finding similar to what has been reported in studies with liraglutide[28]. Therefore, combining semaglutide with treatments that preserve beta cell function may maximize its glycemic benefits[29].

Semaglutide reduced carbohydrate intake, weight and weight-based insulin requirements (a marker of insulin sensitivity), all of which improve glycemic control. As postprandial hyperglycemia is a major challenge with AID systems[10], a reduced prandial load with low carbohydrate intake reduces glucose levels[30]. Weight loss, on the other hand, can improve insulin sensitivity[31], which is also associated with improved glycemia in T1D[14]. This may explain associations of larger reductions in weight in our study with larger improvements in time in range and HbA1c. Of note, the weight loss in our study was comparable to what has been reported in T2D with a similar baseline weight[16] and higher than what has been reported with liraglutide in T1D[23,24].

Unlike the clear glycemic and anthropometric benefits observed in our study, there were minimal changes in nonglycemic laboratory outcomes and in blood pressure. This may be because of the lack of abnormalities at baseline in our study participants. Only HDL-c, bilirubin, and alkaline phosphatase demonstrated statistically significant

Table 4 | AEs

	Placebo (*n*=27)		Semaglutide (*n*=28)	
	Events, *n*	Participants, *n* (%)	Events, *n*	Participants, *n* (%)
Any AE	41	17 (63)	121	27 (96)
Serious AE	0	0 (0)	1	1 (4)[a]
Gastrointestinal AE	14	7 (26)	72	23 (82)
AEs in >10% of participants				
Nausea	2	2 (7)	25	25 (89)
Loss or decrease in appetite	1	1 (4)	9	10 (36)
Constipation	2	2 (7)	8	8 (29)
Fatigue	0	0 (0)	6	6 (21)
Emesis	0	0 (0)	5	5 (18)
Diarrhea	0	0 (0)	5	5 (18)
Upper respiratory tract infection	6	6 (22)	6	6 (21)
Gastroesophageal reflux	1	1 (4)	4	4 (14)
Light-headedness	0	0 (0)	4	4 (14)
AEs of safety interest				
Severe hypoglycemic event	1	1 (4)	0	0
Euglycemic ketosis	0	0	2	2 (7)
Diabetic ketoacidosis	0	0	0	0
Progression of diabetic retinopathy				
Proliferative	1	1 (4)	0	0 (0)
Nonproliferative	0	0 (0)	1	1 (4)

[a]The serious AE was a recurrent tibial fracture after a prior surgery and thought to be unrelated to the study drug; see Supplementary Text 2 for details.

but not clinically meaningful changes. While small increases or no change in HDL cholesterol have been reported in large trials of semaglutide in T2D[32], lowering was also reported in a study in people with obesity[33]. Alkaline phosphatase was also mildly lowered by semaglutide in another study in T2D[34]. Larger studies conducted in subpopulations of T1D with abnormal baseline values are needed to further assess nonglycemic laboratory outcomes and blood pressure.

Two participants in our study had overt episodes of euglycemic ketosis, which did not lead to acidosis and were resolved with carbohydrate and insulin intake. GLP1-RAs have been linked to ketoacidosis in T1D[23,35]; starvation is a known trigger for euglycemic ketoacidosis[36,37]. Recent case studies reported ketoacidosis in T1D with semaglutide and tirzepatide, including during euglycemia[38,39]. Therefore, euglycemic ketosis management should be discussed before semaglutide use in T1D. Larger studies with semaglutide are required to properly assess its ketoacidosis risk in T1D.

We used a research-based AID system in our study. To assess the generalizability of our findings, we performed a post hoc analysis in 12 participants who were on the commercial Control-IQ technology during the last 14 days of the titration period. Placebo-adjusted outcomes of time in range, time in hypoglycemia, insulin use and carbohydrate intake were all comparable to what we observed with our research-based AID. These outcomes are also probably generalizable to other commercial AID systems.

Benefits should be weighed against risks in any drug. The mean improvement in time in range was higher than the three percentage points considered in consensus guidelines to be clinically meaningful for a treatment group difference[40]. The improvements in HbA1c and weight loss were also clinically meaningful, the former reflecting evidence from DCCT/EDIC[2,3] and the latter meeting the minimum weight loss (5%) needed for metabolic improvement[41]. The most common AEs with semaglutide were gastrointestinal in nature and were mostly mild and comparable in frequency to what has been reported in other populations[16,17]. Therefore, overall, our data support the use of semaglutide in T1D, even in those nondetectable C-peptide levels, in particular in those with higher BMI as they had more weight loss and higher glycemic benefits. However, even though the two overt episodes of symptomatic euglycemic ketosis did not lead to ketoacidosis, caution to prevent ketoacidosis should still be exercised, including enhanced patient education, more frequent ketone monitoring and minimization of insulin reductions.

This study has multiple strengths. First, this trial has a double-blind, randomized, controlled design. Second, as AID is the most advanced insulin therapy, the placebo arm represented the best commercially available treatment for T1D at this time.

The study also has several limitations. First, the study size and length were not sufficient to assess long-term efficacy and safety. Our sample size resulted from a crossover study design that aimed to assess differences in time in range of glucose levels with AID as the primary outcome[40], rather than to obtain a comprehensive assessment of the drug's safety profile. The length of each intervention consisted of an 11-week drug titration period as per its monograph, which was followed by 4 weeks of AID use for the primary outcome assessment; previous work indicated that 2–4 weeks of CGM data provide a good approximation of long-term glucose metrics[42,43]. Second, the study had a crossover rather than a parallel design to increase statistical power by fourfold, but this increased the risk of carry-over. Although the analysis of the primary and secondary outcomes did not reveal a drug–intervention interaction, the presence of a carry-over effect that is not captured by the analysis is still possible. Third, the study did not recruit a sufficient number of participants to assess outcomes in those with BMI less than 25 kg m^{-2} or to assess outcomes of metabolic syndrome (for example, blood pressure, lipid profile, metabolic dysfunction-associated steatotic liver disease). Fourth, there were more unscheduled follow-ups with semaglutide compared to placebo, which may have affected the results because of the increase of healthcare or research personnel contact. However, these follow-ups were predominantly during the dose titration period, and, in the minority of participants, using open-loop pump therapy.

In conclusion, in participants with T1D, semaglutide at the maximum tolerated dose increased time in range without increasing hypoglycemia. Semaglutide led to milder gastrointestinal side effects with two episodes of recurrent euglycemic ketosis without acidosis. Larger studies are required to ascertain long-term efficacy and safety in T1D.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-024-03463-z.

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Methods

Study design

The study was a randomized, double-blind, crossover trial carried out at the Research Institute of the McGill University Health Centre in Montreal, Quebec, Canada. Each arm was 15 weeks, with 2 weeks of washout, for a total study duration of 32 weeks. The protocol was approved by the research ethics board of the McGill University Health Centre and Health Canada, and is available in the supplementary materials. The study was registered on the ClinicalTrials.gov website, with registration no. NCT05205928, before study commencement.

Participants

We enrolled participants aged 18 years old and older with a diagnosis of T1D for 1 year or longer, use of an insulin pump for 3 months or longer, HbA1c of 11% or less, and if applicable, agreement to use a highly effective method of birth control in persons of child-bearing potential or active avoidance of pregnancy during the trial. Exclusion criteria included current or recent (<2 weeks) use of an antihyperglycemic agent other than insulin, planned or ongoing pregnancy or breastfeeding, severe hypoglycemic episode within 3 months, diabetic ketoacidosis requiring medical attention and intravenous insulin within 6 months, history of acute or chronic pancreatitis or gallbladder disease, BMI of 21 kg m^{-2} or less, personal or family history of medullary thyroid cancer or type 2 multiple endocrine neoplasia, bariatric surgery within 6 months, any prior adverse reaction to GLP1-RAs, regular use of hydroxyurea, any serious medical or psychiatric illness that may interfere with trial participation, clinically significant diabetic retinopathy or gastroparesis, failure to comply with the study protocol or research group recommendations, inability or unwillingness to comply with safe diabetes management practices, inability to use AID system, or any other concern for safety for the participant as per clinical judgment of the investigator. The BMI cutoff was chosen to best assess the primary endpoint (time in range, that is, glycemic control) through several hypothetical mechanisms of semaglutide, while reducing the risk of participants becoming underweight. This is similar to past trials assessing GLP1-RAs in T1D[23]. Recruitment was performed in the Division of Endocrinology at the McGill University Health Centre and from prior study participants interested in being contacted for future studies.

Procedures

At the initial visit, study procedures began after written informed consent was obtained and documented. Demographics such as age, duration of diabetes, medical history and medications were obtained; both participant-reported biological sex and gender were obtained. Laboratory testing and a physical examination were performed. This was combined with a training visit, where 30–60 min of diabetes management review (for example, hypoglycemia and exercise management) and a training on the drug (semaglutide or placebo) injection technique were performed.

After the initial visit, an 11-week drug dose titration period was initiated: 0.25 mg weekly for 4 weeks, then 0.5 mg weekly for 4 weeks, then 1 mg onward. The study team de-escalated the doses in case of participants' intolerance of side effect. Participants remained on their usual pump therapy throughout the titration period. Remote review of side effects and CGM reports was performed at days 7, 21, 32, 56, 63 and 77 (±2 days) of the dose titration periods, and additionally as prespecified in the study protocol, as needed per the research team's judgment. Insulin adjustments were made to reduce hypoglycemia and overt hyperglycemia.

After the dose titration period, participants used our research-based AID system for 28 days. A research-based AID system was chosen to minimize the selection bias of pump users who had the latest pump hardware, and because commercial AID use was not as widespread in Canada at the time of protocol creation. The system included an Ypsomed pump (Ypsomed), Dexcom G6 CGM (Dexcom) and a Pixel 2 smartphone with an application running the McGill insulin dosing algorithm[44]. The system was initialized with participants' total daily insulin doses, carbohydrate ratios and insulin basal rates. The system target glucose was set at 6 mmol l^{-1} initially but was reduced to 5.5 mmol l^{-1} if time spent below 3.9 mmol l^{-1} was low. Remote follow-ups were performed on days 4, 7 and 21 (±2 days) of AID use to review CGM reports and make adjustments to carbohydrate ratios and basal rates, if needed. Additional follow-ups were made as needed as per the research team's judgment for safety reasons; these additional follow-ups were prespecified in the protocol.

At the end of AID use, laboratory testing and anthropometric measurements were performed. Participants returned to their usual insulin for a washout period of 2 weeks. After the washout period, the second study drug was initiated, with identical procedures to the first intervention. The 2-week period was a 'mock washout'; because of the long (11 weeks) dose titration period and the primary outcome being measured during the following 4 weeks, participants had 13 weeks of functional washout period.

Data handling

Glucose, insulin and meal data from the AID system were automatically synched to a secure cloud server whenever the participant's device was connected to the internet. A research team member manually retrieved the data in JSON format from the cloud server onto a research-dedicated device for further analysis. A custom script preprocessed the JSON data to compute relevant graphs and metrics for follow-ups and study outcomes. For the titration period data, CGM outcomes, insulin requirements and carbohydrate intake were manually input from the pumps and CGM commercial software into a secure database. Manual entries were confirmed independently by two team members.

Randomization and masking

Participants were randomized to their intervention sequence, either semaglutide then placebo, or placebo then semaglutide. Block randomization was performed with randomly selected block sizes of 4, 6 or 8 by a researcher uninvolved with participants using the Sealed Envelope Ltd online tool[45]. After eligibility and enrollment were confirmed, participants were officially entered into the randomization sequence. An envelope with the participant's study ID and randomization sequence was placed in storage to be opened in case of an emergency in the trial; a second envelope with the participant's study ID and randomization sequence was opened and placed in the participant's study case report form. This second envelope was opened, signed and dated by one of the trial's investigators. Randomization sequences were revealed only after the last participant's last visit was completed. Semaglutide or placebo were dispensed by the research pharmacy, who were unblinded to drug allocations.

To mask study drug, semaglutide or placebo (saline) in sterile amber glass vials were given to participants, along with insulin syringes, dispensed by the research pharmacy, who were unblinded to drug allocation. Participants would administer 0.19, 0.37 or 0.74 ml to correspond to 0.25, 0.5 and 1 mg, respectively. Participants, investigators and other research personnel were blinded to allocation.

Outcomes

The primary endpoint was time in the target glucose range of 3.9–10.0 mmol l^{-1} (time in range) between semaglutide (at maximum tolerated dose) and placebo, over the 28 days of AID use. Secondary endpoints included mean glucose level, s.d. and coefficient of variation of glucose levels, and times spent in hyperglycemia (above 10.0 and 13.9 mmol l^{-1}) and hypoglycemia (less than 3.0 and 3.9 mmol l^{-1}). Daytime (6:00–24:00 h) and nighttime (24:00–6:00 h) outcomes were also assessed. Other secondary endpoints included anthropometrics, insulin requirements, carbohydrate intake and laboratory analyses (for example, HbA1c).

Statistical analysis

A difference of 6.25 percentage points (that is, 90 min per day) in time in range was deemed significant[44,46]. Assuming an s.d. of 10% in the difference[46–48], 23 participants would provide 80% power to detect this difference at a 5% significance level. To account for a 20% dropout rate, 28 participants were recruited.

A linear mixed effects model was used to assess the effects of treatment while adjusting for the order of interventions. To examine for carry-over effect in the primary and secondary outcomes, the models were fitted with the treatment by period interaction terms. Residual values were examined for normality and, if skewed, a Wilcoxon signed-rank test was used. $P < 0.05$ was deemed significant. Results are reported as the median (IQR) or mean (s.d.). No correction for multiplicity was made for the secondary comparisons. AE outcomes included all participants in the study to provide comprehensive safety reporting, while all other outcomes were reported for those who completed the study and had analyzable paired measures (that is, for both semaglutide and placebo). Pearson correlation and subanalyses were also performed for the associations of outcomes with baseline characteristics, such as age, sex and duration of diabetes. Sex and gender were to be analyzed separately if there were discrepancies in participants.

Data processing was performed using MATLAB (v.R2024a); statistical analysis were performed with SPSS (v.29.0.1.1).

Safety monitoring

A Data Safety and Monitoring Board consisting of two endocrinologists specialized in T1D adult care, independent of the study, intermittently reviewed data for safety. The Data Safety and Monitoring Board reviewed blinded data and had two meetings. The first meeting reviewed data for participants 1–6 and the second meeting reviewed data for participants 7–14. Meetings could also be scheduled if there was a serious AE suspected to be caused by the study, but this did not occur. The purpose of the data review was to confirm the absence of extreme, potentially unsafe reductions in insulin doses, carbohydrate intake or weight, and the absence of unsafe glucose levels (for example, time spent below 3.9 mmol l^{-1} more than 4%) in either intervention.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The protocol of the study is included in the supplementary material. All raw data collected from the study cannot be made publicly available given limitations from the informed consent form and ethics board approval. The raw data can be shared by the corresponding authors without cost for unrestricted noncommercial purposes; however, the use will be subject to approval from the Research Ethics Board of the McGill University Health Centre. After approval, reasonable efforts will be made for the data to be shared within 3 months.

Code availability

The code used for data processing will be made available when the raw data are shared as per the 'Data availability' statement.

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Author contributions

A.H., A.K., M.-R.P. and M.A.T. designed the study. A.K. wrote the first draft of the protocol. M.-R.P. wrote the final protocol, recruited the participants and performed the study procedures. M.A.T. also performed the study procedures. A.J., W.A., A.H. and M.-R.P. carried out the data and statistical analyses. A.H. is the guarantor of this work; as such, he had full access to the data and takes responsibility for the integrity of the data analysis. All authors read and approved the final version of the manuscript.

Competing interests

M.-R.P. has received speaker honoraria from Medtronic Diabetes Canada and Abbott Diabetes Care. M.A.T. has received speaker honoraria from AstraZeneca, Bausch Health, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk and Sanofi. A.H. has acted as a consultant for Eli Lilly and has received drugs, supplies, equipment and other in-kind support from Tandem, Adocia, Dexcom, Eli Lilly and Ypsomed. A.K., W.A. and A.J. declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-024-03463-z.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-024-03463-z.

Correspondence and requests for materials should be addressed to Melissa-Rosina Pasqua or Ahmad Haidar.

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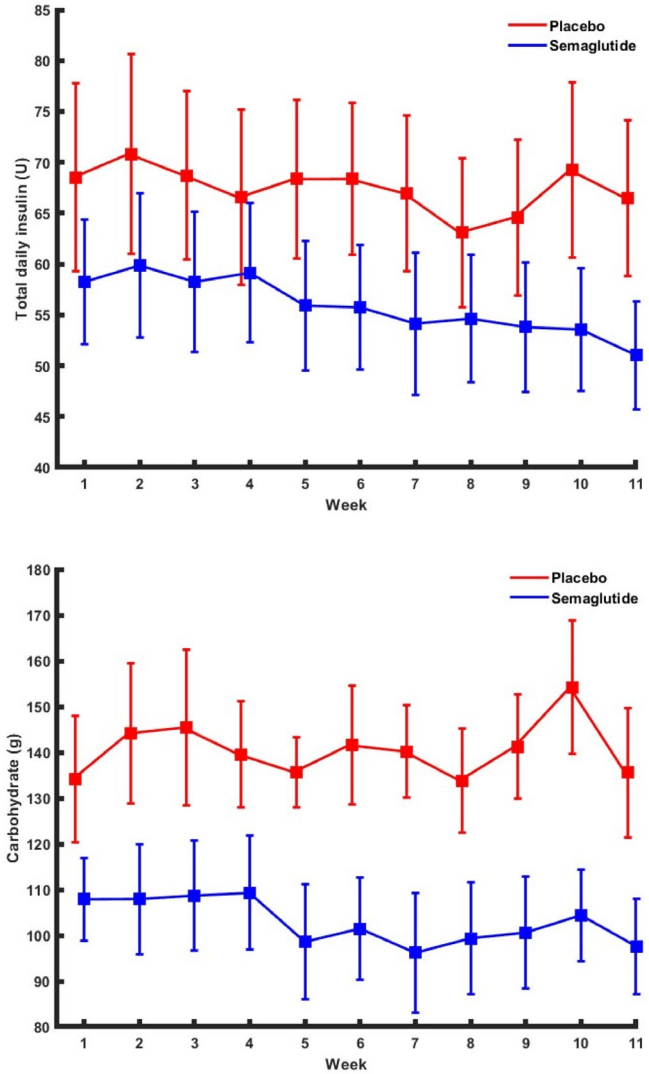
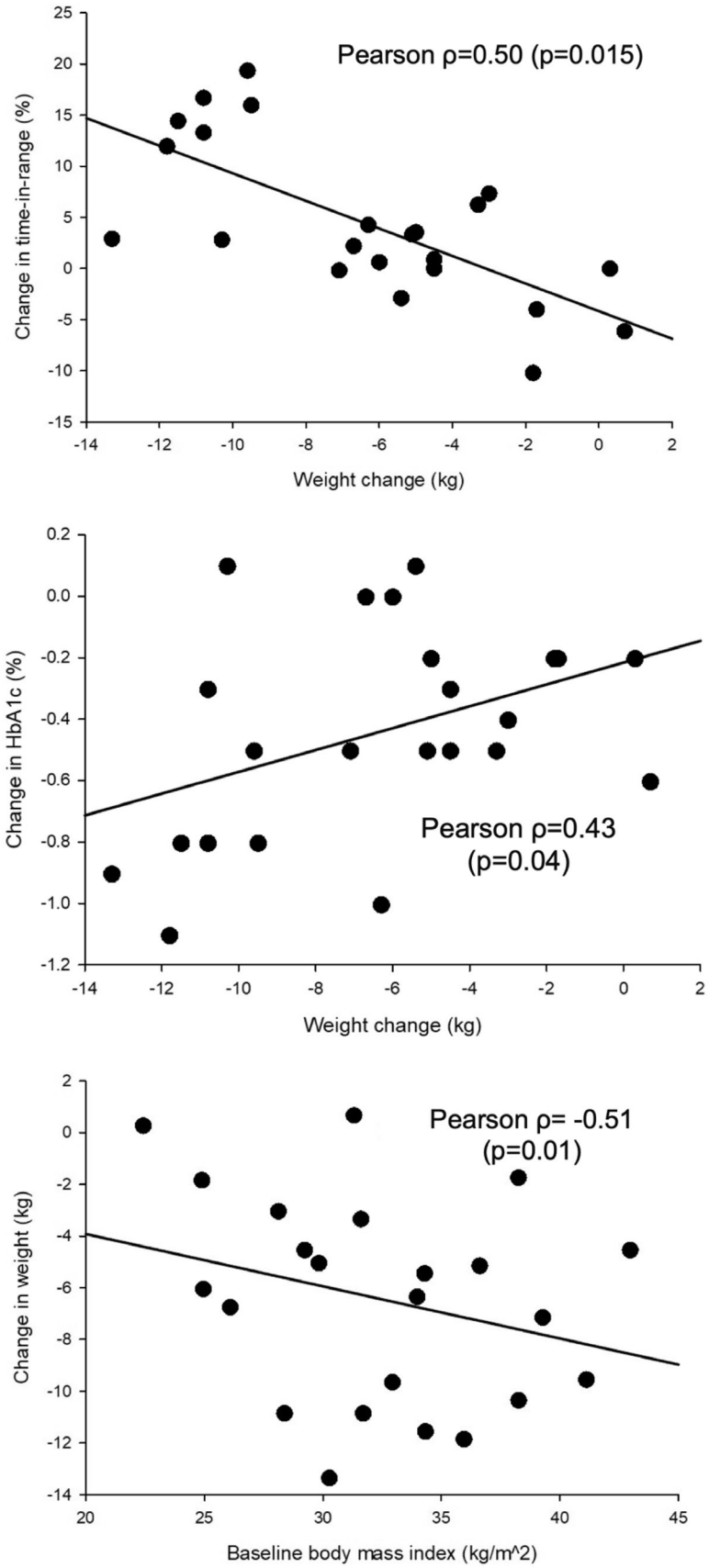


Extended Data Fig. 1 | Participants' insulin and carbohydrate changes over time. Weekly changes in **a**) total daily insulin requirements (upper plot) and **b**) daily carbohydrate intake (lower plot) over the 11-week titration period on participants' own pump therapy ($n = 24$). Square dots depict mean values, with bars depicting standard error.

https://doi.org/10.1038/s41591-024-03463-z



Extended Data Fig. 2 | Scatterplot correlations. Depicted correlations via scatterplot with trendline as per Pearson correlation ($n = 24$), with two-sided analyses used as default. Dots are individual data points. **a**) Placebo-adjusted weight change with placebo-adjusted change in time-in-range (3.9–10.0 mmol/L). **b**) Placebo-adjusted weight change with placebo-adjusted HbA1c change. **c**) Baseline BMI with placebo-adjusted weight change.

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data processing was performed using Matlab.
Data analysis	Data processing was performed using Matlab (R2024a) and statistical analysis were performed using IBM SPSS Statistics (version 29.0.1.1).

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Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	All findings pertain to biological sex. Gender was also obtained at the admission visit but all participants were cisgendered.
Reporting on race, ethnicity, or other socially relevant groupings	Due to the size of the study, race/ ethnicity / socioeconomic status were not taken from participants.
Population characteristics	Full details concerning participant characteristics are available in Table 1 of the manuscript.
Recruitment	Twenty-eight participants were recruited between October 2022 and August 2023. This was performed within the Division of Endocrinology at the McGill University Health Centre as well as past participants who had previously given consent to be contacted for future studies. Certain selection biases that may impact results may include the following: use of prior participants (therefore more familiar with the AID system), the use of an AID system requiring a tube (therefore those preferring tubeless pumps were less likely to enter the study), and selection at a tertiary care centre (therefore may modify complexity and duration of diabetes). Further, the use of semaglutide itself may have impacted recruitment, as more participants familiar with the drug with desire for weight loss may have been recruited.
Ethics oversight	This study was approved by Health Canada and the Research Ethics Board of the McGill University Health Centre.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	6.25 percentage points difference (i.e. 90 minutes/day) in time-in-range was deemed significant. Assuming a standard deviation of 10% in the difference, 23 participants would provide 80% power to detect this difference at a 5% significance level. To account for a 20% drop-out rate, 28 participants were recruited.
Data exclusions	Only participants who withdrew from the study (4 of the 28) had data removal from the analyses.
Replication	Given the nature of the clinical trial, data cannot be replicated. The study was performed in humans, which are sensitive to circumstances that may affect behaviour or metabolism (such as weight, stress, activities).
Randomization	Block randomization was performed with block sizes of 4, 6, or 8 by a research uninvolved with participants.
Blinding	To mask study drug, semaglutide or placebo (saline) in sterile amber glass vials were given to participants, along with insulin syringes, dispensed by the research pharmacy, who were unblinded to drug allocation. Participants would administer 0.19, 0.37, or 0.74 mL to correspond to 0.25, 0.5 and 1 mg, respectively. Participants, investigators, and other research personnel were blinded to group allocation. Unblinding occurred after the last participant, last visit to allow for data analysis.

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Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT05205928
Study protocol	The study protocol has been submitted with this manuscript.
Data collection	Twenty-eight participants (see Table 1) were recruited between Oct 2022 and Aug 2023; see the CONSORT flow diagram (Extended Data Figure 1). Data was collected from Oct 2022 to April 2024 in the form of demographics, laboratory and anthropometric measurements and CGM/pump data from commercial AID use; this was gathered in an encrypted excel spreadsheet. Raw data from the researched-based AID system was uploaded into a protected cloud format and processed through MatLab.
Outcomes	The primary endpoint was time in the target range of 3.9 to 10.0 mmol/L (TIR) between semaglutide (at maximum tolerated dose) vs placebo, over 28 days of AID use. Secondary endpoints included mean glucose, SD, CV, time spent in hypoglycemia, hyperglycemia, etc. Daytime (6h-24h) and nighttime (24h-6h) outcomes were also assessed. Other secondary endpoints included anthropometric and laboratory measurements, insulin requirements, and carbohydrate input into the pump.

Plants

Seed stocks	Not applilcable
Novel plant genotypes	Not applicable
Authentication	Not applicable