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Randomized, Crossover Trial of Control-IQ Technology with a Lower Treatment Range and a Modified Meal Bolus Module in Adults, Adolescents, Children, and Preschoolers with Varying Levels of Baseline Glycemic Control

Sue A. Brown[1], **Lori M. Laffel**[2], **Halis K. Akturk**[3], **Gregory P. Forlenza**[3], **Viral N. Shah**[3,4], **R. Paul Wadwa**[3], **Erin C. Cobry**[3], **Elvira Isganaitis**[2], **Melissa Schoelwer**[1], **Virginia S. Lu**[5], **Ricardo Rueda**[5], **Nicholas Sherer**[5], **John P. Corbett**[5], **Ravid Sasson-Katchalski**[5], **Jordan E. Pinsker**[5]

[1]Division of Endocrinology, Center for Diabetes Technology, University of Virginia, Charlottesville, Virginia, USA

[2]Research Division, Joslin Diabetes Center and Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA.

[3]Barbara Davis Center for Diabetes, University of Colorado, Anschutz Medical Campus, Aurora, Colorado, USA

[4]Indiana University School of Medicine, Indianapolis, Indiana, USA.

[5]Tandem Diabetes Care, San Diego, California, USA

Abstract

Corresponding author: Jordan E. Pinsker, MD, Tandem Diabetes Care, 12400 High Bluff Drive, San Diego, CA 92130, jpinsker@tandemdiabetes.com.

AUTHOR CONTRIBUTIONS

J.E.P., V.S.L., and R.S.K. were involved in the conception and design of the study. S.A.B., L.M.L., H.K.A., G.P.F., R.P.W., E.C.C., E.I., M.S., and V.N.S. conducted the study. All authors were involved in the analysis and interpretation of the results. J.E.P. and V.S.L. wrote the first draft of the article, and all authors edited, reviewed, and approved the final version of the article. J.E.P. is 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 the data and the accuracy of the data analysis.

AUTHOR DISCLOSURE STATEMENT

S.A.B. received research support to her institution from Dexcom, Insulet, Roche, Tandem Diabetes Care, and Tolerion and has served on a data monitoring board for MannKind. L.M.L. has served as an advisor for Boehringer Ingelheim, Janssen, Medtronic, Provention Bio, Sanofi, Sequel, MannKind, Tandem Diabetes Care, and Vertex. H.K.A. received research support from Tandem Diabetes Care, Medtronic, Dexcom, Abbott Diabetes Care, and honorarium for consultation from Tandem Diabetes Care, Medtronic, and Dexcom. G.P.F. conducts research with Medtronic, Dexcom, Abbott, Tandem Diabetes Care, Insulet, Beta Bionics, Lilly, and Sequel Med Tech and has been a speaker/consultant/ad board member for Medtronic, Dexcom, Abbott, Tandem Diabetes Care, Insulet, Beta Bionics, Lilly, and Sequel. V.N.S.'s institute receives research support from Dexcom, Alexion, JDRF, and NIH. V.N.S. has received honoraria from Sanofi, Novo Nordisk, Lilly, Tandem Diabetes Care, Dexcom, Insulet, Embecta, and Ascensia Diabetes Care for speaking, consulting, or advisory work. R.P.W. conducts research with Medtronic, Dexcom, Abbott, Tandem Diabetes Care, Insulet, Beta Bionics, and Eli Lilly and has been a speaker/consultant/ad board member for Dexcom, Tandem Diabetes Care, and Sequel. E.C.C. conducts research with Medtronic, Dexcom, Abbott, Tandem Diabetes Care, Insulet, Beta Bionics, Lilly, Luna Health, and Sequel Med Tech and has been a speaker and ad board member for Dexcom. E.I. has no conflict of interest to report. M.S. reports research support, paid to University of Virginia, from Tandem Diabetes Care and Insulet. V.S.L., R.R., N.S., J.P.C., R.S.K., and J.E.P. are employees and shareholders of Tandem Diabetes Care, Inc.

Objective: We evaluated a modified version of Control-IQ technology with a lower treatment range and a modified meal bolus module in adults, adolescents, children, and preschoolers with type 1 diabetes in a multicenter, randomized, and crossover trial.

Research Design and Methods: After a 2-week run-in with Control-IQ technology v1.5, the modified system was evaluated for 2 weeks using treatment range of 112.5–160 mg/dL (standard range [SR]), and for 2 weeks using lower treatment range of 90–130 mg/dL (lower range, LR), at home in random order. Two late bolus meal challenges were performed in each 2-week period, bolusing 45 min after meals with and without a new late bolus feature.

Results: Overall, 72 participants aged 3–57 years completed the study. There were no diabetic ketoacidosis or severe hypoglycemia events. All meal challenges were completed safely. Time in range (TIR) 70–180 mg/dL improved the most with LR to 68.0% (+3.1%, $P < 0.001$, for LR vs. run-in and +2.1%, $P < 0.001$, for LR vs. SR). Similar improvements were observed for time in tight range (TITR) 70–140 mg/dL (+3.3%, $P < 0.001$, for LR vs. run-in and +4.0%, $P < 0.001$, for LR vs. SR), time >180 mg/dL, and mean glucose. Participants with lower baseline hemoglobin A1c (HbA1c) achieved the highest TIR and TITR with LR use, while the greatest improvements in TIR and TITR were evident in those with higher baseline HbA1c.

Conclusions: The lower treatment range and late bolus feature of the modified Control-IQ system were safe for use in all age-groups. TIR and TITR improved with LR regardless of baseline HbA1c.

Keywords

Control-IQ; t:slim X2; type 1 diabetes; hypoglycemia; DKA

INTRODUCTION

Hybrid closed-loop systems have dramatically improved glycemic outcomes in people of all ages with type 1 diabetes (T1D). [1] The t:slim X2 insulin pump with Control-IQ technology, approved for use down to 2 years of age in the United States, has been shown to improve time in range (TIR) 70–180 mg/dL and reduce user burden in randomized, controlled trials in people with T1D. [2–5] Safety and efficacy have also been established in large post-market studies. [6]

Recent international consensus guidelines have emphasized metrics beyond TIR. [7] For example, time in tight range (TITR) 70–140 mg/dL, mean glucose, and coefficient of variation may have important clinical significance. Improvements in these metrics beyond what has already been achieved with current hybrid closed-loop systems may require additional device modifications to allow for increased flexibility around mealtime insulin dosing, potential changes to target glucose ranges, and further adjustments around activities such as exercise.

In this study, we evaluated a modified version of Control-IQ technology running on a Tandem t:slim X2 insulin pump that offered increased flexibility to achieve improvements in these metrics. The modified system allowed for a lower treatment range and contained a modified meal bolus module with a late bolus feature. Control-IQ autoboluses were also disabled during exercise activity by default and the system included additional autobolus stacking protections. This modified system was evaluated over 6 weeks of use in a multicenter, prospective, randomized crossover study in adults, adolescents, children, and preschoolers with T1D.

METHODS

The multicenter study was performed at four clinical sites in the United States (University of Virginia, Joslin Diabetes Center, Barbara Davis Center Adult Clinic, Barbara Davis Center Pediatric Clinic) and was approved by the Advarra Institutional Review Board. The Food and Drug Administration approved an investigational device exemption, and the study was registered at ClinicalTrials.gov (NCT05683392). Informed consent, or parental consent and assent for children, was obtained as appropriate for the participant's age. The study was performed in accordance with the principles of the Declaration of Helsinki. The authors assume responsibility for the accuracy and completeness of the data and analysis.

After completing a feasibility trial in 30 adults and adolescents (NCT05014789), this trial expanded use of the modified Control-IQ system to include all age-groups. The trial was a prospective randomized crossover multicenter study of the modified Control-IQ system that offered a lower treatment range and a modified meal bolus module with a late bolus feature. Control-IQ autoboluses were also disabled by default when the user activated exercise activity, and the system included additional autobolus stacking protections. The correction target for autoboluses was unchanged at 110 mg/dL. The modified Control-IQ system used in this study was running on a Tandem t:slim X2 insulin pump and paired with Dexcom G6 sensor.

After a 2-week run-in period with Control-IQ technology v1.5, [8] the modified system was evaluated in multiple age-groups for 2 weeks at home with a treatment range of 112.5–160 mg/dL (standard range [SR]), and for 2 weeks at home with a lower treatment range of 90–130 mg/dL (lower range [LR]), in random order. Participants were required to use sleep activity overnight, which was unchanged from prior Control-IQ versions. [9]

Each participant performed two late bolus meal challenges in each 2-week treatment period, using a late bolus feature to bolus 45 min late for one meal, and bolusing 45 min late without the late bolus feature for another meal. Participants were instructed to eat the same meal for each challenge and were required to eat a minimum carbohydrate amount based on age (20 g for 2–5 years, 35 g for 6–13 years, and 50 g for 14 years and older). The late bolus feature automatically reduced the mealtime insulin bolus amount to account for the time selected since eating the meal, with the goal of limiting hypoglycemia when insulin is given after a meal. Participants were able to select the duration of time that had passed since the meal was started, with preset options for 15 min ago, 30 min ago, 45 min ago, and 1 h ago. In this study, participants always chose 45 min ago for the meal challenges.

The study had an enrollment goal of ~50% of participants in each age-group having a hemoglobin A1c (HbA1c) at baseline of ≥7.5%, to assure inclusion of participants with varying levels of baseline glycemic control.

Key inclusion criteria included (1) age 2–80 years old, (2) diagnosis of T1D for at least 1 year or for at least 6 months for ages 2–5 years old, (3) prior Dexcom continuous glucose monitoring (CGM) use, (4) total daily insulin dose at least 2 units/day, (5) weight ≥20 lbs, (6) HbA1c ≤10.5%, and (7) willingness to use only Novolog or Humalog insulin with the study devices. Key exclusion criteria were (1) >1 episode of diabetic ketoacidosis (DKA) or severe hypoglycemia in the last 6 months, (2) pregnancy, and (3) concurrent use of any noninsulin glucose-lowering agent other than metformin. Full inclusion/exclusion criteria are listed in Supplementary Table S1.

The main statistical comparison was between the three 2-week periods (run-in, treatment period SR, treatment period LR). The comparisons were pairwise—run-in versus SR, run-in versus LR, and SR versus LR, using a two-sided Wilcoxon signed rank test for most comparisons where there was non-normally distributed data, or a paired t-test if the data were distributed normally. The sample size for the overall study was chosen to assure a reasonable number of late bolus meal challenges would be completed. Results are reported as medians and median differences between periods unless otherwise specified.

The primary endpoint was frequency of safety events of DKA and severe hypoglycemia. Secondary CGM endpoints were analyzed per international consensus guidelines, [7,10] to include median percent TIR 70–180 mg/dL, TITR 70–140 mg/dL, time >180 mg/dL, time >250 mg/dL, time <70 mg/dL, time <54 mg/dL, mean glucose, coefficient of variation, and standard deviation. CGM metrics were computed per subject over 24 h, during daytime (6 a.m.–11:59 p.m.), and during nighttime (12 a.m.–5:59 a.m.). CGM metrics were also calculated by age cohort (adults age 18+, adolescents aged 14–17, children aged 6–13, and preschoolers aged 2–5 years old), and by baseline HbA1c cohort (HbA1c ≥7.5% or <7.5%).

These same CGM metrics were also compared for the 5-h postprandial period after meal challenges (3-h postprandial for participants aged 2–5 years old). In addition, any extra carbohydrates taken or insulin doses given during the postprandial period for the meal challenges were compared across the challenge types.

Changes in insulin delivery were also compared between arms. Patient-reported outcomes were compared using the INSPIRE questionnaire and the System Usability Scale (SUS) at the end of each 2-week treatment period.

RESULTS

Participant characteristics

Seventy-two participants started Control-IQ v1.5 use for the run-in period, and all 72 participants finished the 6-week study. Participants ranged in age from 3 to 57 years of age (N = 24 age ≥18 years old, N = 6 age 14–17 years old, N = 30 age 6–13 years old, and N = 12 age 2–5 years old). Overall, 48.6% were female. Mean duration of diabetes was 10.8 (9.1) years and ranged from 1.4 to 41.3 years. Almost all participants (94.4%) were prior pump users. Mean HbA1c at enrollment was 7.3% (1.0), with 46% of participant having a baseline HbA1c level ≥7.5%, reflecting a broad range of glycemic control. A full listing of participant demographics is provided in Table 1.

Safety

There were no severe hypoglycemia or DKA events in the study.

Glycemic outcomes

Median sensor use was 98.3%, 98.5%, and 98.7% and median time in closed loop was 94.6%, 95.1%, and 94.9% in the run-in, SR, and LR periods, respectively, demonstrating high adherence with therapy.

Glycemic results for the Control-IQ v1.5 run-in and each 2-week treatment period, overall and by age-group, are shown in Table 2. Overall, TIR improved from 62.4% (57.3, 70.7) during Control-IQ v1.5 run-in and 65.8% (54.4, 73.0) with SR to 68.0% (60.5, 74.3) with LR (median difference +3.1%, P < 0.001, 95% CI [−8.9, 15.8] for LR vs. run-in and median difference +2.1%, P < 0.001, 95% CI [−7.1, 15.8] for LR vs. SR). Similar improvements were seen for TITR, with run-in and SR achieving 38.8% (33.9, 48.0) and 39.2% (30.9, 48.1) TITR, respectively, compared with 43.9% (38.2, 51.3) for LR (median difference +3.3%, P < 0.001, 95% CI [−8.5, 17.6] for LR vs. run-in and median difference +4.0%, P < 0.001, 95% CI [−8.0, 17.3] for LR vs. SR). Time >180 mg/dL and mean glucose also improved with LR use.

There were no differences in time <54 mg/dL. Overall, time <70 mg/dL increased for LR (2.0% [0.9, 3.3]) compared with SR (1.6% [0.7, 3.0]) (median difference +0.3%, P = 0.004, 95% CI [−3.0, 5.1] for LR vs. SR), although this increase was not noted in every age-group.

The greatest improvement in TIR with LR use was seen in children aged 6–13 years old, +5.6%, P < 0.001, 95% CI (−8.2, 17.6) for LR versus run-in and +4.4%, P < 0.001, 95% CI (−3.7, 16.0) for LR versus SR. Children aged 6–13 also saw an improvement in TITR, with a median improvement of +4.4%, P < 0.001, 95% CI (−5.1, 18.3) for LR versus run-in and +5.3%, P < 0.001, 95% CI (−4.3, 19.6) for LR versus SR.

Daytime and nighttime outcomes are shown in Supplementary Tables S2 and Table S3. Nighttime outcomes, primarily reflecting use of sleep activity as mandated by the study protocol, showed the highest TIR but as expected showed few differences between arms.

Participants showed improvement in TIR and TITR with LR use regardless of baseline HbA1c. The highest overall TIR across all treatment periods was achieved by participants with HbA1c <7.5% with LR use, who achieved TIR 69.3% (61.7, 78.7) for run-in, 72.1% (66.2, 78.6) for SR, and 73.4% (66.0, 79.2) for LR (P = 0.044 LR vs. run-in). The greatest TIR improvement with LR use was achieved by participants with HbA1c ≥7.5%, who achieved TIR of 58.4% (55.1, 62.4) for run-in, 56.7% (52.8, 62.3) for SR, and 63.5% (57.2, 68.1) for LR (P = 0.001 for LR vs. run-in and P < 0.001 for LR vs. SR). A similar pattern was seen for TITR, with participants with HbA1c <7.5% achieving a TITR of 45.1% (38.5, 60.1) during run-in, 46.4% (40.0, 58.7) for SR, and 48.7% (40.2, 60.2) for LR (P = 0.017 for LR vs. run-in and P = 0.008 for LR vs. SR), while participants with HbA1c ≥7.5% achieved a greater TITR improvement (35.2% [31.1, 38.6] during run-in, 32.7% [30.1, 37.6] for SR, and 39.1% [36.6, 43.1] for LR, P = 0.002 for LR vs. run-in and P < 0.001 for LR vs. SR).

Late bolus meal challenges

Late bolus meal challenges were completed by all participants twice in each intervention arm, bolusing 45 min late with and without the late bolus feature. A comprehensive listing of the average meal content (carbohydrates, protein, and fat) consumed for the meal challenges by age-group, listed by study period with and without late bolus feature use, is shown in Supplementary Table S4. All late bolus meal challenges were completed safely, with no DKA or severe hypoglycemia events.

A total of 288 late bolus meal challenges were performed. In the 5-h postprandial period following the challenges (3 h for participants aged 2–5 years old), in the SR arm, TIR was significantly higher when bolusing late without the late bolus feature versus using the feature (63.3% [50.0, 80.0] vs. 48.3% [20.0, 68.3], $P < 0.001$). However, there was no significant difference in TIR with late bolus feature use in the LR arm (70% [50.0, 90.0] vs. 62.4% [29.7, 83.6] with late bolus use, $P = 0.06$). Change in CGM values from start of meal is demonstrated in Figure 1.

Although median time <70 mg/dL in the postprandial period after the meal challenges was 0.0% for all arms, with SR time <70 mg/dL was statistically lower with late bolus feature use (0.0% [0.0, 0.0] vs. 0.0% [0.0, 5.6], $P < 0.001$). Similar findings favoring late bolus feature use in the postprandial period occurred with LR (0.0% [0.0, 0.0] vs. 0.0% [0.0, 6.7], $P = 0.006$).

There were few carbohydrate treatments for hypoglycemia in the postprandial period after the meal challenges and no significant differences in time to intervention or number of interventions across arms or feature use (Supplementary Table S5). There were approximately half as many carbohydrate treatments given when the late bolus feature was used with both SR and LR as compared with not using the late bolus feature. There were only four user interventions for hyperglycemia in the postprandial period after the challenges.

Insulin delivery

Insulin dose increased from 0.79 (0.68, 0.99) units/(kg·d) at baseline to 0.85 (0.69, 0.97) units/(kg·d) in the LR arm ($P = 0.01$). This increase was almost exclusively in basal insulin delivery.

Patient-reported outcomes

The mean (standard deviation [SD]) score of the INSPIRE questionnaire for adults was 81.6 (14.9) out of 100 after LR use and 80.6 (15.3) out of 100 after SR use, indicating a positive appraisal of automated insulin dosing. Similar findings for the INSPIRE questionnaire for parents showed a score of 81.5 (13.7) out of 100 after LR use and 80.0 (14.2) out of 100 after SR use, and for youth was 73.6 (19.5) out of 100 after LR use, and 74.5 (13.2) out of 100 after SR use. [11] For the SUS, the mean (SD) score was 85.6 (14.2) out of 100 after LR use, and 88.0 (14.0) out of 100 after SR use, indicating above average and exceptional scores.

CONCLUSIONS

The most recent data from the T1D exchange show only 26% of adults with T1D achieve an HbA1c <7.0%. [11] Although large, randomized controlled trials of automated insulin delivery (AID) systems such as Control-IQ technology show improvements in TIR and HbA1c, [3–5] further improvements in these outcomes may help to reduce diabetes-related complications over time. [12] The lower treatment range of 90–130 mg/dL evaluated in this study was designed to offer further improvements in TIR and TITR than already achievable with currently available AID systems, especially in populations not yet achieving ideal results, such as very young children or those with higher HbA1c at baseline.

In this study, TIR, TITR, time >180 mg/dL, and mean glucose improved in the LR arm. Significant improvements were also seen in age cohorts with the largest number of participants, namely age 6–13 years old and age 18+. With fewer children aged 2–5 and adolescents aged 14–17 in this study, improvements seen were not statistically significant but might have become more apparent with a larger cohort size due to a potential type 1 error.

Along with these improvements in TIR and TITR there was a small but statistically significant increase in time <70 mg/dL with LR use. However, time <70 mg/dL was still well below international consensus guideline recommendations for hypoglycemia (<4%) and is consistent with reports of other AID systems that show similar time <70 mg/dL with lower target use. [13,14] Further, there were no episodes of severe hypoglycemia, despite this modest increase in CGM-captured level 1 hypoglycemia.

Participants with baseline HbA1c <7.5% achieved the highest TIR and TITR in all arms, yet still showed significant improvements with LR use, suggesting the lower treatment range benefited users with well-established diabetes management behaviors before the study. However, participants with an HbA1c ≥7.5% saw the greatest improvement in TIR and TITR in the LR arm, showing the benefit of LR extended to those currently not achieving ideal outcomes.

The late bolus feature evaluated in this study, created as a safety feature, reduced the meal bolus amount automatically based on the time the user selected since eating the meal. This is in line with recent consensus guidelines noting that with an AID system, a user-initiated bolus delivered either during or after carbohydrate consumption could unintentionally lead to insulin stacking and hypoglycemia. [15] Instead of advising users to manually decrease the bolus size by half if the meal bolus is delayed 30–60 min, or only giving only a correction dose if >60 min has elapsed from the start of a meal as recommended by the ATTD 2022 guidance, [15] the late bolus feature offered an automated calculation to implement similar advice for the user.

There were very few interventions for either hypo- or hyperglycemia with use of the late bolus feature. Although TIR in the postprandial period was reduced with use of the late bolus feature in the SR arm, there were no statistical differences in TIR with or without late bolus feature use after bolusing 45 min late in the LR arm (Fig. 1). This is likely explained by the lower treatment range option delivering more insulin earlier on, offsetting the reduced amount of the insulin bolus given by the late bolus feature. This was achieved without increasing the number of hypoglycemia treatments. In fact, the percent of meal challenges requiring intervention with additional carbohydrates was halved with late bolus feature use with both SR and LR, highlighting the success of this feature (Supplementary Table S5).

Strengths of this study include a large sample size and a randomized crossover design. In addition, the study established safety of the modified system across multiple age-groups, including preschool-age children who face many challenges in diabetes management due to unpredictable eating, activity, labile glucose levels, and high insulin sensitivity.

Limitations of the study include that not all features could be fully evaluated in a 6-week period. For example, although Control-IQ autoboluses were disabled during exercise activity with the modified system, there were no exercise challenges and exercise was not logged, so we could not determine the impact of this feature on glycemic control. This will have to be evaluated in a study of longer duration, which could also ascertain changes in HbA1c. The study also had a small number of participants from certain age-groups and was not racially diverse, with 94% of participants identifying as white.

In conclusion, the lower treatment range option and the late bolus feature of the modified Control-IQ system were safe for use in all age-groups. TIR and TITR improved with lower treatment range use in participants with both lower and higher HbA1c at baseline. Future studies of longer duration may show further benefits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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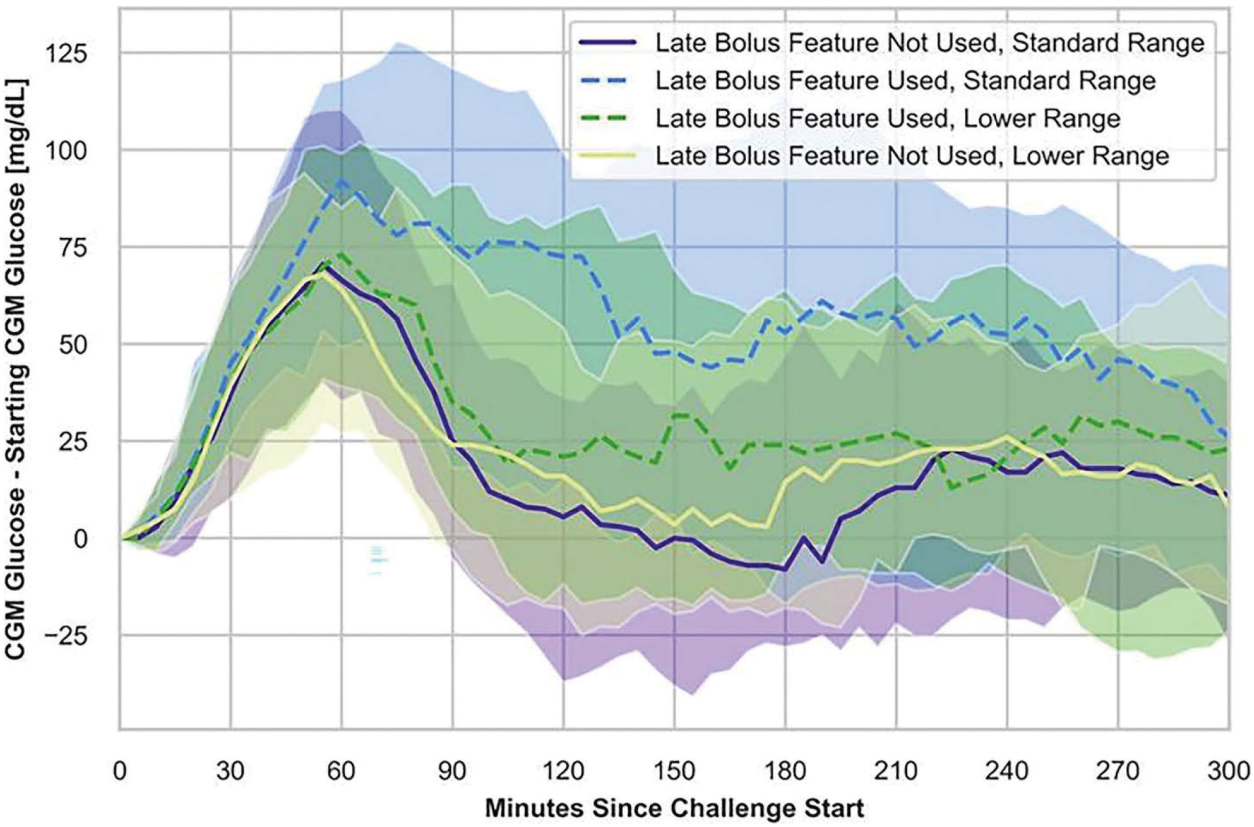

FIGURE 1.

Late bolus meal challenge results. Median (IQR) change in CGM values over time from start of the late bolus meal challenges (start of the meal), where participants then delivered a bolus for the meal 45 min later. CGM values were higher in the 5-h postprandial period with the standard treatment range with late bolus feature use (dashed blue line) compared with bolusing late without using the late bolus feature (solid purple line). However, there was no difference in CGM values in the lower treatment range arm with (dashed green line) or without (sold yellow line) use of the late bolus feature. CGM, continuous glucose monitoring; IQR, interquartile range.

TABLE 1.

Participant Demographics (N=72)

Age (years)	
Mean (SD)	17.0 (13.1)
Range	(3.0, 57.0)
HbA1c (%)	
Mean (SD)	7.3 (1.0)
Range	(5.3, 9.4)
Total daily insulin at enrollment (units/[kg·d])	
Mean (SD)	0.82 (0.21)
Range	(0.42, 1.50)
Sex	
Female (n [%])	35 (48.6%)
Ethnicity (n [%])	
Hispanic	10 (13.9%)
Non-Hispanic	61 (84.7%)
Unknown	1 (1.4%)
Race (not mutually exclusive, n [%])	
American Indian/Alaska Native	1 (1.4%)
Asian	4 (5.6%)
Black	3 (4.2%)
White	68 (94.4%)
Other	2 (2.8%)
Duration of diabetes (years)	
Mean (SD)	10.8 (9.1)
Range	(1.4, 41.3)
Education level (n [%])	
Less than or equal to Bachelor’s degree	68 (94.4%)
Greater than or equal to Master’s degree	4 (5.6%)
Household income level (n [%])	
<$100,000	26 (36.1%)
≥$100,000	42 (58.3%)
Unknown	1 (1.4%)
Not provided	3 (4.2%)
BMI at enrollment (kg/m^2)	
Mean (SD)	22.6 (6.5)
Range	(14.9, 50.5)
BMI Z-score at enrollment	
Mean (SD)	0.9 (0.8)
Range	(−1.0, 3.1)

Pump in use at enrollment	
Tandem t:slim X2	54 (75.0%)
MiniMed 600/700 series	1 (1.4%)
Insulet OmniPod	13 (18.0%)
None	4 (5.6%)

BMI, body mass index; HbA1c, hemoglobin A1c; SD, standard deviation

TABLE 2.

GLYCEMIC OUTCOMES

Glycemic outcomes	Run-in	SR	LR	SR vs. run-in	LR vs. run-in	LR vs. SR
Overall (N=72)						
Time 70–180 mg/dL (%)	62.4 (57.3–70.7)	65.8 (54.4–73.0)	68.0 (60.5–74.3)	0.5, P=0.72, 95% CI (−10.0, 11.1)	**3.1, P<0.001, 95% CI (−8.9, 15.8)**	**2.1, P<0.001, 95% CI (−7.1, 15.8)**
Time 70–140 mg/dL (%)	38.8 (33.9–48.0)	39.2 (30.9–48.1)	43.9 (38.2–51.3)	0.3, P=0.41, 95% CI (−11.5, 8.8)	**3.3, P<0.001, 95% CI (−8.5, 17.6)**	**4.0, P<0.001, 95% CI (−8.0, 17.3)**
Time >180 mg/dL (%)	35.2 (26.1–41.1)	33.0 (25.2–43.8)	30.5 (23.9–36.3)	0.1, P=0.92, 95% CI (−11.0, 11.2)	**−3.5, P<0.001, 95% CI (−16.2, 9.3)**	**−2.5, P<0.001, 95% CI (−16.5, 8.4)**
Time >250 mg/dL (%)	12.1 (5.2–16.9)	10.6 (5.7–18.5)	9.9 (5.1–15.3)	0.0, P=0.66, 95% CI (−10.2, 8.5)	**−1.0, P=0.020, 95% CI (−14.1, 8.0)**	−0.4, P=0.11, 95% CI (−12.3, 5.3)
Time <70 mg/dL (%)	1.7 (0.8–3.3)	1.6 (0.7–3.0)	2.0 (0.9–3.3)	−0.1, P=0.07, 95% CI (−4.1, 2.4)	0.2, P=0.15, 95% CI (−3.6, 2.8)	**0.3, P=0.004, 95% CI (−3.0, 5.1)**
Time <54 mg/dL (%)	0.3 (0.1–0.7)	0.3 (0.1–0.7)	0.4 (0.1–0.8)	0.0, P=0.87, 95% CI (−1.8, 0.9)	0.0, P=0.29, 95% CI (−1.7, 1.4)	0.0, P=0.18, 95% CI (−0.9, 2.0)
Mean Glucose (mg/dL)	167.5 (150.8–178.6)	166.0 (152.6–183.4)	160.2 (149.7–172.6)	−0.3, P=0.89, 95% CI (−23.1, 21.9)	**−5.0, P<0.001, 95% CI (−36.0, 18.3)**	**−5.8, P<0.001, 95% CI (−31.5, 16.7)**
Glucose SD (mg/dL)	66.0 (45.9–73.8)	61.3 (53.8–72.7)	63.5 (52.5–71.0)	−1.3, P=0.17, 95% CI (−16.5, 13.6)	−1.7, P=0.10, 95% CI (−22.9, 15.0)	0.4, P=0.61, 95% CI (−16.6, 12.3)
Glucose CV (%)	39.1 (34.6–42.0)	37.3 (34.0–41.4)	38.1 (34.9–42.5)	**−1.1, P=0.030, 95% CI (−8.0, 4.9)**	0.2, P=0.71, 95% CI (−7.2, 7.6)	**1.6, P=0.013, 95% CI (−4.8, 8.4)**
Age ≥18 (N=24)						
Time 70–180 mg/dL (%)	63.7 (57.3–71.0)	65.3 (52.6–71.6)	67.7 (62.9–73.1)	−1.5, P=0.23, 95% CI (−10.6, 8.8)	2.4, P=0.19, 95% CI (−10.8, 13.9)	**2.1, P=0.014, 95% CI (−4.1, 15.8)**
Time 70–140 mg/dL (%)	37.8 (33.1–48.5)	37.7 (29.5–49.2)	46.8 (38.4–50.2)	0.8, P=0.94, 95% CI (−8.5, 6.0)	**3.6, P=0.028, 95% CI (−7.4, 16.9)**	**3.1, P=0.005, 95% CI (−6.7, 16.6)**
Time >180 mg/dL (%)	33.3 (24.8–40.6)	33.4 (26.0–46.9)	30.8 (23.9–35.9)	0.9, P=0.10, 95% CI (−8.3, 12.4)	−2.1, P=0.24, 95% CI (−14.5, 11.5)	**−2.7, P=0.014, 95% CI (−17.0, 4.3)**
Time >250 mg/dL (%)	9.4 (4.8–15.5)	10.8 (6.2–17.0)	10.2 (6.0–14.9)	1.3, P=0.16, 95% CI (−9.0, 10.7)	0.6, P=0.86, 95% CI (−10.7, 9.2)	0.0, P=0.12, 95% CI (−10.5, 4.5)
Time <70 mg/dL (%)	1.6 (0.5–4.0)	1.3 (0.4–2.8)	1.8 (0.7–3.0)	**−0.4, P=0.043, 95% CI (−3.2, 1.9)**	0.1, P=0.64, 95% CI (−3.6, 2.2)	**0.4, P=0.008, 95% CI (−3.2, 3.8)**
Time <54 mg/dL (%)	0.7 (0.0–1.2)	0.2 (0.1–0.6)	0.4 (0.1–0.8)	**0.02, P=0.036, 95% CI (−2.2, 0.5)**	0.0, P=0.91, 95% CI (−1.5, 1.5)	**0.2, P=0.030, 95% CI (−0.7, 2.7)**
Mean Glucose (mg/dL)	164.8 (149.4–176.5)	164.7 (152.6–183.9)	160.2 (149.8–171.6)	2.6, P=0.14, 95% CI (−17.2, 24.6)	−1.9, P=0.32, 95% CI (−25.0, 22.2)	**−6.2, P=0.008, 95% CI (−30.6, 10.5)**

Glycemic outcomes	**Run-in**	**SR**	**LR**	**SR vs. run-in**	**LR vs. run-in**	**LR vs. SR**
Glucose SD (mg/dL)	58.9 (50.9–59.7)	60.1 (53.5–73.5)	63.5 (54.6–71.8)	1.8, P=0.19, 95% CI (−20.1, 19.4)	2.6, P=0.11, 95% CI (−17.5, 15.3)	1.4, P=0.90, 95% CI (−13.5, 9.3)
Glucose CV (%)	36.8 (30.7–41.5)	35.4 (32.2–42.1)	40.2 (34.7–42.5)	0.2, P=0.73, 95% CI (−8.2, 6.8)	**2.7, P=0.009, 95% CI (−3.7, 6.9)**	2.2, P=0.05, 95% CI (−5.0, 7.4)
Age 14–17 (N=6)						
Time 70–180 mg/dL (%)	57.3 (56.5–58.1)	53.8 (52.8–54.8)	57.7 (48.8–66.6)	−2.9, P=0.50, 95% CI (−5.9, 11.3)	−1.0, P=NS, 95% CI (−7.5, 10.1)	−0.8, P=NS, 95% CI (−6.5, 12.1)
Time 70–140 mg/dL (%)	42.2 (34.5–53.0)	39.4 (30.1–60.1)	47.1 (32.1–56.2)	−3.9, P=0.84, 95% CI (−12.0, 11.7)	−2.0, P=NS, 95% CI (−6.6, 11.0)	1.7, P=0.84, 95% CI (−8.8, 12.1)
Time >180 mg/dL (%)	35.3 (23.4–41.3)	34.9 (18.1–44.9)	28.3 (23.5–46.4)	2.9, P=NS, 95% CI (−11.4, 9.9)	3.5, P=NS, 95% CI (−10.4, 8.8)	1.5, P=0.84, 95% CI (−13.1, 8.4)
Time >250 mg/dL (%)	13.2 (6.8–18.0)	12.9 (4.6–20.5)	8.0 (4.6–23.1)	1.9, P=NS, 95% CI (−5.6, 3.1)	0.6, P=NS, 95% CI (−9.8, 6.2)	2.3, P=0.56, 95% CI (−12.0, 3.8)
Time <70 mg/dL (%)	3.4 (0.6–4.4)	2.3 (0.5–3.2)	1.7 (0.9–3.1)	−0.3, P=0.31, 95% CI (−4.1, 0.4)	−0.8, P=0.44, 95% CI (−3.4, 0.7)	−0.2, P=0.69, 95% CI (−2.0, 1.4)
Time <54 mg/dL (%)	0.7 (0.2–0.9)	0.5 (0.2–0.9)	0.1 (0.0–0.4)	0.0, P=0.63, 95% CI (−0.6, 0.2)	−0.3, P=0.31, 95% CI (−0.7, 0.5)	−0.1, P=0.63, 95% CI (−0.8, 0.4)
Mean Glucose (mg/dL)	166.7 (145.7–180.2)	168.4 (139.2–191.1)	155.2 (146.1–188.8)	6.0, P=0.84, 95% CI (−16.5, 19.2)	6.4, P=NS, 95% CI (−20.1, 15.0)	0.8, P=NS, 95% CI (−27.8, 15.0)
Glucose SD (mg/dL)	68.4 (58.2–74.3)	65.9 (51.2–75.7)	62.4 (55.7–69.0)	1.4, P=NS, 95% CI (−13.8, 3.3)	−3.5, P=0.69, 95% CI (−16.2, 13.1)	3.4, P=0.69, 95% CI (−16.6, 11.4)
Glucose CV (%)	40.7 (40.0–41.2)	38.5 (36.8–39.6)	37.2 (36.0–45.3)	−2.4, P=0.06, 95% CI (−6.6, 0.0)	−2.9, P=0.44, 95% CI (−5.0, 4.7)	1.7, P=0.56, 95% CI (−4.0, 7.9)
Age 6–13 (N=30)						
Time 70–180 mg/dL (%)	61.4 (56.9–69.3)	64.6 (54.0–73.3)	69.3 (61.5–74.9)	1.9, P=0.24, 95% CI (−8.4, 11.5)	**5.6, P<0.001, 95% CI (−8.2, 17.6)**	**4.4, P<0.001, 95% CI (−3.7, 16.0)**
Time 70–140 mg/dL (%)	39.8 (34.1–47.1)	39.8 (31.1–46.4)	43.9 (37.2–53.4)	−0.8, P=0.63, 95% CI (−11.8, 10.5)	**4.4, P<0.001, 95% CI (−5.1, 18.3)**	**5.3, P<0.001, 95% CI (−4.3, 19.6)**
Time >180 mg/dL (%)	37.2 (29.2–41.2)	34.3 (25.1–43.7)	29.5 (21.8–36.3)	−2.1, P=0.23, 95% CI (−11.1, 8.8)	**−5.0, P<0.001, 95% CI (−18.1, 6.7)**	**−4.8, P<0.001, 95% CI (−16.6, 3.9)**
Time >250 mg/dL (%)	13.7 (6.3–17.9)	11.4 (6.1–18.6)	9.7 (3.8–15.5)	−1.9, P=0.18, 95% CI (−8.5, 7.1)	**−2.6, P=0.001, 95% CI (−14.6, 8.0)**	**−1.3, P=0.007, 95% CI (−12.0, 4.6)**
Time <70 mg/dL (%)	1.4 (0.9–2.5)	1.3 (0.7–2.6)	1.9 (0.9–3.4)	0.0, P=0.77, 95% CI (−1.3, 1.9)	**0.3, P=0.004, 95% CI (−0.9, 3.6)**	**0.4, P=0.003, 95% CI (−1.0, 2.9)**
Time <54 mg/dL (%)	0.2 (0.1–0.4)	0.2 (0.1–0.5)	0.4 (0.1–0.7)	0.1, P=0.10, 95% CI (−0.5, 0.9)	**0.1, P=0.017, 95% CI (−0.3, 1.0)**	0.0, P=0.46, 95% CI (−0.5, 0.9)
Mean glucose (mg/dL)	171.4 (156.9–183.6)	168.6 (153.9–184.5)	160.1 (144.7–182.9)	−3.6, P=0.29, 95% CI (−21.6, 17.0)	**−10.0, P<0.001, 95% CI (−36.4, 12.9)**	**−6.9, P<0.001, 95% CI (−30.0, 6.1)**

Glycemic outcomes	Run-in	SR	LR	SR vs. run-in	LR vs. run-in	LR vs. SR
Glucose SD (mg/dL)	69.3 (59.0–73.9)	64.6 (53.5–72.6)	61.5 (51.9–68.3)	**−2.5, P=0.033, 95% CI (−16.1, 11.0)**	**−5.2, P=0.005, 95% CI (−23.1, 16.2)**	−1.1, P=0.13, 95% CI (−18.1, 11.0)
Glucose CV (%)	39.1 (35.1–41.3)	36.9 (34.0–41.3)	36.9 (34.1–41.6)	**−1.3, P=0.020, 95% CI (−8.0, 3.5)**	−1.7, P=0.23, 95% CI (−8.0, 8.6)	0.0, P=0.49, 95% CI (−5.1, 6.8)
Age 2–5 (N=12)						
Time 70–180 mg/dL (%)	63.0 (58.3–71.1)	66.5 (57.2–71.1)	65.0 (59.1–70.2)	1.2, P=0.66, 95% CI (−8.3, 7.6)	1.8, P=0.84, 95% CI (−6.7, 6.3)	−0.1, P=0.80, 95% CI (−10.9, 7.9)
Time 70–140 mg/dL (%)	38.1 (34.8–43.0)	41.0 (34.7–43.6)	39.3 (38.7–45.0)	1.0, P=0.92, 95% CI (−8.7, 6.1)	0.8, P=0.63, 95% CI (−8.8, 9.0)	1.2, P=0.60, 95% CI (−10.0, 9.0)
Time >180 mg/dL (%)	32.7 (26.6–38.4)	30.1 (26.5–39.0)	32.1 (26.9–37.5)	−1.1, P=0.83, 95% CI (−9.3, 11.3)	−1.3, P=0.93, 95% CI (−6.5, 6.7)	1.5, P=0.89, 95% CI (−12.5, 11.1)
Time >250 mg/dL (%)	11.2 (6.5–15.3)	9.9 (5.3–14.1)	11.0 (6.3–16.4)	−0.5, P=0.22, 95% CI (−10.7, 5.9)	−1.0, P=0.68, 95% CI (−7.1, 6.1)	2.0, P=0.36, 95% CI (−7.0, 10.8)
Time <70 mg/dL (%)	2.0 (1.2–5.0)	2.8 (1.9–4.3)	2.5 (1.8–3.1)	0.1, P=0.57, 95% CI (−3.8, 2.4)	0.1, P=0.76, 95% CI (−3.6, 2.1)	−0.3, P=0.43, 95% CI (−2.4, 5.1)
Time <54 mg/dL (%)	0.3 (0.2–1.9)	0.6 (0.3–1.2)	0.5 (0.2–0.9)	0.0, P=0.43, 95% CI (−2.1, 1.2)	0.1, P=0.73, 95% CI (−2.1, 0.6)	−0.0, P=0.73, 95% CI (−1.2, 2.3)
Mean Glucose (mg/dL)	161.1 (155.4–175.8)	160.9 (155.6–174.7)	164.1 (152.3–172.6)	−0.5, P=0.56, 95% CI (−23.5, 18.7)	−1.8, P=0.71, 95% CI (−18.1, 15.2)	2.6, P=0.79, 95% CI (−22.1, 24.5)
Glucose SD (mg/dL)	63.1 (57.3–73.4)	62.8 (55.8–68.5)	66.3 (55.3–76.1)	−2.5, P=0.22, 95% CI (−14.4, 8.1)	0.5, P=0.96, 95% CI (−13.4, 10.7)	1.3, P=0.18, 95% CI (−7.7, 14.6)
Glucose CV (%)	41.4 (34.9–44.3)	37.9 (36.6–41.9)	39.0 (37.7–44.6)	−1.2, P=0.16, 95% CI (−5.2, 3.2)	1.5, P=0.72, 95% CI (−6.1, 6.0)	2.3, P=0.07, 95% CI (−3.2, 4.2)

Median (IQR) 24-h percent times in ranges and median differences compared across each treatment period, overall, and for each age cohort. Significant differences (*P*<0.05) are shown in bold.

CI, confidence interval; IQR, interquartile range; LR, lower range; SR, standard range.