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ORIGINAL ARTICLE

Automated Insulin Delivery with SGLT2i Combination Therapy in Type 1 Diabetes

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Abstract

Background: Use of sodium-glucose cotransporter 2 inhibitors (SGLT2i) as adjunct therapy to insulin in type 1 diabetes (T1D) has been previously studied. In this study, we present data from the first free-living trial combining low-dose SGLT2i with commercial automated insulin delivery (AID) or predictive low glucose suspend (PLGS) systems.
Methods: In an 8-week, randomized, controlled crossover trial, adults with T1D received 5 mg/day empagliflozin (EMPA) or no drug (NOEMPA) as adjunct to insulin therapy. Participants were also randomized to sequential orders of AID (Control-IQ) and PLGS (Basal-IQ) systems for 4 and 2 weeks, respectively. The primary endpoint was percent time-in-range (TIR) 70–180 mg/dL during daytime (7:00–23:00 h) while on AID (NCT04201496).
Findings: A total of 39 subjects were enrolled, 35 were randomized, 34 (EMPA; $n = 18$ and NOEMPA $n = 16$) were analyzed according to the intention-to-treat principle, and 32 (EMPA; $n = 16$ and NOEMPA $n = 16$) completed the trial. On AID, EMPA versus NOEMPA had higher daytime TIR 81% versus 71% with a mean estimated difference of +9.9% (confidence interval [95% CI] 0.6–19.1); $p = 0.04$. On PLGS, the EMPA versus NOEMPA daytime TIR was 80% versus 63%, mean estimated difference of +16.5% (95% CI 7.3–25.7); $p < 0.001$. One subject on SGLT2i and AID had one episode of diabetic ketoacidosis with nonfunctioning insulin pump infusion site occlusion contributory.
Interpretation: In an 8-week outpatient study, addition of 5 mg daily empagliflozin to commercially available AID or PLGS systems significantly improved daytime glucose control in individuals with T1D, without increased hypoglycemia risk. However, the risk of ketosis and ketoacidosis remains. Therefore, future studies with SGLT2i will need modifications to closed-loop control algorithms to enhance safety.

Keywords: Sodium-glucose cotransporter 2 inhibitor, Automated insulin infusion, Free-living conditions, Type 1 diabetes.

Introduction

Given the glycosuric ability of sodium-glucose cotransporter 2 inhibitors (SGLT2i) therapy and their demonstrated capacity of lowering postprandial hyperglycemia, in this study, we assessed the effect of empagliflozin (JARDIANCE®; Boehringer Ingelheim and Eli Lilly and Company), added to commercially available automated insulin delivery (AID) and predictive low glucose suspend (PLGS) systems (Control-IQ and Basal-IQ;

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Tandem Diabetes Care), on daytime glycemic control in an 8-week outpatient clinical trial in adults with type 1 diabetes (T1D).

AID systems are now commercially available and have improved the management of glycemia in people with T1D. In clinical trials and in real-life use, these systems performed better than traditional insulin replacement strategies with respect to greater percentage of glucose time-in-range (TIR), lower time in hypoglycemia, and reduced glucose variability.[1–5] While most AID systems consistently improve overnight control, studies to date, collectively show limitations in achieving optimal daytime control.[6–13]

This is attributed to primarily meal-related daytime glucose excursions and to the slow action of subcutaneously administered insulin, relative to meal glucose rate of appearance. Even with modern rapid-acting insulin analogs, the action of exogenous insulin remains too slow to mitigate postprandial hyperglycemia.[14–16] Several approaches have been tried to improve AID daytime control. New algorithms, attempting to predict meal timing, show promise, but have been only tested in small pilot or in silico studies.[17] Combination therapies use drugs that lower glucose levels or/and slow the appearance of meal carbohydrates in the bloodstream. Agents recently tested with AID include the glucagon-like peptide-1 receptor agonist (GLP-1 RA) liraglutide,[18] exenatide,[19] the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin,[20] and the amylin analog pramlintide.[21]

SGLT2i are a newer class of agents that act in an insulin-independent manner to improve glucose control, while demonstrating significant cardio-renal benefits in type 2 diabetes.[22] Their use as adjuvant therapy to insulin in T1D, however, has been controversial. For example, research on the SGLT2i canagliflozin in T1D has demonstrated improved indices of glycemic variability and improvement in treatment satisfaction versus placebo over 18 weeks.[23] However, even with the potential glycemic benefits in T1D, this drug is not approved for the treatment of T1D due to the risk of diabetic ketoacidosis (DKA). Dapagliflozin and the dual SGLT1 and SGLT2 inhibitor sotagliflozin were approved for use in T1D in Europe, but not in the United States, due to the lack of sufficient data on increased risk of DKA reported in clinical trials,[24] including episodes of euglycemic DKA.[24,25]

Moreover, in 2021, the approval for dapagliflozin for use in T1D was withdrawn across Europe and in United Kingdom. The safety and efficacy of empagliflozin (2.5/10/25 mg doses) have been tested in >1700 patients with T1D on multiple daily injections and continuous subcutaneous insulin infusion therapy in the EASE trials over 26–52 weeks.[24] They demonstrated improvements in glycated hemoglobin (HbA1c) without any increase in hypoglycemia. However, adverse effects, including DKA, were twofold to threefold higher with 10 and 25 mg empagliflozin daily dose, which prompted a recommendation for careful ketone monitoring; in the same studies, the use of 2.5 mg empagliflozin had adverse effects indistinguishable from placebo.[24] On the other hand, recent data indicate that turning ketogenesis off or on is not affected by SGLT2i use.[26] SGLT2i also do not accelerate the rate of ketogenesis following interruption of basal insulin infusion in T1D.[27]

Overall, there are well-documented glycemic benefits of the use of SGLT2i in T1D, as well as documented DKA risk associated with the use of these drugs due to reasons that are a matter of debate. Despite elevated risk of DKA, the testing of this class of drugs for the management of T1D in combination with AID is likely to continue, particularly in low doses, given the reported metabolic and cardio-renal benefits as evidenced in the type 2 diabetes population.[22] Recently, two studies added 10 mg bid dapagliflozin[28] and 25 mg/day empagliflozin[29] to experimental AID systems in two short-term studies (24-h inpatient and 9–14-h outpatient, with study staff on-site, respectively). These studies concluded that this approach could increase TIR during full closed loop[28] and reduce the need for premeal carbohydrate counting.[29]

In this proof-of-concept, safety, and feasibility study, we assessed whether daytime glycemic control using a commercially available hybrid AID Control-IQ™ (CIQ) system or a PLGS Basal-IQ™ (BIQ) system can be improved by a low-dose (5 mg/day) empagliflozin adjuvant therapy.

Methods

Pilot study

A Pilot Study in five subjects was performed at a local hotel (March 7, 2020–March 8, 2020) to collect safety data of the initially chosen 10 mg daily dose of empagliflozin. Fingerstick ketone testing was done two to four times daily. The study data and safety monitoring board (DSMB) reviewed the data and because ketone values >0.6 cutoff occurred in four out of five subjects, the DSMB recommended lowering empagliflozin dose to 5 mg daily for the main study. This was further approved by the U.S. Food and Drug Administration (FDA) on April 24, 2020.

Study design

This single-center, randomized, controlled, unblinded crossover clinical trial (NCT04201496) compared four parallel groups, two groups in the experimental arm (EMPA) with 5 mg daily empagliflozin as adjunctive therapy to BIQ or CIQ, and two groups in the control arm (NOEMPA) with no drug and with BIQ or CIQ. The groups within each arm differed from one another in the order of the randomly assigned crossover technological intervention, BIQ followed by CIQ or CIQ followed by BIQ, respectively (Fig. 1). The study protocol was approved by the University of Virginia Institutional Review Board (IRB). An investigational device exemption (IDE), including an investigational new drug (IND) application for empagliflozin, was approved by the FDA. For the study protocol, please see Supplementary Table S5 in the Supplementary Data. Safety aspects were overseen by an external DSMB.

Participants

In this trial, we recruited participants from outpatient clinics at the University of Virginia (Charlottesville, VA) and an internet-based recruiting database of individuals who indicated interest in studies at the UVA Center for Diabetes Technology. Informed consent was obtained from all participants. Major inclusion criteria were T1D treated with insulin for at least 1 year, use of continuous subcutaneous insulin infusion therapy for at least 6 months, age 18–65 years, no use of glucose-lowering agents other than insulin, and Hb1Ac <9% (75 mmol/mol). A complete list of all inclusion and exclusion criteria is provided in Supplementary Table S1.

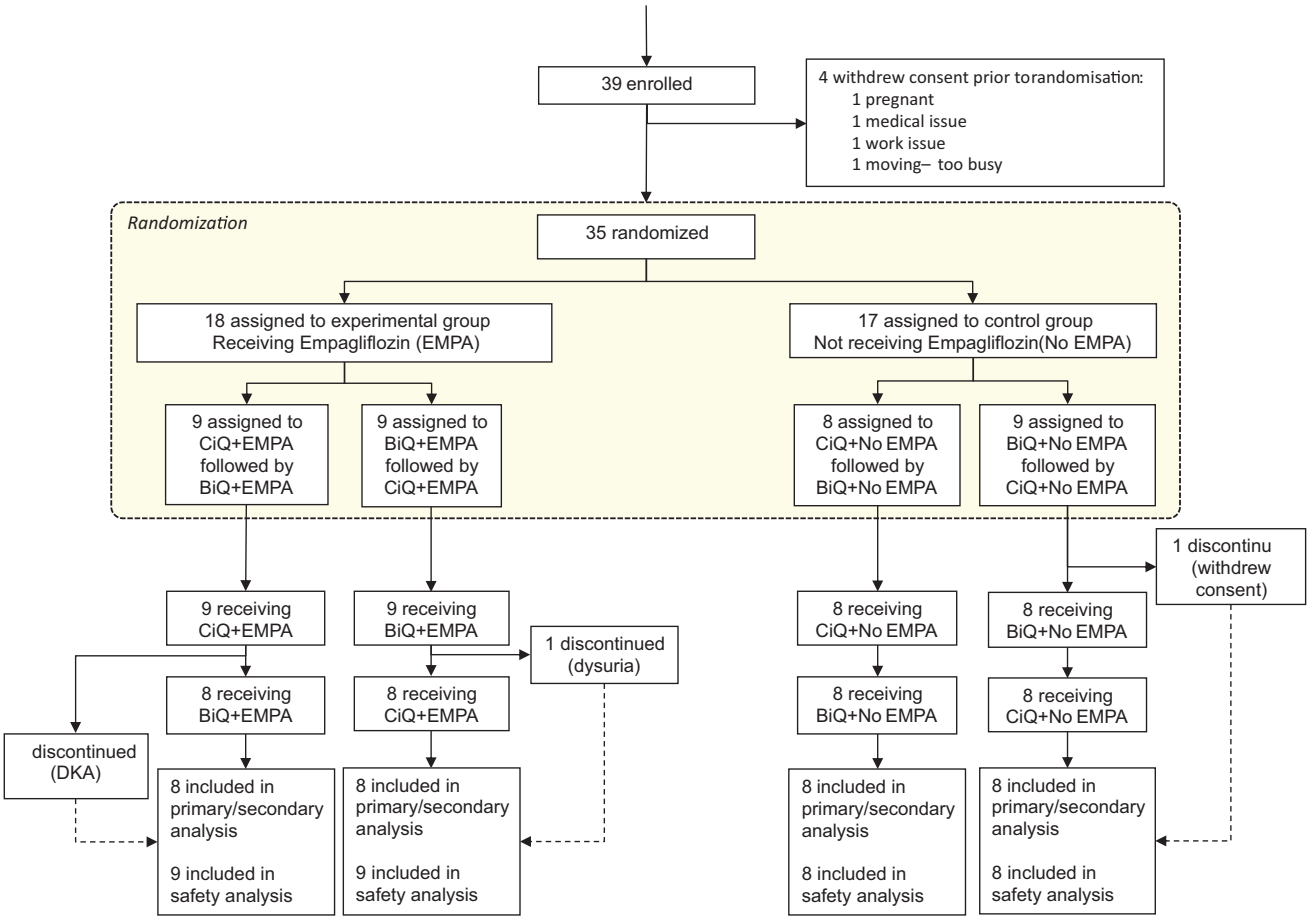

FIG. 1. Trial profile.

Randomization and masking

A (1:1:1:1) randomization assigned participants to Group 1, CIQ-EMPA (4 weeks) followed by BIQ-EMPA (2 weeks), Group 2, BIQ-EMPA (2 weeks) followed by CIQ-EMPA (4 weeks), Group 3, CIQ-NOEMPA (4 weeks) followed by BIQ-NOEMPA (2 weeks), and Group 4, BIQ-NOEMPA (2 weeks) followed by CIQ-NOEMPA (4 weeks). Randomization was performed prospectively using a computer-generated sequence with a permuted block design. Blinding of participants and study team to study groups was not possible in this trial.

Procedures

After confirmation of eligibility, participants underwent study equipment and medication training (experimental arm), or only study equipment training (control arm). Study equipment consisted of Dexcom G6 continuous glucose monitor (CGM; Dexcom, Inc., San Diego, CA), Contour Next blood glucose (Ascensia Diabetes Care, Basel, Switzerland), and Precision Xtra blood ketone meters (Abbott, Alameda, CA) with their respective test strips and infusion sets, and the use of the t:slim X2 insulin pump with Basal-IQ or Control-IQ technologies (Tandem Diabetes Care, San Diego, CA), according to randomization.

The trial had a run-in phase to collect baseline CGM data and to train participants on the use of study devices. Participants in the experimental arm were asked to record 2 days of baseline ketone values before initiating the use of the study drug. Thereafter, participants were directed to use the study CGM with empagliflozin for 1–2 weeks. A tolerance to the medication was assessed before the starting of the next study phase, including adherence to the protocol, ketone testing two to four times per day with monitored values not greater than 0.6 mmol/L on at least two successive occasions (the first testing upon waking in a fasted state), no adverse event relating to perineal infection or symptomatic postural hypotension, and no evidence of significant hypoglycemia <54 mg/dL (3 mmol/L), or any other listed adverse effects of the medication. Participants in the control arm were directed to use the study CGM for 1–2 weeks.

Outcomes

The primary outcome was daytime (7:00–23:00) percent TIR, 70–180 mg/dL (3.9–10 mmol/L), on CIQ-EMPA versus CIQ-NOEMPA. The secondary endpoints, tested in a hierarchical manner to maintain type 1 error at 5%, included 24/7 CGM percent time <70 mg/dL (3.9 mmol/L); 24/7 CGM-measured average glucose; CGM-measured glucose variability (coefficient of variation, CV) during the day; and risks for hypoglycemia and hyperglycemia during the day (Supplementary Fig. S1). In this sense, the secondary endpoints are tested in the prespecified order following the gatekeeping

principle, that is, once a test is not significant, the sequence is stopped, and no further tests are performed.

Additional exploratory outcomes are listed in the statistical analysis plan, which is included with the protocol. Key safety outcomes included the frequency of severe hypoglycemia, DKA, urinary and genital infections, and hyperglycemia >300 mg/dL (16.7 mmol/L). Additional CGM-related metrics, in agreement with the artificial pancreas (AP) outcomes measures consensus statement,[30] are also reported in the Supplementary Data.

Statistical analysis

Sample size. The total sample size was projected to be 40 participants, assuming (1) 1:1:1:1 randomization and (2) 90% power and type 1 error $\alpha = 0.01$, further reinforcing the feasibility of the hierarchical analyses. The projected recruitment sample was $n = 50$, to accommodate up to 20% attrition rate without sacrificing statistical power. Sample size determination was based on data from Protocol 3 of the iDCL Trial[6] conducted with the same algorithm in the same population and indicated effect size >0.7 of AID compared to sensor-augmented pump. In the design of this pilot study, it was assumed that empagliflozin will augment the effect of AID and PLGS during the day and preserve their benefits overnight.

Analytical methods. Statistical analyses were performed according to intention-to-treat (ITT) principles. Means with standard deviations (SDs) and medians with interquartile ranges (IQR) are reported for primary and secondary endpoints for normal/near-normal distributions and skewed distributions, respectively. For the primary analysis, TIR during the day in the 4-week AID period was compared between the two EMPA groups versus the two NOEMPA groups using a linear mixed-effects regression model, while adjusting for prerandomization HbA1c and age. Analyses of the secondary outcomes were conducted by the same method that was used in the primary analysis, but in a hierarchical manner to maintain type 1 error at 5%. Model residuals were confirmed to be approximately normally distributed. Additional details about the statistical methods are provided in the Supplementary Data. All *P*-values are two tailed. Statistical analyses were carried out using SPSS version 28 software.

Results

Between August of 2020 and August of 2021, 39 volunteers signed the study consent form. Four participants dropped out before randomization and 35 entered the randomized trial: 9 participants were randomized to Group 1, 9 to Group 2, 8 to Group 3, and 9 to Group 4. The entire trial was completed by 32 (89%) participants; 1 participant in Group 1 was excluded due an episode of DKA requiring overnight hospitalization; 1 participant in Group 2 was excluded after symptoms of dysuria that spontaneously resolved; and 1 participant in Group 4 dropped after randomization for a reason not related to the study (Fig. 1-consort diagram). Demographic characteristics are shown in Table 1. At the end, 34 participants were considered for the primary endpoint and safety assessments. Study participants performed a median of one and three daily fingerstick ketone measurements in the nondrug groups and drug groups, respectively (Table 4).

Primary endpoint

Mean ± SD percent time in target range 70–180 mg/dL (3.9–10 mmol/L) TIR during daytime (7:00 to 23:00 h) was 81 ± 10 in the CIQ-EMPA versus 71 ± 10 in the CIQ-NOEMPA arm, with a mean adjusted difference of +9.9 percentage points (confidence interval [95% CI] 0.6–19.1) (amounting to 1.6 h per day); $P = 0.04$, as shown in Table 2 and Figure 2A where TIR envelopes (median and IQR) are shown for each hour of the day.

Secondary endpoints

Median (IQR) percent time that the glucose level was <70 mg/dL (3.9 mmol/L) 24/7 was 1.1 (0.5–1.5) in the CIQ-EMPA versus 1.9 (0.7–3.7) in the CIQ-NOEMPA, with a mean adjusted difference of −1.1 percentage points (95% CI −3.2 to 0.9); $P = 0.21$, which did not meet the threshold for

Table 1. Demographics

	EMPA	*NOEMPA*	*Total*
	n = *18*	n = *17*	n = *35*
Age (years)	40 ± 14	42 ± 13	41 ± 14
Diabetes duration (years)	21 ± 13	21 ± 13	21 ± 13
BMI (kg/m^2)	30 ± 6	29 ± 5	29 ± 5
Creatinine (mg/dL)	0.82 ± 0.17	0.84 ± 0.21	0.83 ± 0.19
eGFR (mL/min/1.73 m^2)	91.5 ± 24.5	86.5 ± 25.5	89.1 ± 24.7
Gender (F:M)	13:5	11:6	24:11
Previous pump use (years)	13.1 ± 7.9	12.7 ± 7.3	13.2 ± 7.8
Race/ethnicity			
White—*n*/total *n* (%)	17/18 (94.4)	16/17 (94.1)	33/35 (94.3)
Hispanic or Latino ethnic group, *n* (%)	1 (5.6)	0 (0)	1 (2.9)
African American, *n* (%)	0 (0)	1 (5.9)	1 (2.9)
HbA1c			
%	6.7 ± 1	7.1 ± 1	6.8 ± 0.9
mmol/mol	50 ± 11	54 ± 11	52 ± 10

BMI, body mass index; EMPA, Empagliflozin; HbA1c, glycated hemoglobin; NOEMPA, no drug.

Table 2. Primary and Secondary Hierarchical Efficacy Outcomes

Outcome	*CIQ-EMPA* n = *17*	*CIQ-NOEMPA* n = *16*	*CIQ-EMPA vs. CIQ-NOEMPA* *Difference (95% CI)*[a]	P
Primary: daytime glucose % time in range of 70 to 180 mg/dL (3.9–10.0 mmol/L)	81 ± 10	71 ± 10	9.9 (0.6 to 19.1)	0.04
Secondary hierarchical outcomes in prespecified order[b]				
24/7 glucose level <70 mg/dL (<3.9 mmol/L), median % time (IQR)[c]	1.1 (0.5–1.5)	1.9 (0.7–3.7)	−1.1 (−3.2 to 0.9)	0.21
24/7 Mean glucose level, mg/dL	137 ± 19	154 ± 18	−17.3 (−35.4 to 0.8)	NA
Daytime CGM SD, mg/dL	42.6 ± 9.8	52 ± 9.9	−9.3 (−17.8 to −0.93)	NA
Daytime CGM CV, %	30.4 ± 3.5	34 ± 3.8	−3.3 (−6.1 to −0.5)	NA
24/7 LBGI, median (IQR)[c]	0.5 (0.4–0.6)	0.5 (0.3–1)	0.06 (−0.4 to 0.5)	NA
24/7 HBGI, median (IQR)[c]	2.7 (2–4.4)	5.6	−2.5 (−5.3 to 0.2)	NA

Plus–minus values are mean ± SD. All subjects were included in the model on an intention-to-treat basis. Missing data were handled by means of direct likelihood analyses. To convert the values for glucose to millimoles per liter, multiply by 0.05551. NA denotes not applicable. Baseline outcomes for 18 of the 35 subjects were not available. The baseline HbA1c level was measured at the randomization visit.

[a]Differences were calculated as percentage points (the value in the treatment -EMPA- minus the value in the control -NOEMPA- group) and were model adjusted for the prerandomization value of the HbA1c.

[b]To control the type 1 error, a hierarchical approach was used, in which hypothesis testing was performed sequentially in the order listed in the table. When a *P*-value of 0.05 or higher was observed, the outcomes below that finding on the list were not formally tested.

[c]Distributions were skewed and were thus modeled with the use of rank-based transformation.

CGM, continuous glucose monitor; CI, confidence interval; CIQ, Control-IQ™; HBGI, high blood glucose index; IQR, interquartile ranges; LBGI, low blood glucose index.

statistical significance. Therefore, the remaining outcomes in the hierarchical analysis were not further compared: 24/7 glucose level, daytime glucose SD and coefficient of variation, and 24/7 low blood and high blood glucose indexes (LBGI and HBGI, respectively). Nevertheless, it is worth contrasting the 24/7 mean glucose level in both the experimental and control groups, 137 mg/dL (7.5 mmol/L) versus 154 mg/dL (8.5 mmol/L), respectively (Table 2).

Figure 2 presents daily profiles of CGM-based time in the target range 70–180 mg/dL (3.9–10 mmol/L) TIR (Fig. 2A) and CGM (Fig. 2B), illustrating the difference between AID with/without added SGLT2i. Overall, CIQ-EMPA showed an increase in TIR of +14.7 percentage points. Percentage times above 180 mg/dL (10.0 mmol/L) and 250 mg/dL (13.9 mmol/L) were also in favor of CIQ-EMPA with mean differences −12.3 and −4.9 percent points, when compared to CIQ-NOEMPA, respectively (Supplementary Table S2). The infused insulin amounts were lower in CIQ-EMPA than in CIQ-NOEMPA by −0.17 IU/(kg·day) and −0.06 IU/(kg·day) during 24/7 and overnight periods, respectively, corresponding to an insulin reduction of 24% and 35.3%, respectively.

Supplementary Figure S2 mirrors Figure 2 for PLGS. A summary of glycemic outcomes is presented in Supplementary Tables S2–S4 for both AID (CIQ) and PLGS (BIQ) with and without SGLT2i, for 24/7 (overall), daytime (7:00–23:00), and overnight periods.[30] Mean ± SD percent time in target range 70–180 mg/dL (3.9–10 mmol/L) TIR during daytime (7:00 to 23:00 h) was 80 ± 14.5 in the BIQ-EMPA versus 63.5 ± 15.6 in the BIQ-NOEMPA arm, translating into an increase of 16 percentage points in TIR for BIQ-EMPA versus BIQ-NOEMPA (Table 3 and Supplementary Fig. S2).

In addition, BIQ-EMPA reached a decrease of 24 mg/dL in mean glucose overall and 18.6% decrease in percent time in hyperglycemia (Supplementary Tables S2 and S3). Overnight, BIQ-EMPA, compared to BIQ-NOEMPA, showed 17% increase in percent TIR and 7.6% decrease in time in hyperglycemia (Supplementary Table S4). Similar to CIQ, the infused insulin amounts were lower in BIQ-EMPA than in BIQ-NOEMPA 24/7 and overnight, which corresponded to an insulin decrease of 25% and 40%, respectively.

CIQ-EMPA outperformed BIQ-EMPA in terms of percentage of TIR overnight, with a mean adjusted difference of +10.2 percent points (95% CI 3.6–16.8); $P = 0.004$, meaning that CIQ-EMPA kept the study subjects 7 h out of 8 h of the night time in range versus 6 h out of 8 h for BIQ-EMPA. In addition, CIQ-EMPA was superior to BIQ-EMPA in terms the percentage time <70 mg/dL (3.0 mmol/L), with a mean adjusted difference of −1.5 percent points (95% CI −2.6 to −0.3); $P = 0.01$, and percentage time >180 mg/dL (10.0 mmol/L), with a mean adjusted difference of −9.5 percent points (95% CI −16 to −2.9); $P = 0.006$. During the daytime and overall, CIQ-EMPA was superior to BIQ-EMPA only in the percentage time <70 mg/dL (3.0 mmol/L), with mean adjusted differences of −1 and −1.2 percent points (95% CI −2 to 0); $P = 0.05$ and (95% CI −1.8 to −0.6) $P < 0.001$, respectively.

Safety outcomes and adverse events

During the CIQ-EMPA session, one participant in Group 1 developed an episode of ketoacidosis and required overnight hospitalization. The event was deemed triggered by a nonfunctioning insulin pump insertion site and related to use of SGLT2i therapy. Nevertheless, as per protocol, the patient was asked to discontinue the study medication and was withdrawn from the study. The event was reported to the DSMB, FDA, and IRB. One person in Group 2 developed dysuria during the BIQ-EMPA session, which resolved with increase in fluid intake. This subject was discontinued from the study. Other safety-related events, including fingerstick ketone levels, are listed in Table 4. In the EMPA arm of the study, the frequency of the ketone measurements was higher

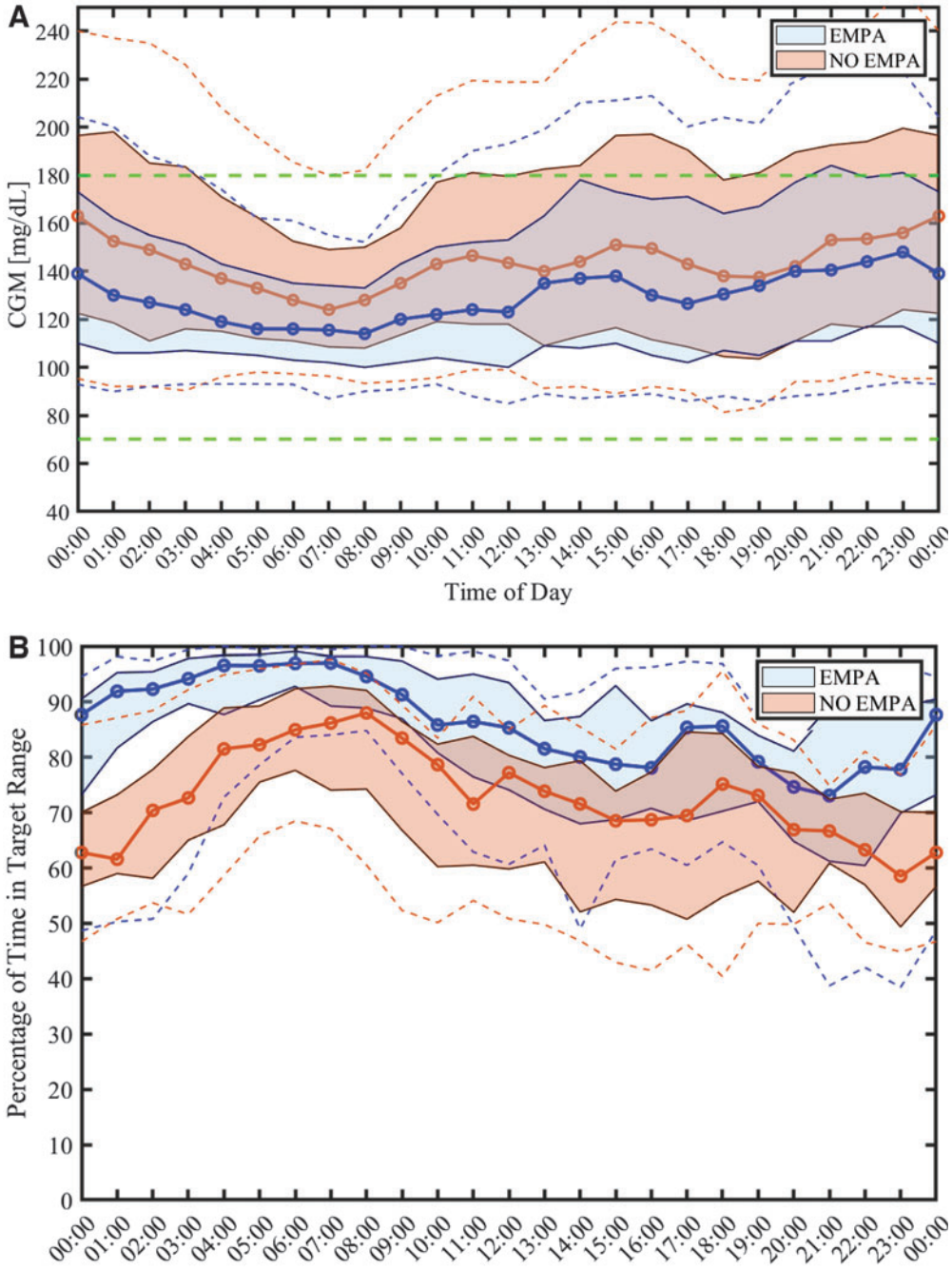

FIG. 2. Detailed CIQ-EMPA versus CIQ-NOEMPA contrast with respect to TIR and CGM for each hour of the day. **(A)** An envelope plot of the percent time in the target range according to the time of day. **(B)** Postrandomization hourly median sensor glucose with interquartile envelope. Green lines represent the 70 and 180 mg/dL glycemic levels. Data points (thick lines) denote the hourly median values, and the lower and upper boundary of each shaded region the 25th and 75th percentiles, respectively. CGM, continuous glucose monitor; CIQ, Control-IQ™; EMPA, empagliflozin; NOEMPA, no drug; TIR, time-in-range.

by design than the NO-EMPA arm of the study. We also note that CIQ-EMPA and BIQ-EMPA did not differ with respect to individual ketone levels.

Discussion

Two recent short-term (<24 h) studies, conducted under controlled conditions, with experimental AID technology combined with SGLT2i at doses approved by the FDA for type 2 diabetes, have demonstrated improvement in glycemic control.[28,29] Our proof-of-concept, safety, and feasibility trial is the first free-living AID home study to report that low-dose SGLT2i (empagliflozin), 5 mg/day, used as adjunct therapy to a commercial hybrid AID system (Control-IQ by Tandem Diabetes Care), significantly increases the percent time spent in the target range 70–180 mg/dL (3.9–10 mmol/L) during

Table 3. Mirroring Primary and Secondary Outcomes for BIQ-EMPA Versus BIQ-NOEMPA

Outcome	*BIQ-EMPA* n = *17*	*BIQ-NOEMPA* n = *16*	*BIQ-EMPA vs. BIQ-NOEMPA* *Difference (95% CI)*[a]	P
Primary: daytime glucose % time in range of 70 to 180 mg/dL (3.9–10.0 mmol/L)	80 ± 14	63 ± 16	16.5 (7.3 to 26)	<0.001
Secondary hierarchical outcomes in prespecified order[b]				
24/7 glucose level <70 mg/dL (<3.9 mmol/L), median % time (IQR)[c]	1.7 (0.9–2.7)	1.1 (0.6–5.1)	0.2 (−1.7 to 2.1)	0.82
24/7 Mean glucose level, mg/dL	141 ± 30	165 ± 32	−24.1 (−42.2 to −6)	NA
Daytime CGM SD, mg/dL	44.9 ± 14.7	58.1 ± 12.1	−13.2 (−21.6 to −4.8)	NA
Daytime CGM CV, %	30.4 ± 3.5	36 ± 3.5	−4.0 (−6.8 to −1.2)	NA
24/7 LBGI, median (IQR)[c]	0.7 (0.6–1)	0.5 (0.3–1.3)	0.1 (−0.3 to 0.6)	NA
24/7 HBGI, median (IQR)[c]	3.3 (1.8–4.7)	7.6 (3.8–10.6)	−3.7 (−6.5 to −1)	NA

Plus–minus values are mean ± SD. All subjects were included in the model on an intention-to-treat basis. Missing data were handled by means of direct likelihood analyses. To convert the values for glucose to millimoles per liter, multiply by 0.05551. NA denotes not applicable. Baseline outcomes for 18 of the 35 subjects were not available. The baseline HbA1c level was measured at the randomization visit.

[a]Differences were calculated as percentage points (the value in the treatment -EMPA- minus the value in the control -NOEMPA- group) and were model adjusted for the prerandomization value of the HbA1c.

[b]To control the type 1 error, a hierarchical approach was used, in which hypothesis testing was performed sequentially in the order listed in the table. When a *P*-value of 0.05 or higher was observed, the outcomes below that finding on the list were not formally tested.

[c]Distributions were skewed and were thus modeled with the use of rank-based transformation.

BIQ, Basal-IQ™.

daytime (7:00–23:00 h) (Table 2 and Fig. 2) without increasing hypoglycemia (Table 4). This improvement was recorded during 4-week AID sessions and amounts to 1.6 more hours/day spent in the target range. Likewise, the same 5 mg/day empagliflozin, in combination with a commercial PLGS system (Basal-IQ by Tandem Diabetes Care) at home, significantly increased daytime percent time spent in the target range (Table 3).

As part of the study original design, both systems, AID and PLGS, were used as indicated by the manufacturer without changes or interventions by the study team. This was done with the intention to facilitate a potential future transfer of the empagliflozin adjuvant therapy to clinical practice if deemed safe to do so. However, we demonstrate that despite using a lower dose of empagliflozin (viz., 5 mg daily), the risk of ketosis and DKA remains. Therefore, future adjuvant use of SGLT2i class of drugs with AID systems would require developing next generation of closed-loop control algorithms that are suitably informed with physiological information regarding ketogenesis coupled with strategies to prevent ketosis.

This trial also demonstrated that SGLT2i use improved the efficacy of both CIQ and BIQ overnight, and overall, with CIQ maintaining superiority over BIQ in several key aspects. In particular, CIQ-EMPA exhibited consistent decrease in average glycemia over CIQ-NOEMPA overall (24/7). Percent time in target range was higher for CIQ-EMPA and percentage times above 180 and 250 mg/dL were also in favor of CIQ-EMPA (Supplementary Table S2). In addition, during the day, CIQ-EMPA outperformed CIQ-NOEMPA

Table 4. Safety Outcomes

Event	*CIQ-EMPA* n = *18*	*CIQ-NOEMPA* n = *17*	*BIQ-EMPA* n = *18*	*BIQ-NOEMPA* n = *17*
Any reportable adverse event				
No. of events	1	0	0	0
Specific events, No. of subjects (%) [No. of events]				
Severe hypoglycemia	0	0	0	0
Diabetic ketoacidosis	1 (3.1) [1]	0	0	0
Genital infection	0	0	0	0
Dysuria	0	0	1 (3.1) [1]	0
Other adverse events	0	0	0	0
Ketone-related measurements				
Median No. of ketone measurements per day (IQR)	3 (2–4)	1 (0–2)	3 (2–4)	1 (0–2)
Ketosis, without diabetic ketoacidosis, No. of subjects (%) [No. of events]	13 (38.2) [25]	3 (8.8) [4]	7 (20.6) [18]	2 (6.2) [4]
0.6 to 1.5 mmol/L	13 (38.2) [25]	2 (6) [3]	7 (20.6) [17]	2 (6) [4]
1.5 to 3.0 mmol/L	0 (0) [0]	1 (3) [1]	0 (0) [0]	0 (0) [0]
≥3.0 mmol/L	0 (0) [0]	0 (0) [0]	1 (3) [1]	0 (0) [0]
Max reading, mmol/L	1.3	2.0	4.4	1.3

in terms of percent time above 180 mg/dL (Supplementary Table S3). Overnight, percentage TIR was higher in CIQ-EMPA versus CIQ-NOEMPA and CIQ-EMPA had lower percentage time above 180 mg/dL (Supplementary Table S4). As expected, the total daily insulin delivered by CIQ was lower in CIQ-EMPA versus CIQ-NOEMPA during 24/7 and overnight periods with insulin reduction of 24% and 35.3%, respectively.

BIQ-EMPA also showed improved glycemic outcomes compared to BIQ-NOEMPA with more than 16% increase in percent TIR during daytime (Table 3 and Supplementary Fig. S2). Overall, and during daytime, BIQ-EMPA showed a decrease in mean glucose, increase in percentage TIR, and decrease in percent time in hyperglycemia (Supplementary Tables S2 and S3). Overnight, the percentage TIR was higher in BIQ-EMPA than in BIQ-NOEMPA and BIQ-EMPA also exhibited a decrease in percentage time in hyperglycemia (Supplementary Table S4). Finally, the total daily insulin dose was lower with BIQ-EMPA than in BIQ-NOEMPA 24/7 and overnight, corresponding to decreases of 25% and 40%, respectively.

Even though we observed a marked improvement in daytime TIR achieved by the empagliflozin adjuvant therapy in combination with PLGS, SGLT2i+AID outperformed SGLT2i+PLGS overnight in terms of higher percent TIR with less time spent in hypoglycemia and hyperglycemia, and lower glucose variability. The AID system was also superior to the PLGS system in terms of percent time in hypoglycemia, not only overnight but also during daytime and overall. Despite SGLT2i+AID and SGLT2i+PLGS systems not differing with respect to ketone levels (Table 4), AID does not necessarily resort to insulin suspension to achieve the glycemic target, which may be seen as a protection factor against ketogenesis. This last fact needs to be confirmed in larger studies.

As reported in the EASE trials, there was a twofold to threefold higher DKA risk associated with the use of SGLT2i empagliflozin in T1Dm which was dose related, occurring with the 10 and 25 mg dosages, but not with the 2.5 mg dose.[24] However, the 2.5 mg dose did show improved glucose control with reduction of HbA1c.[24] Recently, dapagliflozin was withdrawn in Europe for treatment in T1D by the manufacturer over safety concerns.[31] In our study, we used a low 5 mg daily dose as recommended by the study DSMB and recorded one episode of DKA triggered by a nonfunctioning insulin pump insertion site.

The 5 mg daily dose, while highly effective, although, places the challenge of maximizing the glucose control benefits, while minimizing the safety concerns, especially the risk of DKA. Future studies may test whether reducing the dose of empagliflozin even further, for example, to 2.5 mg daily, will have a clinically beneficial effect on time in range, without increasing the risk of ketosis.

Currently, the use of SGLT inhibitors as adjuvant therapy to AID in T1D faces significant challenges with respect to the risk of DKA, reflected in the reluctance of regulatory bodies, both in the United States and Europe, to grant approval to these therapies. Nevertheless, the associated glycemic and cardiovascular benefits of these therapies, including the results of this pilot trial, are substantial and many current efforts are directed to address the DKA risk in the T1D population.[32] These include, but are not limited to, patient selection (e.g., those with relatively well-controlled diabetes with HbA1c <9%, not on a low carbohydrate or very low carbohydrate diet, and with no history of ketoacidosis in the preceding year) and extensive patient education before initiation of SGLT2i adjunctive therapy.

Other strategies could include frequent fingerstick ketone monitoring (although this would add to the patient burden and cost) or continuous ketone monitoring, once approved and available commercially.[33] Such sensors could also inform next generation of smart AID systems that are better equipped with physiological information on ketogenesis related to SGLT2i use. Such algorithms could be tested for safety and efficacy in carefully controlled clinical trials after appropriate in silico experiments. Future studies may also explore delivering a proportion of basal insulin as ultra-long-acting insulin analog (e.g., Insulin Icodec-weekly insulin), in an attempt to mitigate DKA risk caused by insulin cannula occlusion. However, this strategy would likely require modification of the control algorithms, individualizing the ratio between basal insulin delivered by the AP system and as long-acting analog, lowering the SGLT2i dose, and/or using a combined SGLT1i and SGLT2i.[32]

One limitation of the study is that approximately half the study subjects did not have a sufficiently long run-in period before they were treated with either AID or PLGS. As a result, the statistical analysis was performed by adjusting for prerandomization HbA1c rather than adjusting for baseline CGM data as originally planned. Another limitation was that a suitable placebo was not available. This was because the manufacturer of empagliflozin did not provide drug or placebo for this relatively small, proof-of-concept, safety, and feasibility study.

We fell slightly short of the prespecified recruitment goals largely due to the restrictive effects of the pandemic on clinical research participants and study staff. Like all such studies, there was likely recruitment bias in this population compared to the general T1D population, which limits the generalizability of the results. Future, larger scale, blinded, and placebo-controlled studies with similar degree of monitoring are needed with next-generation closed-loop control systems to address these limitations, while mitigating risks for ketosis.

In this proof-of-concept, safety, and feasibility clinical trial, we have demonstrated the added benefit of low-dose SGLT2i therapy to a commercially available AID system in adults with T1D. The increase in TIR to above 80%, coupled with an $\sim$17 mg/dL reduction in average CGM glucose, translates to a predicted improvement of HbA1c by at least 0.5% over a longer duration. The mean HbA1c at enrolment in our study subjects was 6.8%. It is therefore feasible that with a longer duration study, an HbA1c target of <6.5% could be achievable with a combination SGLT2i+AID approach. However, we also report one episode of DKA in one of 16 participants and instances of ketosis without DKA on SGLT2i therapy.

This event highlights the need for further research to develop smarter closed-loop control algorithms, which would help mitigate the risks for ketosis and ketoacidosis that this class of drugs possesses. However, given the cardio-renal benefit of this class of agents, as long as the DKA risk is adequately addressed and mitigated in research involving next generation of closed-loop control algorithms, SGLT2i adjunctive therapies could be an added benefit for people with T1D.

Authors' Contributions

J G-T. was involved in verifying and analyzing the data, performed the statistical analyses, and was involved in writing and editing the article. L.F. was involved in the study design and execution, data interpretation, verifying the underlying data, and writing and editing the article. L.K. was the research coordinator for the study and responsible for all participant interaction and operations during the trial. She also reviewed and edited the article. M.C.O. was the project manager and regulatory manager for the study. She also reviewed and edited the article. R.N. was the study physician responsible for all participant activities and reviewed and edited the article.

R.B. was involved in the study design and conceptualization and data interpretation and reviewed and edited the article. B.K. participated in the study design and conceptualization, development of the analysis plan, and the statistical analyses, and was involved in writing and editing the article. He was also the sponsor of the IDE. A.B. was the University of Virginia site principal investigator, contributed to the study design, answered queries from the regulatory boards, including the Food and Drug Administration, and was involved in writing and editing the article. He is also the guarantor of this work and, as such, had full access to all the data in the study, and takes responsibility for the integrity of data and the accuracy of data analysis.

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Data Sharing

All data requests should be submitted to the corresponding author (A.B.) for consideration as agreed in our publication plan. Access to anonymized data may be granted following review with the Trial Management Group and agreement of the chief investigator (A.B.). Related documents, including the statistical analyses plan, will be available on request.

Author Disclosure Statement

J.G. reports receiving industry research support and royalties from Dexcom through his institution. L.F. reports receiving industry research support from NovoNordisk and Dexcom through his institution. B.K. reports receiving a grant from the National Institutes of Health (NIH) and material support from Tandem Diabetes Care, related to the study; grants from Dexcom, Novo Nordisk, and Sanofi, outside the submitted work; and consulting fees from Sanofi and Tandem Diabetes Care, and reports having received speaking honoraria from Dexcom.

B.K. has patents (Nos. 8562587 and 9750438 B2) for continuous glucose monitor-based prevention of hypoglycemia by hypoglycemia risk assessment and smooth reduction of insulin delivery, with royalties paid to Dexcom, and a patent (No. 9430022 B2) for a method and apparatus for modular power management and protection of critical services in ambulatory medical devices, with royalties paid to Dexcom. A.B. reports receiving grant or material support from Tandem Diabetes Care and Dexcom as supplies for the study. No other potential conflicts of interest relevant to this article were reported.

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Supplementary Material

Supplementary Data

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