Predictive Low-Glucose Suspend Reduces Hypoglycemia in Adults, Adolescents, and Children With Type 1 Diabetes in an At-Home Randomized Crossover Study: Results of the PROLOG Trial

Gregory P. Forlenza,[1] Zoey Li,[2] Bruce A. Buckingham,[3] Jordan E. Pinsker,[4] Eda Cengiz,[5] R. Paul Wadwa,[1] Laya Ekhlaspour,[3] Mei Mei Church,[4] Stuart A. Weinzimer,[5] Emily Jost,[1] Tatiana Marcal,[3] Camille Andre,[4] Lori Carria,[5] Vance Swanson,[6] John W. Lum,[2] Craig Kollman,[2] William Woodall,[2] and Roy W. Beck[2]

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OBJECTIVE

This study evaluated a new insulin delivery system designed to reduce insulin delivery when trends in continuous glucose monitoring (CGM) glucose concentrations predict future hypoglycemia.

RESEARCH DESIGN AND METHODS

Individuals with type 1 diabetes (*n* = 103, age 6–72 years, mean HbA_{1c} 7.3% [56 mmol/mol]) participated in a 6-week randomized crossover trial to evaluate the efficacy and safety of a Tandem Diabetes Care t:slim X2 pump with Basal-IQ integrated with a Dexcom G5 sensor and a predictive low-glucose suspend algorithm (PLGS) compared with sensor-augmented pump (SAP) therapy. The primary outcome was CGM-measured time <70 mg/dL.

RESULTS

Both study periods were completed by 99% of participants; median CGM usage exceeded 90% in both arms. Median time <70 mg/dL was reduced from 3.6% at baseline to 2.6% during the 3-week period in the PLGS arm compared with 3.2% in the SAP arm (difference [PLGS − SAP] = −0.8%, 95% CI −1.1 to −0.5, $P < 0.001$). The corresponding mean values were 4.4%, 3.1%, and 4.5%, respectively, representing a 31% reduction in the time <70 mg/dL with PLGS. There was no increase in mean glucose concentration (159 vs. 159 mg/dL, $P = 0.40$) or percentage of time spent >180 mg/dL (32% vs. 33%, $P = 0.12$). One severe hypoglycemic event occurred in the SAP arm and none in the PLGS arm. Mean pump suspension time was 104 min/day.

CONCLUSIONS

The Tandem Diabetes Care Basal-IQ PLGS system significantly reduced hypoglycemia without rebound hyperglycemia, indicating that the system can benefit adults and youth with type 1 diabetes in improving glycemic control.

[1]Barbara Davis Center for Diabetes, University of Colorado Denver, Aurora, CO
[2]Diabetes Study Group, Jaeb Center for Health Research, Tampa, FL
[3]Division of Pediatric Endocrinology and Diabetes, Stanford University, Stanford, CA
[4]Clinical Research, Sansum Diabetes Research Institute, Santa Barbara, CA
[5]Division of Pediatric Endocrinology and Diabetes, Yale University, New Haven, CT
[6]Clinical Affairs, Tandem Diabetes Care, San Diego, CA

Corresponding author: John W. Lum, jl_manuscripts@jaeb.org.

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Hypoglycemia continues to be a major cause of morbidity and mortality in patients with type 1 diabetes and presents a significant barrier to improved glycemic control (1–4). Young patients and older patients with a long duration of type 1 diabetes are at high risk for severe hypoglycemia due to impaired hypoglycemia awareness (2,5,6). This is particularly concerning in children, in whom recurrent hypoglycemia has been associated with declines in cognitive performance and memory (7,8). As of 2015, 6% of T1D Exchange Clinic Registry participants reported having experienced a seizure or loss of consciousness due to hypoglycemia in the prior 3 months (9).

Automated integration of real-time continuous glucose monitoring (CGM) data with continuous subcutaneous insulin infusion (CSII) pump delivery has shown promise in reducing the burden of hypoglycemia. Threshold suspend technology allows for automated suspension of insulin delivery when the sensor glucose falls below a predefined lower limit. The ASPIRE (Automation to Simulate Pancreatic Insulin REsponse) trial documented 31.8% fewer nocturnal hypoglycemia events using a threshold suspend system compared with sensor-augmented pump (SAP) therapy (10). Predictive low-glucose suspend (PLGS) technology uses sensor glucose concentration trends to predict glucose values into the future (e.g., 30 min) and then suspends insulin delivery when hypoglycemia is predicted, ideally before hypoglycemia occurs. PLGS has shown a reduction in nocturnal hypoglycemia by ~50% compared with SAP therapy without resultant morning ketosis or hyperglycemia (11–19).

The PROLOG (PLGS for Reduction Of LOw Glucose) trial was a multicenter, randomized controlled crossover outpatient pivotal trial in which the Tandem Diabetes Care Basal-IQ PLGS algorithm was run on a t:slim X2 CSII pump integrated with a Dexcom G5 CGM. This trial assessed the efficacy and safety of the PLGS system to reduce hypoglycemia compared with SAP therapy, using the same pump and sensor that was part of the PLGS system.

RESEARCH DESIGN AND METHODS

The study was conducted at four clinical centers. A central Institutional Review Board approved the protocol, and written informed consent was obtained from each participant or parent, with assent obtained as required. The study is listed on clinicaltrials.gov (NCT03195140). Key aspects of the study protocol are described below.

Major eligibility criteria included age ≥6 years old, type 1 diabetes with use of daily insulin therapy for ≥1 year, and investigator judgment that there were no medical contraindications to participation.

The PLGS system was the Tandem Diabetes Care t:slim X2 with Basal-IQ Technology, an insulin pump with an embedded PLGS algorithm integrated with a Dexcom G5 sensor (Tandem Diabetes Care, San Diego, CA; Dexcom, San Diego, CA). The algorithm uses the last four sensor glucose values to predict the sensor glucose concentration 30 min into the future. Insulin delivery is suspended if the predicted glucose is <80 mg/dL or if the observed glucose concentration falls below 70 mg/dL. Insulin delivery resumes the first time the system receives a CGM glucose reading higher than the previous reading, if glucose is no longer predicted to drop below 80 mg/dL, if no CGM data are available for 10 min, or if the insulin suspension exceeds 120 min in any 150-min period. There is a fixed low-glucose alarm at 55 mg/dL, but no audible alarms by default when the PLGS feature automatically suspends or resumes insulin delivery.

A run-in phase preceded the randomized trial for pump and CGM training, which was customized based on the participant's prior device experience (Supplementary Fig. 1). Successful completion required daily pump use plus CGM use on at least 85% of possible days during the run-in period (Dexcom CGM users could qualify based on the use of their personal CGM). Four of 107 participants enrolled in the run-in phase withdrew before the randomized trial.

After successful completion of the run-in phase, participants began the crossover trial, which consisted of two 3-week periods. They were randomly assigned to use the PLGS version during one period and the non-PLGS version of the pump (SAP) during the other period. Each participant was provided with an Accu-Chek Guide Blood Glucose Monitoring System (Roche Diabetes Care, Indianapolis, IN) for CGM calibration and blood glucose meter checks and with an Abbott Precision Xtra meter (Abbott Diabetes Care, Alameda, CA) for measuring blood ketones when CGM glucose was >300 mg/dL on awakening or for at least 1 h at other times or >400 mg/dL at any time.

Adverse event reporting included severe hypoglycemia, diabetic ketoacidosis, and any study or device-related event.

Outcomes

The primary outcome was CGM-measured percentage of time <70 mg/dL in each 3-week period. Secondary hypoglycemia outcomes included percentage of glucose values <60 mg/dL, <50 mg/dL, area over the curve (70 mg/dL), low blood glucose index (20), and frequency of CGM-measured hypoglycemic events (defined as at least two sensor values <54 mg/dL that were ≥15 min apart plus no intervening values ≥54 mg/dL, with the end of the event defined as at least two sensor values ≥70 mg/dL that were ≥30 min apart with no intervening values <70 mg/dL). Percentage of time <54 mg/dL was added as a post hoc outcome to conform with a recent consensus classification of hypoglycemia (21). CGM-measured glucose coefficient of variation was also added as a post hoc outcome. Safety outcomes in addition to the aforementioned adverse events included calendar days with ketone level >1.0 mmol/L, CGM-measured hyperglycemia (percentage of time >180 mg/dL and >250 mg/dL, area under the curve 180 mg/dL, and high blood glucose index), mean glucose, time in range of 70–180 mg/dL, and daily insulin units (total, basal, and bolus). CGM metrics were calculated overall and separately for daytime (6 A.M.–10 P.M.) and nighttime (10 P.M.–6 A.M.). Participant satisfaction with the PLGS system was assessed with System Usability Scale (10-item technology-agnostic questionnaire that measures the perceived usability of a system) (22).

Statistical Methods

Sample size was computed to be 52 participants to have 90% power with a type 1 error rate of 5% to reject the null hypothesis of no difference in time <70 mg/dL between periods, assuming a true relative treatment effect of a 33% reduction in time <70 mg/dL and a SD of the paired difference of 3.0%. The sample size was increased to 90 participants to

provide increased precision for feasibility and safety analyses in accordance with regulatory needs.

For the primary outcome and the secondary CGM and insulin outcomes, treatment arm differences were analyzed using repeated-measures models with an unstructured covariance structure and with study period as a covariate. For outcomes with a skewed paired treatment difference distribution, a nonparametric analysis based on ranks was performed (23). Time of day–by–treatment interaction effects were assessed in similar models. The association of age with the treatment arm difference in time <70 mg/dL was assessed by including age in a model as described above for the primary analysis. For ketosis events, treatment group difference in incidence rate was analyzed through a repeated measures Poisson regression model.

The analyses followed the intention-to-treat principle. Medians are reported with interquartile ranges (IQR) and means with SD. All *P* values are two-tailed. All nominal (uncorrected) *P* values except those from the primary and safety analyses were adjusted for multiple comparisons using the Benjamini-Hochberg adaptive false discovery procedure (24). Analyses were performed using SAS 9.4 software.

RESULTS

Participant Characteristics

The randomized trial included 103 individuals with type 1 diabetes. Their age range was 6–72 years (60 [58%] were <18 years old, 16 [16%] were 6 to <12 years old, 44 [43%] were 12 to <18 years old, and 43 [42%] were ≥18 years old), 56% were female, and 80% were non-Hispanic white. Median diabetes duration was 8 years, and mean HbA_{1c} was 7.3%. At the time they entered the study, 17% injected insulin, and 16% were not using CGM (Table 1).

Both study periods were completed by 102 of the 103 participants (99%) (Supplementary Fig. 1). One participant dropped during the SAP arm and did not do the PLGS arm and was not included in the CGM analyses as prespecified in the statistical analysis plan. Median CGM use during the 21-day study periods was 95% (IQR 90–97) for the PLGS arm and 94% (IQR 89–96) for the SAP arm. The study pump was used throughout the two study periods by all 102 participants.

Table 1—Patient characteristics at enrollment (*N* = 103)

Age (years)	
Mean ± SD	24 ± 17
Range	6–72
Female sex, *n* (%)	58 (56)
Race/ethnicity, *n* (%)	
White non-Hispanic	82 (80)
Black non-Hispanic	2 (2)
Hispanic or Latino	7 (7)
Asian	3 (3)
Native Hawaiian/other Pacific Islander	1 (<1)
More than one race	8 (8)
Diabetes duration (years)	
Median (IQR)	8 (3–16)
Range	1–52
BMI, mean ± SD*	
Participants ≥18 years old (kg/m^2)	25 ± 4
Participants <18 years old (percentile)	70 ± 23
HbA_{1c} (%), mean ± SD	7.3 ± 0.9
HbA_{1c} (mmol/mol), mean ± SD	56 ± 9.8
CGM metrics†	
%Time <70 mg/dL	
Median (IQR)	3.6 (1.9–5.6)
Mean ± SD	4.4 ± 3.5
%Time in range 70–180 mg/dL, mean ± SD	64 ± 15
Glucose (mg/dL), mean ± SD	158 ± 27
%Time >250 mg/dL, median (IQR)	7 (3–15)
Current insulin modality, *n* (%)	
Injections	17 (17)
Pump	86 (83)
CGM use status, *n* (%)	
Current	87 (84)
In past, but not current	14 (14)
Never	2 (2)
1 or more events in the last 12 months, *n* (%)	
Severe hypoglycemia‡	4 (4)
Diabetic ketoacidosis§	1 (<1)
N of glucose tests/day from self-report, mean ± SD	4.1 ± 2.4
Other noninsulin blood glucose control medications taken, *n* (%)	
Prescription drug‖	3 (3)

*43 participants were 18 or older. †Missing for one participant due to unusable baseline CGM data. ‡A severe hypoglycemia event is defined as a hypoglycemia event in which the participant required assistance from another person to actively administer carbohydrate, glucagon, or engage in other resuscitative actions. §Diabetic ketoacidosis is defined as having all of the following: *1*) symptoms such as polyuria, polydipsia, nausea, or vomiting; *2*) serum ketones >1.5 mmol/L or large/moderate urine ketones; *3*) arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15 mmol/L; and *4*) treatment provided in a health care facility. ‖Includes empagliflozin, metformin, Invokana, and Victoza.

Time Spent in Hypoglycemia

Median time <70 mg/dL was reduced from 3.6% at baseline to 2.6% during the 3-week period in the PLGS arm compared with 3.2% in the SAP arm (difference [PLGS − SAP] = −0.8%, 95% CI −1.1 to −0.5, $P < 0.001$). The corresponding mean values were 4.4% at baseline, 3.1% in the PLGS arm, and 4.5% in the SAP arm, representing a 31% reduction in time <70 mg/dL with PLGS (Fig. 1). All secondary hypoglycemia outcomes also favored the PLGS arm: greater reduction in time <60 mg/dL ($P < 0.001$), time <54 mg/dL ($P < 0.001$), time <50 mg/dL ($P = 0.002$), area over the curve <70 mg/dL ($P < 0.001$), low blood glucose index ($P < 0.001$), and frequency of CGM-defined hypoglycemic events ($P < 0.001$) (Table 2). A greater hypoglycemia reduction in the PLGS arm compared with the SAP arm was consistent in subgroups based on baseline time <70 mg/dL, baseline HbA_{1c}, prior CGM and pump use (Supplementary Table 1), and time of day (daytime vs. nighttime) (Supplementary

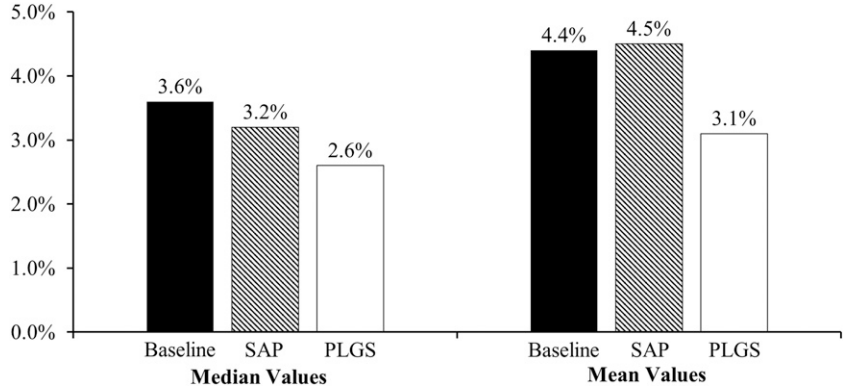

Figure 1—Percentage of time <70 mg/dL at baseline and during SAP and PLGS arms. Baseline values are from Table 1. The SAP and PLGS values are from the 102 participants who completed the postrandomization phase of the study.

Table 2). The treatment effect appeared to be greater in adults than in youth ($P < 0.001$) (Supplementary Fig. 3). During hypoglycemic events, mean time <54 mg/dL was 41.0 min during the PLGS arm and 47.6 min during the SAP arm, with 14% of PLGS events versus 16% of SAP events being <54 mg/dL for at least 1 h and 4% versus 5% for at least 2 h.

Glycemic Control

The mean of each participant's mean glucose concentration was 158 mg/dL at baseline and 159 mg/dL during both the PLGS and SAP arms ($P = 0.40$). Mean time in range 70–180 mg/dL increased in the PLGS arm compared with the SAP arm (64% at baseline, 65% with PLGS, and 63% with SAP; $P < 0.001$). Hyperglycemia outcomes were similar to slightly lower in the PLGS arm compared with the SAP arm (Table 2). Mean coefficient of variation showed a small but statistically significant greater reduction in the PLGS arm compared with the SAP arm (difference [PLGS − SAP] = −1%, 95% CI −2 to 0, $P = 0.007$).

Adverse Events

There was one severe hypoglycemic event in the SAP arm and none in the PLGS arm. One other serious adverse event (bowel obstruction) occurred during the SAP arm. The incidence rate of ketone levels ≥1.0 mmol/L was 0.2 per person-week in each arm ($P = 0.72$).

PLGS Function and Effect on Insulin Delivery

CGM-pump communication was very good. During the PLGS arm when the PLGS algorithm was on, the sensor was transmitting to the pump a median of 91% of the time (IQR 83–93). At least one suspension of insulin delivery occurred on 93% of days (Supplementary Table 3), with the mean number of pump suspensions being 5.7 per day (4.0 between 6 A.M. and 10 P.M. and 1.8 between 10 P.M. and 6 A.M.). A manual override of a suspension by the participant occurred during 3.9% of the suspensions. Mean duration of each suspension was 18 min, which was the same during daytime and nighttime; 37% of suspensions were <10 min and 3% were >60 min. The mean cumulative

Table 2—CGM outcome metrics (N = 102)*

	Baseline	PLGS	SAP	PLGS – SAP treatment difference (95% CI)†	P value†
Hours of data	312 (297, 560)	473 (447, 485)	467 (447, 482)	N/A	N/A
Percent of glucose <70 mg/dL	3.6 (1.9, 5.6)‡	2.6 (1.4, 4.0)	3.2 (1.9, 6.1)	−0.8 (−1.1, −0.5)	<0.001
Overall glucose control					
Mean glucose (mg/dL)	158 ± 27	159 ± 25	159 ± 27	−1 (−3, +1)	0.40
%Glucose 70–180 mg/dL	64 ± 15	65 ± 15	63 ± 15	+2 (+1, +4)	<0.001
Coefficient of variation, %§	37 ± 5	36 ± 5	37 ± 5	−1% (−2, 0)‖	0.007
Hypoglycemia					
%Glucose <60 mg/dL	1.2 (0.6, 2.1)	0.9 (0.4, 1.6)	1.2 (0.6, 2.7)	−0.3 (−0.5, −0.2)	<0.001
%Glucose <54 mg/dL§	0.6 (0.2, 1.0)	0.4 (0.1, 0.8)	0.5 (0.2, 1.4)	−0.1 (−0.2, −0.1)	<0.001
%Glucose <50 mg/dL	0.3 (0.1, 0.6)	0.2 (0.1, 0.5)	0.3 (0.1, 0.7)	0.0 (−0.1, 0.0)‖	0.002
Area over curve <70 mg/dL	0.31 (0.19, 0.55)	0.25 (0.11, 0.40)	0.30 (0.17, 0.65)	−0.07 (−0.11, −0.05)	<0.001
Low blood glucose index	0.9 (0.6, 1.3)	0.8 (0.5, 1.1)	0.9 (0.6, 1.5)	−0.1 (−0.2, −0.1)	<0.001
Hypoglycemic events per week¶	1.1 (0.5, 2.4)	0.8 (0.3, 1.9)	1.1 (0.4, 3.0)	−0.3 (−0.4, 0.0)‖	<0.001
Hyperglycemia					
%Glucose >250 mg/dL	7 (3, 15)	8 (3, 13)	8 (3, 16)	−1 (−1, 0)‖	0.008
%Glucose >180 mg/dL	32 ± 17	32 ± 15	33 ± 16	−1 (−3, 0)	0.12
Area under curve >180 mg/dL	14.7 (7.5, 24.7)	15.8 (8.3, 24.1)	16.9 (7.4, 25.8)	−0.87 (−1.76, −0.03)	0.04
High blood glucose index	6.7 (3.9, 9.9)	6.9 (4.4, 9.6)	7.4 (4.2, 10.1)	−0.3 (−0.6, 0.0)	0.05

Baseline, PLGS, and SAP data are presented as median (quartiles) or as mean ± SD. *Includes all participants with at least one CGM glucose sensor reading in each treatment period. One participant did not have useable baseline data. †Based on a repeated-measures regression model adjusting for period. Nonparametric analysis was conducted for variables with a skewed distribution (exceptions are mean glucose, glucose coefficient of variation, percentage 70–180 mg/dL, and percentage >180 mg/dL). P values were adjusted for multiple comparisons using the Benjamini-Hochberg adaptive false discovery rate procedure with the exception of the primary outcome, percentage <70 mg/dL. ‡From Table 1. §Post hoc analysis. ‖CI may include 0 even though P value <0.05 due to rounding. ¶A hypoglycemia event was defined as at least two sensor values <54 mg/dL that were ≥15 min apart with no intervening values >54 mg/dL. At least two sensor values >70 mg/dL that are ≥30 min apart with no intervening values <70 mg/dL are required to end a hypoglycemic event.

suspension time per day was 104 min (72 daytime and 32 nighttime) (Supplementary Table 4). Median glucose nadir during a suspension period was 82 mg/dL, and median peak glucose within 2 h after a suspension was 131 mg/dL. Mean basal insulin delivery was 1.2 units/day lower (95% CI −1.5 to −0.8) during the PLGS arm compared with the SAP arm ($P < 0.001$) (Supplementary Table 5). Bolus insulin delivery was the same during both arms (0.0 units/day difference, 95% CI −0.8 to +0.8, $P = 0.97$).

System Usability

On the System Usability Questionnaire, scores were very high (mean composite score 88.8 of 100), with more than 90% indicating that they would like to use the PLGS system frequently and very few indicating that the system was difficult to use (Table 3).

CONCLUSIONS

The PROLOG trial was successful in achieving the primary efficacy outcome of significantly reduced time <70 mg/dL in the PLGS period compared with the SAP period, with a 31% relative reduction in mean time <70 mg/dL. PLGS use also met all safety criteria, with no participants experiencing severe hypoglycemia or diabetic ketoacidosis during the PLGS period and without differences in ketonemia ≥1.0 mmol/L between the PLGS and SAP arms. These 24-h outpatient results of a commercial system support the findings of our previous overnight-only studies that showed the efficacy and safety of PLGS in adults, adolescents, and children (11–14). A similar hypoglycemia reduction was seen in all groups irrespective of age, baseline HbA_{1c}, or baseline hypoglycemia exposure. Participants with higher baseline hypoglycemia exposure saw the largest magnitude of hypoglycemia reduction with PLGS. Overall study adherence was remarkably high, with 99% of those enrolled completing the trial and with the system active for 95% of the time during the PLGS period. Such levels of adherence are reflected in the very high scores on the System Usability Questionnaire.

There has been concern that hypoglycemia prevention with PLGS could involve a tradeoff of increased mean glucose and greater hyperglycemia in exchange for the protection of decreased hypoglycemia exposure (15,18). However, participants in the current study had identical mean glucose concentrations during the PLGS and SAP portions and no increase in hyperglycemia with PLGS, along with a small, but statistically significant increased time in target range of 70–180 mg/dL of 2%, corresponding to ~30 min/day more time in range. This could possibly be due to design of the algorithm used in the current study that is aggressive in insulin resumption, which occurs on the first glucose reading past the nadir, whereas other systems do not resume insulin delivery until the sensor glucose has increased above a specified threshold and/or include a future predicted glucose value increasing above a predefined threshold. Relatively shorter suspensions were seen in the current study, with a mean suspension duration of 18 min per event, whereas suspensions for other trials were 56 and 58 min (16,17). The similar mean glucose seen in the current study is especially notable because mean daily bolus insulin amounts were identical between periods, whereas the basal insulin dose was reduced by ~4% in the PLGS phase compared with the SAP phase. This appears to suggest that the algorithm was successful in decreasing basal insulin delivery only during times when basal insulin was unwanted without affecting insulin delivery during other periods of the day.

It is notable that while use of PLGS reduced the amount of daily hypoglycemia, the duration of discrete biochemical hypoglycemic events was similar in

Table 3—System Usability Questionnaire score summary ($N = 102$)*

Question	Score, mean ± SD†	Response categories, *n* (%) 0 (strongly disagree)	1	2	3	4 (strongly agree)
1. I think that I would like to use this system frequently.	3.7 ± 0.7	1 (<1)	1 (<1)	5 (5)	16 (16)	79 (77)
2. ►I found the system unnecessarily complex.	3.6 ± 0.8	73 (72)	18 (18)	7 (7)	4 (4)	0 (0)
3. I thought the system was easy to use.	3.6 ± 0.7	0 (0)	0 (0)	9 (9)	26 (25)	67 (66)
4. ►I think that I would need the support of a technical person to be able to use this system.	3.7 ± 0.7	83 (81)	14 (14)	1 (<1)	3 (3)	1 (<1)
5. I found the various functions in this system were well integrated.	3.4 ± 0.7	0 (0)	1 (<1)	10 (10)	34 (33)	57 (56)
6. ►I thought there was too much inconsistency in this system.	3.5 ± 0.7	65 (64)	26 (25)	10 (10)	1 (<1)	0 (0)
7. I would imagine that most people would learn to use this system very quickly.	3.3 ± 0.8	1 (<1)	2 (2)	12 (12)	34 (33)	53 (52)
8. ►I found the system very cumbersome to use.	3.6 ± 0.7	72 (71)	22 (22)	5 (5)	3 (3)	0 (0)
9. I felt very confident using the system.	3.7 ± 0.6	0 (0)	1 (<1)	2 (2)	28 (27)	71 (70)
10. ►I needed to learn a lot of things before I could get going with this system.	3.4 ± 0.9	63 (62)	29 (28)	3 (3)	4 (4)	3 (3)
Composite score‡	88.8 ± 10.4					

*The System Usability Questionnaire is a 10-item questionnaire administered at the end of the study period in which the participant used the PLGS system to determine the system usability of the PLGS feature. †Responses are ranked on a 5-point scale from 0 (strongly disagree) to 4 (strongly agree). For positively worded items (items 1, 3, 5, 7, and 9), each participant's response is scored as recorded. Items denoted by "►" (items 2, 4, 6, 8, and 10) were reverse-scored by subtracting the response ranking from 4. Higher scores denote better perceived usability. ‡Composite scores are calculated in accordance with the System Usability Questionnaire scoring manual by taking the sum of the individual item scores from each participant and multiplying by 2.5. Possible composite scores range from 0 to 100, with higher scores denoting better perceived usability.

the two arms. This could reflect the amount of insulin on board that continues to have an effect after pump suspension. Patients and providers should be aware that prolonged hypoglycemic events, though uncommon, can still occur with PLGS.

Several other trials have recently investigated PLGS systems in an outpatient setting. Abraham et al. (15) compared the Medtronic MiniMed 640G PLGS pump to SAP therapy in a 6-month randomized trial in children and found a significantly greater reduction from baseline in percentage of time <63 mg/dL (3.5 mmol/L) in the PLGS arm compared with the SAP arm (2.8% reduced to 1.5% with PLGS compared with 3.0% reduced to 2.6% with SAP). This was seen without a significant change in HbA_{1c} levels, although with a small but significant increase in mean sensor glucose concentrations in the PLGS group (176 vs. 167 mg/dL). Biester et al. (25) also have published outpatient results for the MiniMed 640G compared against SAP in a crossover trial in which they showed that use of the PLGS system was associated with a reduction in time <70 mg/dL from 73 to 31 min/day. They reported no change in HbA_{1c} between periods but an increase in mean glucose of 10 mg/dL during the PLGS period. Use of hybrid closed-loop control (26–30) or a hyperglycemia/hypoglycemia minimization algorithm (31,32) has shown additional success in alleviating both hyperglycemia and hypoglycemia.

The strengths of the study included a randomized crossover design, which is efficient and limits bias by allowing participants to serve as their own controls. The study completion rate exceeded 99%, and CGM in the PLGS and SAP arms was used for ~95% of each period.

Several limitations in interpreting the results are worthy of mention. The intervention and control periods lasted 3 weeks, which was determined to be adequate for evaluation of the effect of the PLGS system on hypoglycemia and hyperglycemia but too short to fully evaluate long-term feasibility and effects on hypoglycemia and hyperglycemia outcomes as well as HbA_{1c}. In addition, participants received device training and support from highly trained and experienced study staff, which may have helped improve device adherence and retention. The proportions of participants using an insulin pump and CGM before the study were higher and baseline HbA_{1c} levels were lower than the national averages for adults and children with type 1 diabetes (9). However, the age range was broad, and the magnitude of the treatment effect was similar in participants with higher or lower baseline HbA_{1c} levels and device users or nonusers (participants using multiple daily injections and participants not using sensors), suggesting that the results could be generalized to a broad range of adults and youth with type 1 diabetes. It is important to note that this system is designed only to reduce hypoglycemia. Although use of the system did not increase hyperglycemia, only a minority of youth and adults with type 1 diabetes meet the HbA_{1c} goals of the American Diabetes Association (9), reflecting the potential value for automated insulin delivery systems to not only reduce insulin delivery to prevent hypoglycemia but also increase insulin delivery to reduce hyperglycemia.

In conclusion, the PROLOG pivotal trial of the Tandem Diabetes Care Basal-IQ PLGS system showed significant reduction in hypoglycemia along with improved time in target range without increased mean glucose or hyperglycemia in an outpatient 6-week randomized crossover study. Adherence with system use was very high, and participants rated the system highly on a usability scale. These results indicate that this system can be expected to benefit adults, adolescents, and children in reducing hypoglycemia and improving control of their diabetes.

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