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Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections
The DIAMOND Randomized Clinical Trial

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IMPORTANCE Previous clinical trials showing the benefit of continuous glucose monitoring (CGM) in the management of type 1 diabetes predominantly have included adults using insulin pumps, even though the majority of adults with type 1 diabetes administer insulin by injection.

OBJECTIVE To determine the effectiveness of CGM in adults with type 1 diabetes treated with insulin injections.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted between October 2014 and May 2016 at 24 endocrinology practices in the United States that included 158 adults with type 1 diabetes who were using multiple daily insulin injections and had hemoglobin A_{1c} (HbA_{1c}) levels of 7.5% to 9.9%.

INTERVENTIONS Random assignment 2:1 to CGM (n = 105) or usual care (control group; n = 53).

MAIN OUTCOMES AND MEASURES Primary outcome measure was the difference in change in central-laboratory–measured HbA_{1c} level from baseline to 24 weeks. There were 18 secondary or exploratory end points, of which 15 are reported in this article, including duration of hypoglycemia at less than 70 mg/dL, measured with CGM for 7 days at 12 and 24 weeks.

RESULTS Among the 158 randomized participants (mean age, 48 years [SD, 13]; 44% women; mean baseline HbA_{1c} level, 8.6% [SD, 0.6%]; and median diabetes duration, 19 years [interquartile range, 10-31 years]), 155 (98%) completed the study. In the CGM group, 93% used CGM 6 d/wk or more in month 6. Mean HbA_{1c} reduction from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group and 0.5% and 0.4%, respectively, in the control group (repeated-measures model $P < .001$). At 24 weeks, the adjusted treatment-group difference in mean change in HbA_{1c} level from baseline was −0.6% (95% CI, −0.8% to −0.3%; $P < .001$). Median duration of hypoglycemia at less than <70 mg/dL was 43 min/d (IQR, 27-69) in the CGM group vs 80 min/d (IQR, 36-111) in the control group ($P = .002$). Severe hypoglycemia events occurred in 2 participants in each group.

CONCLUSIONS AND RELEVANCE Among adults with type 1 diabetes who used multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA_{1c} level during 24 weeks. Further research is needed to assess longer-term effectiveness, as well as clinical outcomes and adverse effects.

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Editorial page 363

Related article page 379

Supplemental content

CME Quiz at jamanetworkcme.com and CME Questions page 436

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Only approximately 30% of individuals with type 1 diabetes meet the American Diabetes Association goal of hemoglobin A_{1c} (HbA_{1c}) level of 7.5% (58 mmol/mol) for children (<18 years) and 7.0% (53 mmol/mol) for adults (≥18 years),[1] indicating the need for better approaches to diabetes management. Continuous glucose monitoring (CGM) with glucose measurements as often as every 5 minutes, plus low and high glucose level alerts and glucose trend information, has the capability of better informing diabetes management decisions than blood glucose meter testing performed several times a day. Randomized clinical trials have demonstrated the benefit of CGM in adults with type 1 diabetes, but not consistently in children, to improve glycemic control as measured by HbA_{1c} level and to reduce hypoglycemia.[2-6] These previous trials have either completely or predominantly included insulin pump users,[2,4,5] although the majority of adults with type 1 diabetes deliver insulin via injections.[7,8]

Only a small proportion of individuals with type 1 diabetes who inject insulin use CGM, although the limited available observational data suggest that the glycemic benefit may be comparable to that for pump users. In T1D Exchange registry 2015 data, mean HbA_{1c} level in the 410 adult insulin injecters using CGM was similar to that in 2316 pump users using CGM (7.6% vs 7.7%, respectively) and lower than mean HbA_{1c} level in the 6222 injection users not using CGM (7.6% vs 8.8%; $P < .001$).[9]

Whether individuals receiving insulin injections would be willing to regularly wear CGM sensors and would derive glycemic benefits from CGM needs investigation. Accordingly, this randomized multicenter clinical trial was conducted to evaluate the effect of CGM in adults with type 1 diabetes who have elevated HbA_{1c} levels and use multiple daily injections of insulin.

Key Points

Question For adults with type 1 diabetes who are using multiple daily insulin injections, does continuous glucose monitoring improve hemoglobin A_{1c} (HbA_{1c}) levels compared with self-monitored blood glucose management?

Findings In a randomized clinical trial of 158 adults with type 1 diabetes, there was a significantly greater decrease in HbA_{1c} level during 24 weeks with continuous glucose monitoring vs usual care (−1.0% vs −0.4%).

Meaning Continuous glucose monitoring resulted in better glycemic control compared with usual care, but further research is needed to assess clinical outcomes, as well as effectiveness, in a typical clinical population.

Methods

The trial was conducted at 24 endocrinology practices in the United States (19 community-based and 5 academic centers). The protocol and Health Insurance Portability and Accountability Act–compliant informed consent forms were approved by institutional review boards (central commercial board for 17 sites and local boards for the other 7 sites). Written informed consent was obtained from each participant. The protocol is provided online and the statistical analysis plan is available in Supplement 1.

Study Participants

Major eligibility criteria included age 25 years or older, diagnosis of type 1 diabetes treated for at least 1 year with multiple daily insulin injections, central laboratory–measured HbA_{1c} level of 7.5% to 10.0%, no home use of a personal CGM device in the 3 months before the trial, and a negative pregnancy test for women of childbearing potential (eTable 1 in Supplement 2 has a complete listing of the inclusion and exclusion criteria).

Synopsis of Study Design

Each participant was required to complete a 2-week prerandomization phase using a CGM system that was configured to record glucose concentrations not visible to the participant (referred to as a "blinded" CGM). Eligibility required that the blinded CGM be worn on at least 85% of possible days, the CGM be calibrated at least 2 times per day, and blood glucose meter testing (with a study-provided meter and test strips) be performed at least 3 times daily. Fourteen participants did not meet these criteria and did not continue into the randomized trial (**Figure 1**). One participant had a sudden death during the prerandomization phase.

On the study website, after verification of eligibility from data entered, each participant was assigned randomly from a computer-generated sequence to either the CGM or control group in a 2:1 ratio, with a permuted block design (block sizes of 3 and 6) stratified by HbA_{1c} level (<8.5% and ≥8.5%). A 2:1 randomization was used rather than 1:1 to provide a larger sample size for a separate follow-on randomized trial assessing glycemic benefits of initiating pump therapy in CGM users using insulin injections.

Participants in the CGM group were provided with a CGM system (Dexcom G4 Platinum CGM System with an enhanced algorithm, software 505, Dexcom Inc) that measured glucose concentrations from interstitial fluid in the range of 40 to 400 mg/dL every 5 minutes for up to 7 days. Participants in both groups were provided with a Bayer Contour Next USB meter and test strips. The CGM group was instructed to use the CGM daily, calibrate the CGM twice daily, and verify the CGM glucose concentration with the blood glucose meter before injecting insulin (as per the regulatory labeling of the device at the time the trial was conducted). General guidelines were provided to participants about using CGM, and individualized recommendations were made by their clinician about incorporating CGM trend information into their diabetes management. The control group was asked to perform home blood glucose monitoring at least 4 times daily. Participants in both groups were provided general diabetes management education, and clinicians were encouraged to review downloaded glucose data at each visit to inform treatment recommendations, which were at clinician discretion and not prescriptive in the protocol. eTable 2 in Supplement 2 describes the participant education as well as guidelines for clinicians. CGM guidelines for participants are included in Supplement 1.

Follow-up visits for both treatment groups occurred after 4, 12, and 24 weeks. The CGM group had an additional visit 1 week after randomization. The control group had 2 additional visits 1 week before the 12- and 24-week visits, at which a CGM sensor in blinded mode was inserted to collect glucose data for 1 week. Telephone contacts for both groups occurred 2 and 3 weeks after randomization.

Hemoglobin A_{1c} level was measured at baseline, 12 weeks, and 24 weeks at the Northwest Lipid Research Laboratories, University of Washington, Seattle, with the Diabetes Control and Complications Trial standardized analyzer (TOSOH, Biosciences Inc).

Outcomes

The primary outcome was change in the central laboratory-measured HbA_{1c} level. Prespecified secondary outcomes included percentage of participants with HbA_{1c} level less than 7.0%; CGM-measured time in range (70-180 mg/dL), duration of hypoglycemia (<70 mg/dL, <60 mg/dL, and <50 mg/dL), duration of hyperglycemia (>180 mg/dL, >250 mg/dL, and >300 mg/dL), and glucose variability (coefficient of variation); change in hypoglycemia unawareness[10]; and change in frequency of blood glucose meter testing (longitudinal changes in blood glucose meter testing were not assessed). Prespecified exploratory outcomes included CGM-measured mean glucose concentration and the following binary HbA_{1c} outcomes to assist in translation of the primary HbA_{1c} analysis to a participant level: HbA_{1c} level less than 7.5% and relative HbA_{1c} reduction greater than or equal to 10%. Post hoc outcomes included HbA_{1c} reduction of 1% or more, HbA_{1c} level less than 7.0% or reduction of 1% or more, CGM-measured area above the curve 70 mg/dL and area under the curve 180 mg/dL, change in insulin dose, and change in body weight.

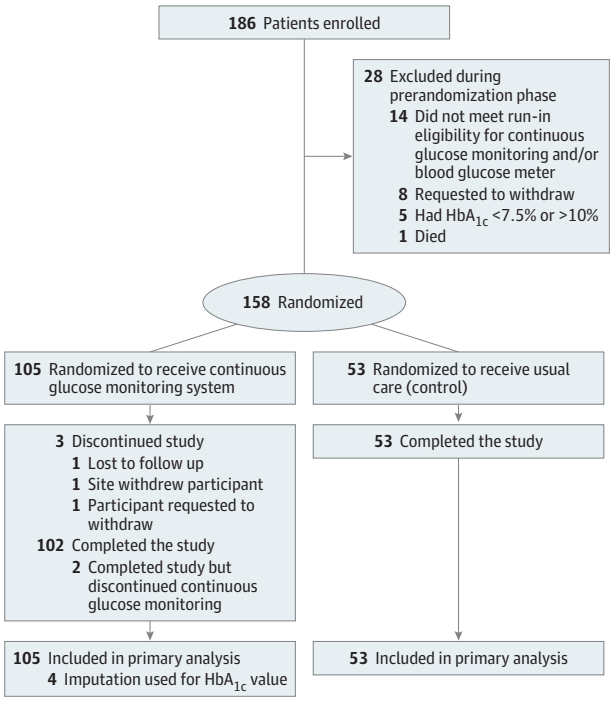
Satisfaction with CGM was assessed by completion at 24 weeks of the CGM Satisfaction Survey (44 items on a 1-5 Likert scale, with the computed score representing the mean of the 44 items and subscales of benefits and lack of hassles).[11] Quality-of-life and health economic outcomes will be reported in separate articles.

Safety outcomes included severe hypoglycemia (defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions), diabetic ketoacidosis, and serious adverse events regardless of causality.

Statistical Methods

A sample size of 147 for the 2:1 randomization was calculated to have 90% power to detect a difference in mean HbA_{1c} level between treatment groups, assuming a population difference of 0.4%, standard deviation of the 24-week values of 0.7 adjusted for the correlation between baseline and 24-week values (based on data from the Juvenile Diabetes Research Foundation CGM randomized trial[5]), and a 2-sided α level of .05. Sample size initially was increased to 169 to account for potential loss to follow-up. When it was recognized by the coordinating center that the trial completion rate was higher than anticipated, the recruitment goal was changed to a minimum of 150, with the approval of the steering committee and the sponsor.

Figure 1. Flowchart of Continuous Glucose Monitoring Study Completion



All enrolled participants started the run-in phase; 28 did not proceed to randomization for the reasons indicated in the figure. The number eligible for screening who did not sign the informed consent form was not recorded.

Analyses followed the intent-to-treat principle. The following change was made from the protocol and statistical analysis plan before the data lock: the primary analysis was a treatment group comparison of the change in HbA_{1c} level from baseline to 24 weeks, adjusted for baseline HbA_{1c} level and clinical site as a random effect, in a repeated-measures linear model in the protocol and with analysis of covariance in the statistical analysis plan; both are reported in this article. Confounding was assessed by repeating the analysis, including potential confounding variables as covariates. The Rubin method was used to impute for missing data.[12] Exploratory analyses were conducted to assess for interaction between the treatment effect on the change in HbA_{1c} level from baseline to 24 weeks and baseline factors by including interaction terms in analysis of covariance models. The following changes were made from the protocol and statistical analysis plan during the peer-review process: in post hoc analyses, binary HbA_{1c} outcomes were evaluated with propensity scores[13] instead of logistic regression, adjusted for baseline HbA_{1c} level and clinical site; and for secondary, exploratory, and post hoc analyses, 99% CIs instead of 95% CIs are reported.

For CGM outcomes, treatment group comparisons using the CGM data collected in each group for 7 days at 12 and 24 weeks were made with analysis of covariance models based on ranks using van der Waerden scores if the metric was

Table 1. Baseline Participant Characteristics

	Group, No. (%)	
	CGM (n = 105)	Control (n = 53)
Age, y		
25-<45	53 (50)	16 (30)
45-<60	32 (30)	23 (43)
≥60	20 (19)	14 (26)
Mean (SD) [range]	46 (14) [26-72]	51 (11) [26-73]
Diabetes duration, median (IQR), y	19 (9-29)	19 (11-35)
Female sex	47 (45)	23 (43)
Highest education[a]		
<Bachelor's degree	47 (47)	22 (43)
Bachelor's degree	43 (43)	19 (37)
Graduate degree	10 (10)	10 (20)
BMI, mean (SD)	28 (6)	27 (5)
Weight, mean (SD), kg	84 (20)	81 (18)
HbA_{1c}, %		
7.5-<8.5	47 (45)	24 (45)
8.5-≤9.9	58 (55)	29 (55)
Mean (SD) [range]	8.6 (0.7) [7.5-9.9]	8.6 (0.6) [7.5-9.9]
Self-reported No. of self-monitoring blood glucose tests per day, mean (SD)	3.9 (1.3)	4.1 (1.6)
Event in previous 12 mo		
≥1 Severe hypoglycemia	8 (8)	9 (17)
≥1 Diabetic ketoacidosis	1 (<1)	1 (2)
Use of noninsulin glucose-lowering medication	8 (8)	4 (8)
Total daily insulin dose, median (IQR), U/kg/d	0.7 (0.5-0.9)	0.6 (0.5-0.9)
No. of long-acting insulin injections per day		
1	78 (74)	34 (64)
2	26 (25)	19 (36)
3	1 (<1)	0
No. of rapid-acting insulin injections per day		
2	0	1 (2)
3	71 (68)	32 (60)
4	23 (22)	15 (28)
≥5	11 (10)	5 (9)
CGM use previously	17 (16)	9 (17)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CGM, continuous glucose monitoring; HbA_{1c}, hemoglobin A_{1c}; IQR, interquartile range.

SI Conversions: to convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percentage value × 10.93 and subtract 23.5 from the product.

[a] Education data missing for 5 in the CGM group and 2 in the control group.

skewed, adjusted for the corresponding baseline value, baseline HbA_{1c} level, and clinical site as a random effect. Similar analyses were performed separately for daytime and nighttime. Frequency of blood glucose monitoring was compared between groups with an analysis of covariance model, adjusted for the baseline frequency and clinical site as a random effect.

Statistical methods for other analyses are described in table footnotes. Standard deviations are reported for means and interquartile ranges (IQRs) for medians where applicable. Reported point estimates are unadjusted unless otherwise noted. Analyses were conducted with SAS version 9.4. All *P* values are 2 sided. $P < .05$ was considered significant for the primary analysis and $P < .01$ for all other analyses to account for multiple comparisons (with 99% CIs accordingly provided).

SI Unit Conversions

Throughout, to convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percentage value × 10.93 and subtract 23.5 from the product. For example, an HbA_{1c} value of 7.0% corresponds to 53 mmol/mol. To convert glucose to mmol/L, multiply the values × 0.0555.

Results

Between October 2014 and December 2015, 158 participants were assigned to the CGM group (n = 105) or control group (n = 53). Mean age was 48 years (SD, 13) (range, 26-73 years, with 34 participants [22%] ≥60 years); 44% were women. Median diabetes duration was 19 years (IQR, 10-31 years), and mean baseline HbA_{1c} level was 8.6% (SD, 0.6%; range, 7.5%-9.9%). Participant characteristics according to randomized group are shown in **Table 1.**

The 24-week primary study outcome visit was completed by 102 participants (97%) in the CGM group and all 53 (100%) in the control group (Figure 1). Overall visit completion was 99% and 98%, respectively. Three participants in the CGM group (4 total visits) and 3 in the control group (3 total visits) had additional visits, not required in the protocol, for diabetes management.

Among the 102 participants in the CGM group who completed the trial, median CGM use was 7.0 d/wk (IQR, 7.0-7.0) at 4, 12, and 24 weeks; only 2 (2%) discontinued CGM before the 24-week visit. During month 6 (weeks 21-24), CGM use was 6 or more d/wk for 93% of the 102 participants (eTable 3 in Supplement 2). No participant in the control group initiated unblinded CGM use before the primary outcome.

According to meter downloads, mean blood glucose self-monitoring was 5.1 tests per day (SD, 1.8) in the CGM group and 5.1 tests per day (SD, 1.4) in the control group during the baseline period of blinded CGM wear and 3.6 tests per day (SD, 1.6) and 4.6 tests per day (SD, 1.6), respectively, at 24 weeks (adjusted mean difference for the change, -1.0; 99% CI, -1.7 to -0.4; $P < .001$).

Glycemic Control and Other Outcomes

Primary Outcome

Mean reduction in HbA_{1c} level from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group and 0.5% and 0.4%, respectively, in the control group (primary analysis repeated-measures $P < .001$). At 24 weeks, the adjusted treatment group difference in mean change in HbA_{1c} level was -0.6% (95% CI, -0.8% to -0.3%; $P < .001$) (**Table 2**). For each treatment group, baseline and 24-week HbA_{1c} values for each

Table 2. Primary Outcome and Hemoglobin A_{1c} Outcomes at 12 and 24 Weeks[a]

	12 Weeks		24 Weeks			
	CGM Group (n = 103)	Control Group (n = 52)	CGM Group (n = 105)[b]	Control Group (n = 53)	Between-Group Difference[c,d]	*P* Value[c,d]
Primary outcome, mean (SD), %					Mean adjusted difference, % (95% CI)	
HbA_{1c}	7.6 (0.7)	8.1 (0.7)	7.7 (0.8)	8.2 (0.8)		
Change in HbA_{1c} from baseline	−1.1 (0.7)	−0.5 (0.7)	−1.0 (0.8)	−0.4 (0.7)	−0.6 (−0.8 to −0.3)	<.001
Prespecified secondary outcome, No. (%)					Mean adjusted difference, % (99% CI)	
HbA_{1c} <7.0%	14 (14)	2 (4)	18 (18)	2 (4)	15 (0 to 30)	.01
Prespecified exploratory outcomes, No. (%)						
HbA_{1c} <7.5%	49 (48)	6 (12)	39 (38)	6 (11)	31 (12 to 51)	<.001
Relative reduction in HbA_{1c} ≥10%	62 (60)	12 (23)	58 (57)	10 (19)	37 (16 to 58)	<.001
Post hoc outcomes, No. (%)						
Reduction in HbA_{1c} ≥1%	55 (53)	12 (23)	53 (52)	10 (19)	33 (11 to 54)	<.001
Reduction in HbA_{1c} ≥1% or HbA_{1c} <7.0%	57 (55)	12 (23)	53 (52)	11 (21)	31 (9 to 52)	<.001

Abbreviations: CGM, continuous glucose monitoring; HbA_{1c}, hemoglobin A_{1c}.

SI Conversion: to convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percentage value × 10.93 and subtract 23.5 from the product.

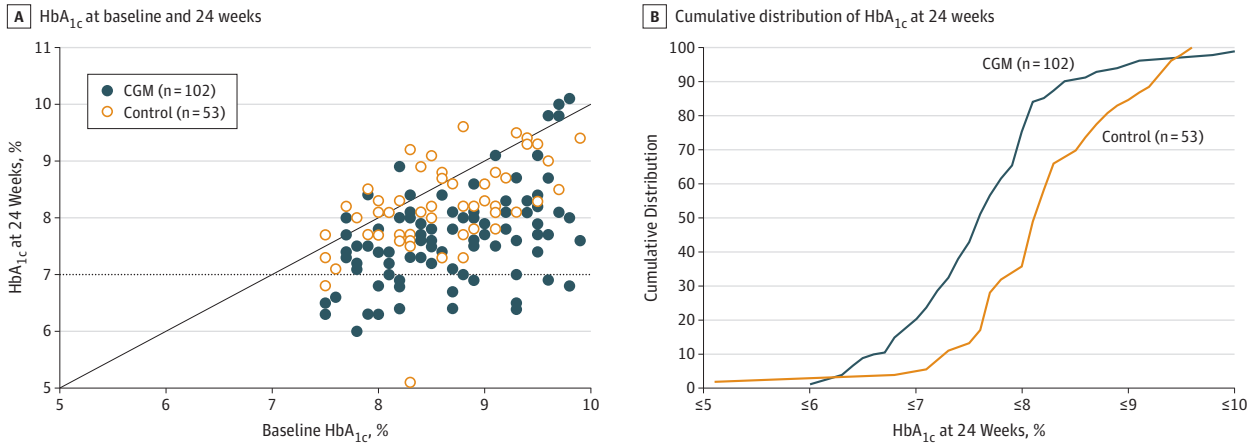
[a] Mean baseline HbA_{1c} level was 8.6% in each group. For all analyses, missing HbA_{1c} values in which the central laboratory value was missing but the local laboratory value was known were imputed with a regression line based on the site's local HbA_{1c} measurements (CGM/control: 1/0 at 12 weeks; 1/0 at 24 weeks).

[b] For the 24-week primary outcome only, the Rubin method was used to impute missing HbA_{1c} values when both the central and local laboratory values were missing (3 in the CGM group and 0 in the control group). For the secondary, exploratory, and post hoc analyses, n = 102.

[c] For the primary analysis, treatment group comparisons were made with analysis of covariance models, adjusted for baseline HbA_{1c} level and clinical site as a random effect. Model residuals were verified to have an approximate normal distribution.

[d] For the secondary, exploratory, and post hoc outcomes, treatment group comparisons were made with propensity scores, adjusted for baseline HbA_{1c} level and clinical site. $P < .01$ was considered significant to account for multiple comparisons (with 99% CIs accordingly provided).

Figure 2. Hemoglobin A_{1c} Values at Baseline and 24 Weeks, by Group



A, Scatterplot of 24-week hemoglobin A_{1c} (HbA_{1c}) levels by baseline HbA_{1c} level. The horizontal line at 7.0% represents the American Diabetes Association HbA_{1c} goal for adults with type 1 diabetes. Points below the diagonal line represent cases in which the 24-week HbA_{1c} level was lower than the baseline HbA_{1c} level, points above the diagonal line represent cases in which the 24-week HbA_{1c} level was higher than the baseline HbA_{1c} level, and points on the diagonal line represent cases in which the 24-week and baseline HbA_{1c} values were the same. B, Cumulative distribution of 24-week HbA_{1c} values. For any given 24-week HbA_{1c} level, the percentage of cases in each treatment group with an HbA_{1c} value at that level or lower can be determined from the figure. To convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percentage value × 10.93 and subtract 23.5 from the product.

participant are shown in **Figure 2**A, and the cumulative distribution of the 24-week HbA_{1c} values is shown in Figure 2B.

Secondary, Exploratory, and Post Hoc HbA_{1c} Outcomes

The greater HbA_{1c} improvement in the CGM group also was reflected in multiple participant-level secondary, exploratory, and post hoc HbA_{1c} outcomes (Table 2). There was no significant interaction of the effect of treatment on 24-week HbA_{1c} level according to baseline HbA_{1c}, age, education level, or type of site (eTable 4 in Supplement 2).

Secondary and Exploratory CGM Outcomes

As secondary outcomes, CGM metrics for time in the range of 70 to 180 mg/dL, hyperglycemia, hypoglycemia, and glycemic

Table 3. Continuous Glucose Monitoring Metrics

	Baseline		12 and 24 Weeks Pooled[a]			
	CGM Group (n = 105)	Control Group (n = 53)	CGM Group (n = 103)	Control Group (n = 53)	Mean Adjusted Difference (99% CI)[b]	*P* Value[b]
Hours of data, mean (SD)	322 (50)	325 (51)	301 (41)	301 (54)		
Prespecified secondary outcomes						
Glucose variability: coefficient of variation, mean (SD), %	42 (7)	42 (7)	38 (6)	42 (7)	−4 (−6 to −2)	<.001
Minutes per day in range 70-180 mg/dL, mean (SD)	660 (179)	650 (170)	736 (206)	650 (194)	77 (6 to 147)	.005
Hypoglycemia, median (IQR)						
Minutes per day <70 mg/dL	65 (33 to 103)	72 (35 to 136)	43 (27 to 69)	80 (36 to 111)		.002
Minutes per day <60 mg/dL	32 (15 to 61)	39 (15 to 78)	20 (9 to 30)	40 (16 to 68)		.002
Minutes per day <50 mg/dL	13 (5 to 29)	18 (4 to 39)	6 (2 to 12)	20 (4 to 42)		.001
Hyperglycemia, median (IQR)						
Minutes per day >180 mg/dL	687 (554 to 810)	725 (537 to 798)	638 (503 to 807)	740 (625 to 854)		.03
Minutes per day >250 mg/dL	301 (190 to 401)	269 (184 to 383)	223 (128 to 351)	347 (241 to 429)		<.001
Minutes per day >300 mg/dL	129 (66 to 201)	109 (71 to 204)	78 (36 to 142)	167 (89 to 226)		<.001
Prespecified exploratory outcome						
Mean glucose, mean (SD), mg/dL	187 (27)	186 (30)	180 (27)	189 (25)	−9 (−19 to 0)	.01
Post hoc outcomes, median (IQR)[c]						
Area above curve 70 mg/dL	0.5 (0.3 to 1.1)	0.7 (0.2 to 1.4)	0.3 (0.2 to 0.5)	0.7 (0.2 to 1.3)		<.001
Area under curve 180 mg/dL	34 (25 to 46)	33 (26 to 45)	27 (17 to 40)	40 (31 to 51)		<.001

Abbreviations: CGM, continuous glucose monitoring; IQR, interquartile range.

SI Conversion: to convert glucose to mmol/L, multiply the values × 0.0555.

[a] Excludes 2 participants in the CGM group with less than 72 hours of data (a prespecified condition).

[b] Treatment group comparisons made with analysis of covariance models, adjusted for the corresponding baseline value, baseline hemoglobin A_{1c} level, and clinical site as a random effect, using pooled data from 12 and 24 weeks. Because of skewed distributions for the hypoglycemia and hyperglycemia metrics (including area above the curve 70 mg/dL and area below the curve 180 mg/dL), these models were based on ranks using van der Waerden scores. $P < .01$ was considered significant to account for multiple comparisons (with 99% CI accordingly provided for the metrics that are approximately normally distributed).

[c] Area above (the glucose) curve 70 mg/dL reflects both percentage and severity of glucose values in the hypoglycemic range. Area under (the glucose) curve 180 mg/dL is the analogous measure for hyperglycemia.

variability favored the CGM group compared with the control group (**Table 3**, eTable 5 in Supplement 2). In exploratory analyses, hypoglycemia treatment group differences favored the CGM group during both daytime and nighttime, but hyperglycemia treatment group differences favoring the CGM group were present only during the daytime (eTables 6 and 7 in Supplement 2).

Other Analyses

At 24 weeks, in post hoc analyses there were no significant differences between the CGM group and control group in median change in total daily insulin dose per kilogram of body weight (-0.02 vs 0.03 U/kg; $P = .23$), median ratio of long-acting to rapid-acting daily insulin dose (0.9 vs 1.0; $P = .54$), proportion of participants with an increase in number of injections of rapid-acting insulin per day (26% vs 26%; $P = .90$), or mean change in body weight (1.7 vs 0.7 kg; mean difference, 1.0 kg; 99% CI, -0.7 to 2.8; $P = .12$) (eTable 8 in Supplement 2). Clarke Hypoglycemia Unawareness scores did not differ between groups (mean difference, -0.1; 99% CI, -0.7 to 0.5; $P = .64$).

Severe Hypoglycemia and Other Adverse Events

Severe hypoglycemic events occurred in 2 participants in each group ($P = .67$). There were no occurrences of diabetic ketoacidosis. Other serious adverse events, unrelated to the study intervention, occurred in 2 participants in the CGM group and none in the control group (eTable 9 in Supplement 2).

CGM Satisfaction

In the CGM group, satisfaction with use of CGM was high, as indicated by the mean (SD) score of 4.2 (0.4) on the CGM Satisfaction Survey, with mean (SD) scores of 4.2 (0.5) on the benefits subscale and 4.3 (0.5) on the subscale for lack of hassles (eTable 10 in Supplement 2).

Discussion

Among adults with type 1 diabetes using multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA_{1c} level during 24 weeks. The HbA_{1c} benefit in the CGM group was consistently present across the age range of 26 to 73 years, the baseline HbA_{1c} level range of 7.5% to 9.9%, and all education levels. In addition, CGM use was associated with a high degree of participant satisfaction with CGM, increased time with glucose concentrations between 70 and 180 mg/dL, decreased time with glucose concentrations less than 70 mg/dL, and decreased glycemic variability, measured with the coefficient

of variation. The trial was not designed to demonstrate a benefit in reducing clinical severe hypoglycemia events, and the low event rate in the control group precluded a meaningful analysis. However, less biochemical hypoglycemia, as was observed in the trial, has been associated with a lower risk for subsequent severe hypoglycemic events[14,15] and improved quality of life.[16-18]

The amount of CGM use by the participants was high (median CGM use 7 d/wk in month 6) despite a protocol approximating usual practice, with only 1 visit after week 4 and no visits or other protocol-specified contacts between 12 and 24 weeks. The amount of use was similar to or greater than the frequency of use in pump-using adults with type 1 diabetes in previous trials and observational studies,[2-5,19] which could be related to CGM accuracy being significantly improved from the generation of sensors in previous trials.[20-22] The observed benefits of CGM occurred despite the CGM group's having significantly less blood glucose meter testing per day than the control group.

The magnitude of benefit of CGM on HbA_{1c} levels relative to control in this trial of insulin injection users is comparable to the magnitude of benefit of CGM observed in pump users in previous randomized trials.[2,4,5] This finding was not a foregone conclusion. Insulin injection users have less flexibility in adjusting their insulin delivery in response to CGM glucose concentrations and trends than do pump users. Basal insulin delivery for pump users is continuous, can be programmed to vary at different times of the day, and can be temporarily changed in response to decreasing or increasing glucose concentrations or planned activities such as exercise. In contrast, injection users have fixed basal insulin based on the absorption of their long-acting insulin and can make adjustments only to rapid-acting insulin boluses.

The strengths of the trial included a high retention rate, high adherence to treatment group assignment, central laboratory measurement of HbA_{1c} level, a protocol approximating usual clinical practice, and participation in the trial by both community-based and academic sites. Assignment to the CGM and control groups could not be blinded because of the nature of the intervention; however, the groups had a similar number of visits. The 0.4% mean improvement in HbA_{1c} level in the control group likely reflects both a study effect related to clinical trial participation and more structured training in using blood glucose monitoring in adjusting insulin regimens than was occurring for these individuals before the study.

This study also had several limitations. In light of the eligibility criteria, the results may not apply to individuals with type 1 diabetes who are younger than 26 years or have HbA_{1c} levels outside the range of 7.5% to 9.9% and should not be applied to individuals with type 2 diabetes who receive multiple daily injections of insulin. The informed consent process and the run-in phase had the potential to exclude individuals who might be less adherent with CGM than the cohort that was studied.

Conclusions

Among adults with type 1 diabetes who use multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA_{1c} level during 24 weeks. Further research is needed to assess longer-term effectiveness, as well as clinical outcomes and adverse effects.

ARTICLE INFORMATION

Author Contributions: Dr Beck 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.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Beck, Riddlesworth.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Riddlesworth, Kollman.
Obtained funding: Price.
Administrative, technical, or material support: All authors.
Supervision: All authors.

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PROTOCOL

Multiple **D**aily **I**njections **a**nd Continuous Glucose **Mon**itoring in **D**iabetes: **DIaMonD Study**

Protocol Number:	PTL-901148
Study Sponsor:	**Dexcom, Inc.** 6340 Sequence Drive San Diego, CA 92121 Tel: (858) 200-0200 Fax: (858) 200-0201
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Version Date:	**20 May 2015**
Version Number:	**03**

CONFIDENTIAL

TABLE OF CONTENTS

1. ABBREVIATIONS AND DEFINITIONS i
2. INVESTIGATOR SIGNATURE SHEET iv
3. PROTOCOL SYNOPSIS v
4. INTRODUCTION 1
5. STUDY OBJECTIVES 3
6. PRIMARY ENDPOINTS 3
7. SECONDARY ENDPOINTS 3
8. STUDY POPULATION 4
9. STUDY ELIGIBILITY 4
9.1 Inclusion Criteria 4
9.2 Exclusion Criteria 4
10. STUDY DESIGN 5
10.1 Design Summary 5
11. PATIENT PARTICIPATION 7
12. STUDY DURATION 7
13. CLINICAL RESEARCH SITE(S) 7
14. OVERVIEW of STUDY DEVICES 7
14.1 Dexcom G4 Continuous Glucose Monitoring System (System) 7
14.2 Insulin Pump Overview 8
14.3 Blood Glucose Meter Overview 8
15. OVERVIEW OF PRO INSTRUMENTS 9
15.1 Patient Reported Outcome (PROs) Measures 9
16. DATA COLLECTION AND DATA MANAGEMENT 11
17. STATISTICAL ANALYSIS 11
17.1 Randomization 11
17.2 Data Analysis 11
17.3 Cost-effectiveness Analysis: 13
17.4 Sample Size Justification 13
18. STUDY PROCEDURES (Run-in Period) 14
18.1 Visit S1 –Screening, Consenting, and Blinded CGM Initiated (Time = 0-14) 14
18.2 Visit S2 – Week 1 – Blinded CGM Use (Time = 0- 7 days; Window ± 2 days) 15
18.3 Visit S3 – Week 2 - Run-In Completion, Subject Compliance Assessment, Randomization (Time = 0; Window ± 2 days) Note: 16
19. STUDY PROCEDURES (PHASE 1) 17
19.1 Visit 1 – Week 1 – CGM Troubleshooting - *CGM Group Only* (Window ± 2 days) 17
19.2 Phone Visits (Week 2 Phone & Week 3 Phone): Window ± 2 days) 18
19.3 Visit 2 – Week 4 – Follow-Up (Window ± 4 days) 18

19.4 Visit 3 – Week 11 – Blinded CGM - *SMBG Group only* (Window ± 5 days) 19
19.5 Visit 4 – Week 12 – (Month 3) – Mid Phase 1 Assessment (Window ± 1 days – SMBG; ± 7 days – CGM) 19
19.6 Visit 5 – Week 23 – Blinded CGM - *SMBG Group Only* (Window ± 5 days) 20
19.7 Visit 6 -- Week 24 (Month 6) – Phase 1 Final Assessments (Window ± 1 days – SMBG; ± 7 days – CGM) & Commencement of Phase 2 20
20. STUDY PROCEDURES (PHASE 2 – Follow-up Study) 21
20.1 Visit 1 - Week 26 – Follow-up – *CGM/CSII Group Only* (Window ± 4 days) 22
20.2 Visit 2 – Week 30 - Follow-Up (Window ± 4 days) 22
20.3 Visit 3 – Week 38 (Month 9) –Follow-Up (Window ± 7 days) 22
20.4 Visit 4 – Week 52 (Month 12) – Final Assessment (Window ± 7 days) 23
20.5 Device Replacements 24
21. RISKS 24
21.1 Sensor Insertion/Use/Removal 24
21.2 Hypoglycemia 24
21.3 Diabetic Ketoacidosis (DKA) 25
22. Non-Significant Risk Rationale 25
23. ADVERSE EVENTS 26
23.1 Adverse Event (AE) 26
23.2 Serious Adverse Event (SAE) 27
23.3 Severity of Adverse Events 27
23.4 Relationship of Adverse Event to the Study, Disease, or Device 27
23.5 Anticipated Adverse Device Effects 28
23.6 Unanticipated Adverse Device Effects 29
23.7 MDR Reportable Events/MDR Reporting 29
24. ETHICAL CONSIDERATIONS 29
24.1 Informed Consent 29
24.2 Institutional Review Board 30
25. DATA COLLECTION 30
26. DEVICE ACCOUNTABILITY 30
27. MONITORING 30
28. STUDY TERMINATION 31
29. INVESTIGATOR RESPONSIBILITIES 31
30. SPONSOR RESPONSIBILITIES 31
31. CONFIDENTIALITY OF RECORDS 32
32. REFERENCES 33
33. APPENDICES 35
Appendix A: Informed Consent 36
Appendix B: Overall Study Flowchart 37
Appendix C: Clinician Guidelines: General Diabetes Education 38

Appendix D: Clinician Guidelines for Follow-Up Visits 39
Appendix E: Visit Flowchart 40
Appendix F: Diabetes Management Guidelines Using CGM 41
Appendix G: Patient Reported Outcome (PRO) Measures 42
Appendix H: Test and Exam Table 43
Appendix I: Sample CGM Information Guide 44
Appendix J: OmniPod Guidance Documents 45

1. ABBREVIATIONS AND DEFINITIONS

A1C	Hemoglobin A1C (aka HbA1C)
AE	Adverse Event
BGM	**Blood Glucose Meter**
BLINDED CGM	Receiver does not display CGM values, trends, or glucose alerts/alarms in real time. Receiver provides use prompts and features such as calibration requests, device failures, troubleshooting icons, event markers, etc.
Carb counting	Carbohydrate counting, or "carb counting," is a meal planning technique for managing blood glucose. Carbohydrate counting helps to keep track of how much carbohydrate is consumed. A limit for a maximum amount of carbohydrate is set to maintain glucose levels within a targeted range.
CBC	Complete Blood Count
CF	Glucose Correction Factor; as known as insulin sensitivity factor
CGM	Continuous Glucose Monitoring
CMP	Complete Metabolic Panel
CRA	Clinical Research Associate
CRF	Case Report Form
CSII	Continuous Subcutaneous Insulin Infusion
CT	Computed Tomography
DCCT	Diabetes Control & Complications Trial
DKA	Diabetic Ketoacidosis (as defined by the DCCT) involves all of the following symptoms such as polyuria, polydipsia, nausea, or vomiting; serum ketones >1.5 mmol/L or large/moderate urine ketones; either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and treatment provided in a health care facility.
DM	Diabetes Mellitus
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate: a renal function test determined by a blood test for creatinine
EQ5D	EuroQol 5D PRO measure
HCP	Health Care Professional
Hypoglycemia, Severe	Reduced cognitive function, diaphoresis, tachycardia, coma and seizure. Hypoglycemia is deemed severe if the event required assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that the subject was unable to treat his or herself, was unable to

	verbalize his or her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma.
IAH	Impaired awareness of hypoglycemia
I:C	Insulin to carb ratio, used to determine dosing parameters
ICER	Incremental Cost Effectiveness Ratios
IFG	Impaired Fasting Glucose
IFU	Instructions for Use
IGT	Impaired Glucose Tolerance
IRB	Institutional Review Board
ITT	Intent to treat (analysis)
MDI	Multiple Daily Injections: Includes a minimum of 3 injections total: 2 injections a day of rapid acting human insulin or analog (an injection with each major meal) along with 1 daily basal insulin (NPH, detemir, or glargine).
MDR	Medical Device Reporting
mg/dL	milligrams per deciliter
MRI	Magnetic Resonance Imaging
PC	Personal computer, specifically using Intel hardware & MicroSoft software; not Apple computers
PDM	Personal Diabetes Manager: Insulet's insulin delivery programmer used with the OmniPod insulin pump.
Personal RT-CGM	Personal RT-CGM refers to frequent and continued use of CGM, owned by the user.
Professional RT-CGM	Professional CGM (real time or blinded) is defined as episodic use of CGM as provided by HCP and owned by physician's practice.
POC	Point of Care (Approved Guideline)
PP	Per Protocol (analysis)
PRO	Patient Reported Outcome
QALY	Quality-Adjusted Life-Years
QoL	Quality of Life
RCT	Randomized Controlled Trial
RT-CGM	Real-Time Continuous Glucose Monitoring System
SAE	Serious Adverse Event
SMBG	Self-Monitored Blood Glucose
SC	Study Coordinator
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus

UADE	Unanticipated Adverse Device Effect
VAS	Visual Analog Scale

2. INVESTIGATOR SIGNATURE SHEET

I have read the attached protocol and hereby agree that it contains all the necessary details for performing the study.

I will provide details of the protocol to all members of the study team responsible for conducting the study.

I will discuss the protocol with them to ensure that all participating staff members are fully informed regarding the study device and the conduct of the protocol.

Once the Institutional Review Board approves the protocol, I will not modify study procedures without obtaining prior approval of the Sponsor and, if required, of the Institutional Review Board (and FDA, as applicable).

I will submit any protocol and/or any informed consent modifications to the Sponsor and the Institutional Review Board (and FDA, as applicable) and approval will be obtained before any modifications are implemented.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

222 **3. PROTOCOL SYNOPSIS**

TITLE	Multiple **D**aily **I**njections **a**nd Continuous Glucose **Mon**itoring in **D**iabetes: **DIaMonD Study**
SPONSOR	Dexcom, Inc.
STUDY DEVICE	Dexcom G4® Continuous Glucose Monitoring System ("System")
STUDY DESIGN	Prospective, randomized, parallel arm, controlled trial with 2 phases
HYPOTHESIS	Addition of real time continuous glucose monitoring (RT-CGM) improves glycemic outcome in patients using multiple daily injections (MDI) and self-monitored blood glucose (SMBG), who are not at target A1C.
STUDY OBJECTIVES	1) To assess glycemic, health-economic, and quality of life (QoL) benefits of adding and using RT-CGM in MDI patients with Type 1 Diabetes Mellitus (T1DM) or Type 2 Diabetes Mellitus (T2DM), not at their A1C goal and relying on SMBG for diabetes-management decisions. 2) To assess the incremental benefits of changing the insulin delivery method from MDI to continuous subcutaneous insulin infusion (CSII) in patients with T1DM already using RT-CGM. Specific health economics objectives are to evaluate cost effectiveness and quality of life measures between the two groups. • For cost effectiveness: Evaluate within-trial cost-effectiveness attributable to the use of continuous glucose monitoring (CGM), as well as, the lifetime cost-effectiveness of the intervention attributable to the use of CGM. • For quality of life measures: Evaluate diabetes-related health states and measure health care utilization and economic consequences attributable to the CGM group compared to the SMBG group.
STUDY ENDPOINTS	**Primary Endpoint at Month 6:** Change in A1C from baseline to six months between groups. **Primary Endpoint at Month 12:** Change in %Time-in-Range as determined by CGM from month 6 between groups. **Secondary Endpoints** **Month 6 (within and between groups analyses)**: • Percent A1C ≤ 7% • %Time-in-Range • %Time-in-Hypoglycemia • %Time-in-Hyperglycemia • QoL changes • Cost effectiveness

	• Incidence of severe hypoglycemia • Change in hypoglycemia awareness • Changes in glucose variability • Change in SMBG frequency over time **Month 12** (within and between groups analyses) • Percent A1C ≤7% from month 6 • Change in A1C from month 6 to month 12 • %Time-in-Hypoglycemia • %Time-in-Hyperglycemia • Incidence of severe hypoglycemia • QoL changes • Cost effectiveness • Change in hypoglycemia awareness • Changes in glucose variability
SAMPLE SIZE	338 randomized (assuming a 15% drop rate in Phase 1) for 294 subjects to complete Phase 1: 147 for each diabetes cohort (T1DM and T2DM). Up to 169 subjects will be randomized per cohort, assuming a 15% drop-out rate in Phase 1. Up to 500 subjects may be enrolled to achieve randomization of 338 subjects.
STUDY CENTER	Up to 35 sites
ENVIRONMENT OF USE	Home Use
PATIENT POPULATION	Adults diagnosed with diabetes mellitus without optimized glycemic control, using MDI.
INCLUSION CRITERIA	Individuals may be **included** if they meet the following criteria: 1. Age 25 years or older 2. Diagnosis of T1DM or insulin-requiring T2DM 3. Followed regularly by a physician or diabetes educator for their diabetes management – with at least 2 office visits in last year as documented by clinical history 4. Using MDI for at least 12 months prior to study entry 5. Sub-optimal glycemic control, defined as persistent hyperglycemia, confirmed initially by historical or local (POC or site's lab) A1C of ≥7.7% to ≤10%, then followed with a confirmatory result by central lab of ≥7.5% to ≤10%. **NOTE**: Use of a historical local A1C test must be within 1 month of study entry. 6. Desire to lower A1C such as a goal of 7% 7. Stable control of diabetes, as determined per investigator assessment

	8. Stable diabetes medication regimen for 3 months prior to study entry 9. Stable weight maintained 3 months prior to study entry, per investigator's assessment, and not planning any structured weight reduction interventions such as prescription weight loss medications, bariatric surgery, or protein sparing modified fast during the course of the study 10. Willing to wear a device (CGM/pump) 11. Willing to avoid use of acetaminophen medications throughout the study 12. Currently performing SMBG management (by history): **Type 1** – an average of 3 or more times per day; and **Type 2** – an average of 2 or more times per day 13. Able to speak, read, and write English 14. **For Phase 2**, total daily insulin dose is <100 units
EXCLUSION CRITERIA	Individuals will be **excluded** for any of the following criteria: 1. Use of *personal* RT-CGM 3 months prior to study entry (professional CGM use is allowed, whether it was blinded or un-blinded) 2. Use of CSII 3 months prior to study entry (including patch pumps) 3. Plan to use personal CGM and/or pump during the course of the study 4. Addition of any new oral or injectable hypoglycemic agents (including GLP-1 analogues, Pramlintide, and SGLT-2 inhibitors – these agents are *only* for T2DM subjects) within 3 months prior to study entry. (Use of these agents does not affect eligibility if used 3 or more months prior to study entry.) For these medications, must be on a stable dose, and the GLP-1 medication will be maintained throughout the study. **Note**: These agents should not be added or modified during course of the study; if use of this class medication is planned, the patient is not eligible. 5. Use of pre-mixed insulin (e.g. 70/30 or 50/50) 6 months prior to study entry 6. Current or anticipated *acute* uses of glucocorticoids (oral, injectable, or IV), that will affect glycemic control and impact A1C – such as frequent steroid bursts required for inflammatory arthritis or inflammatory bowel disease, recurrent lumbar epidural steroid injections, etc. (Long-term stable glucocorticoid doses are allowed, such as when used for the treatment of rheumatoid arthritis or Addison's disease). 7. Pregnancy (as demonstrated by a positive test at study entry screening) or are planning to become pregnant during the study

	8. Medical conditions that, per investigator determination, make it inappropriate or unsafe to target an A1C of <7%, such as, but not limited to, recent cardio- or cerebro- vascular disease, malignancy, severe recurrent hypoglycemia, or cognitive decline 9. History of visual impairment which would hinder subject's participation in the study and perform all study procedures safely, as determined by investigator 10. History of psychiatric, psychological disorder, or psycho-social issues that could limit adherence to the required study tasks 11. Renal disease defined as estimated Glomerular Filtration Rate (eGFR) <45) 12. Extensive skin changes/disease that preclude wearing the sensor on normal skin (e.g. extensive psoriasis, recent burns or severe sunburn, extensive eczema, extensive scarring, extensive tattoos, dermatitis herpetiformis) 13. Known allergy to medical-grade adhesives 14. Current participation in another investigational study (must have completed any previous studies at least 30 days prior to being enrolled in this study) 15. Recent hospitalization or emergency room visit in the 6 months prior to screening resulting in a primary diagnosis of uncontrolled diabetes 16. Currently abusing illicit drugs, alcohol, or prescription drugs 17. Any condition per investigator assessment, that could impact reliability of the A1C measurement, such as (but not limited to) hemoglobinopathy, hemolytic anemia, chronic liver disease; chronic GI blood loss, recent red blood cell transfusion or erythropoietin administration within 3 months prior to screening
STUDY OVERVIEW	This is a prospective, randomized, parallel, controlled study to be conducted in two phases: **Phase 1- Comparing outcomes of diabetes management using RT-CGM vs. SMBG alone** **Phase 2- Comparing outcomes of insulin delivery via a pump vs. injections in RT-CGM users.** The DIaMonD study comprises a Run-in period and two randomization phases. Subjects must successfully complete the run-in period by demonstrating appropriate self-management and compliance with CGM and SMBG prior to being randomized. Prior to Phase 1, subjects will be asked to undergo a two week Run-in period, using blinded CGM, for the purpose of assessing if willing and able to use CGM in the study and to collect

	baseline glucose data. Eligible subjects will continue on to **Phase 1** and will be randomized to either use RT-CGM (Group 1- CGM) or to manage their diabetes based on use of SMBG (Group 2-SMBG). A1C levels will be obtained by central lab determination at baseline, 3, 6, 9, and 12 months with subjects and site blinded to central lab results. At six months, subjects in Group 1–CGM with T2DM and Group 2-SMBG, will complete their participation in the study. At six months, subjects with T1DM, in Group 1-CGM who have been using CGM regularly, are willing to continue RT-CGM, are using <100 units of insulin a day, and are willing to use an insulin pump, will proceed on to **Phase 2** and undergo a second randomization. Subjects will all use CGM and will either continue MDI (Group 1a-CGM/MDI) or change insulin delivery to CSII (Group 1b-CGM/CSII). All health utilization will be tracked via 2 mechanisms – self reporting (e.g., hospital visits, emergency services, home glucagon use, etc.) and clinic reporting (extra office visits, additional education, etc.). Patient reported outcome (PRO) measurements will be obtained at the beginning and end of each study phase.
STUDY VISIT OVERVIEW	**Run-in Period**: Eligible subjects will participate in a run-in period using blinded CGM for up to 3 weeks. The Run-in period comprises up to 4 clinic visits and concludes with an assessment of the subject's compliance to use study devices (including ability to self-deploy sensors) to continue on to Phase 1 or terminate from the study. During the Run-in, subjects will be trained on the study-assigned meter and CGM use in blinded mode. Baseline data and labs will be collected. All subjects will return to the clinic after the first sensor session for assessment and deployment of a second sensor for the second week of blinded CGM use. For subjects eligible to continue on to Phase 1, additional diabetes and device training will be provided, baseline clinical data will be collected, and baseline PRO instruments will be administered. Any subject who does not provide ample data from two sensor sessions due to device issues (i.e., adhesive or sensor failures) may extend the run-in period in order to collect the total required baseline data. **Phase 1**: Comprises up to 5 clinic visits over 6 months, depending on randomization group. Frequency of clinic visits for all subjects is at month 1, 3, and 6.

	Additional group-specific visits: Group 1-CGM subjects will have a follow-up clinic visit after the first week of un-blinded CGM use to trouble-shoot device issues Group 2-SMBG subjects will use blinded CGM for 1 week at months 3 and 6 to collect glycemic data During Phase 1 visits, subjects will: 1) be assessed for any AEs or device issues; 2) have their devices downloaded; 3) have their diabetes management decisions evaluated by clinicians with possible adjustments to the diabetes therapy; 4) complete PRO instruments and 5) have A1C levels drawn. Ad hoc visits may be conducted throughout the study as needed. Eligibility to continue on to Phase 2 will be determined upon completion of Phase 1. Subjects in Group 1-CGM who have T1DM, have regularly used CGM in month 6, and who are using <100 units of insulin a day are eligible to continue on to Phase 2 and undergo a second randomization. Subjects will be randomized to either remain on MDI therapy with CGM (Group 1a-CGM/MDI) or CSII therapy with CGM (Group 1b-CGM/CSII). **Phase 2**: Eligible subjects with T1DM will continue on study for an additional six months to evaluate the outcome of diabetes management delivering insulin via CSII vs. MDI in RT-CGM users. This phase comprises up to 4 clinic visits over 6 months, depending on secondary randomization group. Group 1b-CGM/CSII will have additional training and an additional follow-up visit to troubleshoot for any device issues. In addition, the insulin regimen will be modified as necessary. During Phase 2 visits, subjects will 1) be assessed for any AEs or device issues, 2) have their devices downloaded, 3) have their diabetes management decisions evaluated with possible adjustments to the diabetes therapy , 4) be asked to complete PRO instruments and 5) have A1C levels drawn. This phase and the study conclude upon review of final CGM data and completion of PRO measures.
PATIENT DURATION	Up to 15 months to allow for screening, follow-up, and scheduled visit windows.
STUDY DURATION	Total study duration is estimated at 2 years. Full recruitment is estimated at 9-12 months. Follow-up period is estimated at 13 months.

4. INTRODUCTION

Diabetes mellitus is a group of diseases characterized by abnormally high blood glucose levels. There are two major classifications of diabetes mellitus: Type 1 Diabetes Mellitus (T1DM), autoimmune destruction of the insulin producing pancreatic beta cells resulting in diminished or absent insulin secretion; and Type 2 Diabetes Mellitus (T2DM), resulting from constellation of defects including but not limited to impaired insulin action, decreased insulin production, and enhanced hepatic glucose production.[1] The Centers for Disease Control and Prevention reported that diabetes affects approximately 25.8 million people in the United States, or roughly 8.3% of the population, with approximately 1.9 million new cases being diagnosed each year. There are also 79 million people in the United States with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).[2] The global prevalence of diabetes in 2003 was 189 million and it is projected that 324 million people will have diabetes by the year 2025.[3]

Large-scale, randomized, prospective trials of various interventional therapies in patients with both T1DM and T2DM have clearly shown that improved glycemic control significantly reduces the development and progression of microvascular complications of diabetes in both adults and adolescents. The Diabetes Control and Complications Trial (DCCT) and the Kumamoto Trials showed that intensive treatment methods reduced the incidence of these complications by approximately 50 to 70%.[4, 5, 6] These studies have demonstrated that intensive monitoring and better control of blood glucose in people with T1DM and T2DM both delays the onset and reduces the progression of diabetic retinopathy, nephropathy, and neuropathy. However, the lower A1C in the intensively managed treatment arm came at the cost of nearly three-fold increase in the risk of severe hypoglycemia.

Subsequent studies have shown that performing as many as seven finger sticks per day was not sufficient to detect a number of severe hypoglycemic and hyperglycemic events.[7] A study by Bode et al. using a blinded continuous glucose monitoring system (CGM) found that even when patients performed capillary finger stick measurements as frequently as nine times per day, there were still, on average, approximately two hours per day of clinical hypoglycemia (<70 mg/dL) and seven hours per day of clinical hyperglycemia (>180 mg/dL).[8]

For the above reasons, as well as, to provide the direction and rate of glucose change to help guide diabetes management decisions, there has been interest in developing devices that measure glucose frequently, accurately, and automatically. All real-time CGM systems are adjunctive devices with user-configurable low and high glucose alerts. The Dexcom G4® PLATINUM CGM System (FDA approved) was deemed safe and effective for use in persons with diabetes 18 years of age and older. In addition, formative and summative usability studies were conducted on adults using the Dexcom G4™ PLATINUM CGM System. These studies validated the effectiveness of the training, labeling, and product design.

Two intensive insulin therapies exist for people with T1DM and insulin-requiring T2DM: multiple daily injections (MDI) and subcutaneous insulin infusion (CSII). In MDI therapy, insulin is administered via vial and syringe or insulin pen. In CSII, insulin is infused via a catheter inserted under the skin attached to an external pump. It is estimated that 80% percent of insulin used in the United States is administered by MDI therapy and that many people still have suboptimal glycemic control.

People with diabetes who treat using MDI therapy have challenges achieving target A1C levels for numerous reasons. It is known that increased frequency of self-monitoring of blood glucose (SMBG) levels is correlated with better A1C levels, however, for practical reasons, most patients only perform no more than four to five glucose measurements per day.

Consequently, postprandial hyperglycemia and nocturnal hyperglycemia often remain unnoticed, even in individuals with well-controlled diabetes (by A1C). Therefore, detecting and treating these events may improve the patient's glycemic control and have an impact on quality of life. [9]

The use of CGM has been studied as an adjunct to intensive insulin therapy with most studies performed in CSII using patients only. In other studies, there has been little to no distinction made between MDI and CSII use.[10-17]

Detailed below, are four studies which compared the response to CGM between study subjects using CSII and those using MDI; three studies were randomized clinical trials (RCTs), and one was a prospective-observational study.

In the JDRF study[11] in adults greater than 25 years old, 83% of subjects used CSII, 17% used MDI (9/52 in CGM arm, 7/56 in the control arm). The MDI CGM users reduced A1C −0.54 ± 0.85% vs. control MDI users raising A1C +0.04 ± 0.34%. In the CSII users, A1C reduced by −0.50 ± 0.51% vs. control CSII users raising their A1C +0.02 ± 0.47%.

In the Battelino hypoglycemia reduction study[12], 24% of subjects in the CGM group used MDI; whereas, in the control group, 41% used MDI. In this study, time spent hypoglycemic was greater in the MDI group compared to the pump group -59% vs. -41%, however, the A1C reduction was less A1C,-0.06% vs. -0.39%.

In the French Evadiac study[13], approximately half the participants used MDI. The average A1C reduction was less in the MDI users, -0.28% vs. -0.67% in those using CSII.

Finally, in the Garg prospective observational study[14], the reduction in hypoglycemia was greater in subjects using MDI, -30% vs. subjects using CSII -21%. However, whether the analysis was intent to treat (ITT) or per protocol (PP), MDI users had less reduction in the time spent hyperglycemic (ITT- 8.2 to 8.0 hours hyper/day in MDI users, 8.9-6.9 hours hyper/day in CSII users; PP- 8.8 to 8.6 hours hyper/day in MDI users, 8.4-6.8 hours hyper/day in CSII users).

There have been no prospective randomized controlled studies exploring the clinical benefits of CGM use solely in poorly-controlled MDI users compared with those who use SMBG as their glycemia monitoring tool. Therefore, this study will examine the potential benefit of adding CGM to patients with sub-optimal glycemic control using MDI therapy, and also the potential benefit of adding CSII therapy in patients randomized to CGM alone.

5. STUDY OBJECTIVES

The purpose of this study is to:

1) Assess glycemic, health-economic, and quality-of-life (QoL) benefits of adding and using RT-CGM in MDI patients with T1DM and T2DM not at their A1C goal and relying on SMBG for diabetes management decisions
2) Assess incremental benefits of changing the insulin delivery method from MDI to CSII in patients with T1DM already using RT-CGM who are not at their glycemic goals

Specific health economics objectives are to evaluate cost-effectiveness and quality-of-life measures between the two groups.

- **For cost effectiveness**: Evaluate within-trial cost-effectiveness attributable to use of CGM, as well as, the lifetime cost-effectiveness attributable to the use of CGM.
- **For quality-of-life measures**: Evaluate diabetes-related health states for patients and measure health care utilization and economic consequences attributable to the CGM group compared to the SMBG group.

6. PRIMARY ENDPOINTS

- **Primary endpoint at Month 6**: Change in A1C from baseline to six months between groups. A 0.4% or greater difference between Group 1-CGM and Group 2-SMBG is considered clinically significant.
- **Primary endpoint at Month 12**: Change in %Time-in-Range (defined as a glucose value of 70-180 mg/dL) as determined by CGM from Month 6 between groups.

7. SECONDARY ENDPOINTS

Month 6 (within and between group analyses) endpoints:

- Percent A1C $\leq$ 7%
- %Time-in-Range (70-180 mg/dL)
- %Time-in-Hypoglycemia
- %Time-in-Hyperglycemia
- QoL changes
- Cost effectiveness
- Incidence of severe hypoglycemia
- Change in hypoglycemia awareness
- Changes in glucose variability
- Change in SMBG frequency over time and impact on A1C

Month 12 (within and between group analyses) endpoints:

- Percent A1C $\leq$ 7% from month 6
- Change in A1C from month 6 to month 12
- % Time-in-Hypoglycemia
- %Time-in-Hyperglycemia
- Incidence of severe hypoglycemia
- QoL changes
- Cost Effectiveness
- Change in hypoglycemia awareness
- Changes in glucose variability

8. STUDY POPULATION

The study population comprises adults with T1DM and T2DM mellitus on MDI therapy in Phase 1, and adults with T1DM in Phase 2.

Determination of classification for diabetes will be based on American Diabetes Association Clinical Practice Guidelines, accounting for several patient characteristics such as age of onset, patient's weight or BMI, history of diabetic ketoacidosis, history of therapy management, and medical records, if available.

9. STUDY ELIGIBILITY

9.1 Inclusion Criteria

Individuals may be included if they meet the following criteria:

1. Age 25 years of age and older
2. Diagnosis of T1DM or insulin-requiring T2DM
3. Followed regularly by a physician or diabetes educator for their diabetes management – with at least 2 office visits in last year as documented by clinical history
4. Using MDI for at least 12 months prior to study entry
5. Sub-optimal glycemic control, defined as persistent hyperglycemia, confirmed initially by historical or local lab (POC or site's lab) A1C of ≥7.7% to ≤10%, then followed with a confirmatory result by central lab of ≥7.5% to ≤10%
   NOTE: Use of a historical local A1C test must be within 1 month of study entry.
6. Desire to lower A1C such as a goal of 7%
7. Stable control of diabetes, as determined per investigator assessment
8. Stable diabetes medication regimen for 3 months prior to study entry
9. Stable weight maintained 3 months prior to study entry, per investigator's assessment, and not planning any structured weight reduction interventions such as prescription weight loss medications, bariatric surgery, or protein sparing modified fast during the course of the study.
10. Willing to wear a device (CGM/pump)
11. Willing to avoid use of acetaminophen medications throughout the study
12. Currently performing SMBG management (by history):
    Type 1 – an average of 3 or more times per day; and
    Type 2 – an average of 2 or more times per day
13. Able to speak, read, and write English
14. **For Phase 2**, total daily insulin dose is <100 units

9.2 Exclusion Criteria

Individuals will be excluded for any of the following criteria:

1. Use of *personal* RT-CGM 3 months prior to study entry (professional CGM use, blinded or un-blinded, is acceptable)
2. Use of CSII 3 months prior to study entry (including patch pumps)
3. Plan to use personal CGM and/or pump during the course of the study
4. Addition of any new oral or injectable hypoglycemic agents (including GLP-1 analogues, Pramlintide, and SGLT-2 inhibitors – these agents are *only* for T2DM subjects) within 3 months prior to study entry. (Use of these agents does not affect eligibility if used 3 or more months prior to study entry.) For GLP-1 medications, must be on stable dose and the GLP-1 medication will be maintained throughout the study.

Note: These agents should not be added or modified during course of the study. If use of this class medication is planned, the patient is not eligible.

5. Use of pre-mixed insulin (e.g. 70/30 or 50/50) 6 months prior to study entry
6. Current or anticipated *acute* uses of glucocorticoids (oral, injectable, or IV), that will affect glycemic control and impact A1C – such as frequent steroid bursts required for inflammatory arthritis or inflammatory bowel disease, recurrent lumbar epidural steroid injections, etc. (Long-term stable glucocorticoid doses are allowed, such as when used for the treatment of rheumatoid arthritis or Addison's disease).
7. Pregnancy (as demonstrated by a positive test at study entry) at time of screening or are planning to become pregnant during the study
8. Medical conditions that, per investigator determination, make it *inappropriate or unsafe* to target an A1C of <7%. Conditions *may* include but are not limited to:
   - Unstable. recent cardiovascular disease,
   - Recent myocardial infarction
   - Significant heart failure
   - Ventricular rhythm disturbances
   - Recent transient ischemic attack, or cerebrovascular accident
   - Significant malignancy
   - Other conditions resulting in physical or cognitive decline
   - Recurrent severe hypoglycemia
9. History of visual impairment which would hinder subject's participation in the study and perform all study procedures safely, as determined by investigator
10. History of psychiatric, psychological disorder, or psycho-social issues that could limit adherence to the required study tasks
11. Renal disease defined as estimated Glomerular Filtration Rate eGFR <45
12. Extensive skin changes/disease that preclude wearing the sensor on normal skin (e.g. extensive psoriasis, recent burns or severe sunburn, extensive eczema, extensive scarring, extensive tattoos, dermatitis herpetiformis)
13. Known allergy to medical-grade adhesives
14. Current participation in another investigational study (must have completed any previous studies at least 30 days prior to being enrolled in this study)
15. Recent hospitalization or emergency room visit in the 6 months prior to screening resulting in a primary diagnosis of uncontrolled diabetes
16. Currently abusing illicit drugs, alcohol, or prescription drugs
17. Any condition, per investigator assessment, that could impact reliability of the A1C measurement, such as (but not limited to) hemoglobinopathy, hemolytic anemia, chronic liver disease; chronic GI blood loss, red blood cell transfusion or erythropoietin administration within 3 months prior to screening

10. STUDY DESIGN

10.1 Design Summary

Eligible persons will provide voluntary consent for enrollment into the study (see **Appendix A, Informed Consent**).

This is a prospective, randomized, parallel, controlled study that will be conducted in two phases:

Phase 1- Comparing outcomes of diabetes management using RT-CGM vs. SMBG alone

Phase 2- Comparing outcomes of insulin delivery via a pump vs. injections in RT-CGM users (see **Appendix B** Study Flowchart)

Following screening and a Run-in period of blinded CGM use, up to 338 subjects with diabetes mellitus, not at optimal glycemic control, using MDI, will be randomized. Two diabetes cohorts (T1DM and T2DM) will be randomized to be independently powered for change in A1C. Randomization in Phase 1 for the T1DM cohort will be performed using an unbalanced 2:1 randomization scheme resulting in two groups. **Group 1-CGM** uses CGM as part of their diabetes management, and will be twice as large as the SMBG group. **Group 2-SMBG** uses SMBG as per usual care.

Prior to Phase 1, all subjects will have a run-in period lasting up to 3 weeks in which they will use the Dexcom™ G4 PLATINUM System in blinded mode to establish compliance with CGM procedures, willingness to use CGM, and to collect baseline glucose data. Subjects who are willing and adherent will continue on to **Phase 1** and be randomized to either use RT-CGM (Group 1-CGM) or to manage their diabetes based on use of SMBG (Group 2-SMBG).

Assessment of subject's willingness to proceed in the study include:

1) Demonstrated ability to comprehend study procedures during the run-in phase, as evaluated by appropriate research staff

2) Willing to perform required sensor calibrations

3) Willing to wear the device(s) continuously throughout the study

Subjects in both arms will be provided basic diabetes education (**See Appendix C**: Clinician Guidelines: General Diabetes Education). Subjects randomized to Group 1-CGM will be instructed to use the CGM as an adjunct to their current diabetes management regimen to help guide diabetes-related decisions.

<u>Most of the study visits will be divided into two parts:</u>

1) **Part 1**: Perform study related tasks. These tasks can be performed by clinical coordinators, and include tasks such as collecting SAE info, drawing labs, and administering PRO surveys.
2) **Part 2**: Provide diabetes management. This will be provided by a clinician well-versed in MDI therapy, use of real-time CGM, and use of insulin pumps. The time for these discussions should generally reflect the typical time spent for diabetes management during a routine, follow-up physician visit. Guidelines for these discussions are included in **Appendix D,** Clinician Guidelines for Follow-Up Visits.

Additional visits and phone calls between the scheduled visits are allowed if required for device or diabetes management issues. Additional diabetes education, if needed per clinician assessment, is also acceptable in both Groups. Guidelines for follow-up are in Appendix D.

For Group 1-CGM, the CGM downloads will be reviewed with subjects and should be considered by clinicians to formulate their diabetes management recommendations.

For Group 2-SMBG, downloads will be reviewed with subjects if this is the standard practice of the site. The blinded CGM downloads will not be reviewed with the subjects and should not be used or considered by clinicians for diabetes management recommendations.

A1C levels will be obtained at baseline, 3, 6, 9, and 12 months with subjects and sites *blinded* to the central lab results.

Note: A1C testing conducted at the clinical site for clinical management will be obtained at 3, 6, 9, and 12 months by sites' POC A1C or local lab. These A1C results can be reviewed with the subjects as part of their routine visit care.

At the end of **Phase 1**, subjects with T2DM, subjects in Group 1-CGM using ≥100 units/day of insulin, and subjects in Group 2-SMBG will complete their participation in the study.

Those in Group 1-CGM who have T1DM, have used CGM on 21 of the last 28 days, and are using <100 units/day of insulin are eligible to continue on to **Phase 2** and undergo a second randomization.

During **Phase 2**, all subjects will use CGM and will either continue MDI therapy (Group 1a-CGM/MDI) or change insulin delivery to CSII (Group 1b-CGM/CSII). **Appendix E, Visit Flowchart,** provides a graphical illustration of the visits time points.

Throughout the course of the study, subjects using CGM will be encouraged to follow diabetes management guidelines **(Appendix F, Diabetes Management Guidelines Using CGM).**

All health utilization will be will be tracked via 2 mechanisms:

1. Self-reporting using PRO - Health Service Utilization Form, (e.g. hospital visits, emergency services, home glucagon use, etc.) and
2. Clinic reporting using the Care Management Form (extra office visits, additional education, etc.).

Patient reported outcome (PRO) measurements will be obtained at the beginning and end of each study phase (see **Appendix G, PRO Measures, for list of the PRO instruments)**.

All tests and exams required for the study are listed in **Appendix H, Test & Exam Table.**

11. PATIENT PARTICIPATION

Up to 15 months to allow for screening, follow-up, and scheduled visit windows.

12. STUDY DURATION

Total study duration estimated at 2 years.

Recruitment estimated at 9-12 months.

Follow-up period estimated at 13 months.

13. CLINICAL RESEARCH SITE(S)

This study will be conducted at up to 35 sites.

Investigational centers will be selected across the United States. Selection is based on each Investigator's experience and qualifications, availability of sufficient resources to carry out the required study procedures and the investigator's ability to recruit subjects into the study. Enrollment will be competitive.

14. OVERVIEW of STUDY DEVICES

14.1 Dexcom G4 Continuous Glucose Monitoring System (System)

The Dexcom G4 PLATINUM CGM System is intended for single-patient use. The System was FDA-approved with Software 505 in October 2014 (PMA# P120005/S018).

The System continuously tracks and reports glucose values and trending information for people with diabetes mellitus. The System is designed to provide continuous measurements of glucose concentrations over a 40-400 mg/dL range.

As part of the System's instructions for use, users are informed of the following:

- System does not replace blood glucose measurements
- Blood glucose values may differ from sensor glucose readings and the value from the blood glucose meter should be used for treatment decisions, such as how much insulin to take. The direction, rate of glucose change, and trend graph on the system provide additional information to help with these decisions
- Symptoms of high and low glucose should not be ignored. If sensor readings do not fit with symptoms, blood glucose should be measured with a blood glucose meter
- If at any time during use a subject requires a magnetic resonance imaging (MRI) scan, computed tomography (CT) scan or diathermy treatment, the subject is advised to discontinue current sensor session prior to the test/treatment, and then replace with a new sensor after completion of the test/procedure
- The device is not approved for use in pregnancy and study participation will be terminated if a subject becomes pregnant

14.1.1 Dexcom CGM Software

A currently-marketed/FDA-approved Dexcom CGM computer software program will be used to transfer glucose data stored in the receiver to a site's computer system, as per their standard practice. This software may be used in two places:

1. At home, if subjects choose to use the reports and have a personal computer (PC)
2. At the site, for downloading devices for Group 1-CGM to be used for diabetes management purposes

14.2 Insulin Pump Overview

The insulin pump to be used in this study is the OmniPod, manufactured by Insulet Corporation. The OmniPod is a wireless, waterproof, insulin pump consisting of two parts:

- Wearable Pod
- Personal Diabetes Manager (PDM) with a built-in Abbott Freestyle Glucose Meter

Contained within the Pod is an insulin reservoir, angled infusion set, automated inserter, pumping mechanism and power supply. The OmniPod can hold up to 200 units of insulin; it requires a minimum of 85 units of insulin to begin operation. Depending on insulin usage, the OmniPod can be used 48-72 hours.

Subjects who are randomized to add an insulin pump in **Phase 2** will be trained on proper insertion and use. Software used in conjunction with the OmniPod system will be utilized for downloading data at the sites.

14.3 Blood Glucose Meter Overview

Subjects will use the Bayer Contour Next USB meter to record their blood glucose values throughout Phase 1 of the study. During Phase 2, subjects randomized to the OmniPod will receive test strips compatible with the Abbott Freestyle, as this meter is part of the OmniPod PDM. All other CGM subjects in Phase 2 will continue to use strips for the Bayer Contour Next USB. Appropriate blood glucose test strips will be provided to subjects throughout their participation in the study, based on quantities routinely used by the subjects. Software used in conjunction with Bayer Contour Next USB will be utilized for downloading data at the sites.

15. OVERVIEW OF PRO INSTRUMENTS

15.1 Patient Reported Outcome (PROs) Measures

15.1.1 **PRO measures** will be administered at Baseline, 6 and 12 months. PROs will assess QoL dimensions – health state, psychological well-being, diabetes management, and interaction with CGM. PROs will also assess treatment satisfaction and behavioral changes throughout the study, as well as capturing health economic benefits. (See **Appendix G: Patient Reported Outcome (PRO) Measures**).

The following PROs will be utilized (all PROs will be captured in electronic data capture, except EQ-5D-5L, which is paper based):

15.1.2 **WHO-5 Well-Being Index**[18] – This is a validated, 5-question scale, utilized to assess general outlook and overall well-being. This scale also examines aspects other than just the absence of depressive symptoms. Administration time is approximately 5 minutes.

15.1.3 EuroQol (EQ-5D)[19] – An EQ-5D health state (or profile) is a set of observations about a person defined by the descriptive system. An EQ-5D health state may be converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. This formula is based on the valuation of EQ-5D health states from general population samples. The EQ-5D-5L consists of a descriptive system and a visual analogue scale (VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. Time to completion is approximately 5-10 minutes.

15.1.4 Health Service Utilization Form –
This form captures the frequency of Emergency Room visits, calls to 911, after-hours/urgent care visits, hospital visits, the number of visits to their health care provider/physician/nurse practitioner office visit**s**, **as well as** visits to dieticians. This form captures these visits whether diabetes-related or not. Additionally, this form captures self-care time and work/work capability status in relation to their diabetes needs. Time to completion is approximately 10 minutes.

15.1.5 Diabetes Distress Scale (DDS)[20] – This scale lists 17 potential problem areas that people with diabetes may experience, and can denote the degree to which they are or are not affected. Administration time is approximately 10 minutes.

15.1.6 Hypoglycemic Fear Survey, Worry Subscale (HFS-W)[21] – This validated survey consists of 18 questions which measure several dimensions of anxiety and fear surrounding hypoglycemia among adults with diabetes. Administration time is approximately 10 minutes.

15.1.7 Hypoglycemia Confidence[22] – This scale addresses how confident people with diabetes are to stay safe and avoid serious problems related to hypoglycemia. This scale consists of 9 questions, with an approximate administration time of 5 minutes.

15.1.8 Bolus Insulin Questionnaire[23] – This scale consists of 8 questions, which asks people with diabetes to look back at the past week to assess their usage of fast-acting insulin over breakfast, lunch, dinner, and snacks; also looks at the ease or difficulty of calculating correct doses. Administration time is approximately 5 minutes.

15.1.9 Diabetes Numeracy Test (DNT5)[24] – The Diabetes Numeracy Test is a validated tool that consists of 5 questions. This is an actual test to determine how accurately a person with diabetes can calculate commonly ingested carbohydrates. Approximate administration time is 10 minutes.

15.1.10 Clarke Hypoglycemia Scale[25] – A validated tool that uses 8 questions to assess awareness of hypoglycemia in adults. A score of 1 or 2 is classified as aware; a score of 3 or more is classified as impaired awareness of hypoglycemia (IAH). Approximate administration time is 10 minutes.

15.1.11 CGM Expectations Questionnaire[26]: This questionnaire consists of 5 questions and looks at potential expectations people with diabetes may have prior to using CGM. Administration time is approximately 5 minutes.

15.1.12 CGM Attitudes[27]: This questionnaire consists of 7 questions which will examine how a person feels about using CGM, based on accuracy, convenience, ease-of-use, general performance, as well as their trust and confidence in the device. Approximate time is 5 minutes.

15.1.13 CGM Satisfaction[28]: The CGM Satisfaction scale is a validated tool which consists of 44 questions which assesses satisfaction regarding various aspects of CGM use. Administration time is approximately 10 minutes.

Prior to randomization, the baseline PROs will be administered to all subjects as follows:

15.1.14 Baseline PROs (Visit S3):

1. WHO-5 Well-Being Index
2. EQ-5D-5L
3. Health Service Utilization Form
4. Diabetes Distress Scale (DDS)
5. Hypoglycemic Fear Survey, Worry Subscale (HFS-W)
6. Hypoglycemia Confidence
7. Bolus Insulin Questionnaire
8. Diabetes Numeracy Test (DNT5)
9. Clarke Hypoglycemia Scale
10. CGM Expectations Questionnaire

15.1.15 Month 6 PROs:

1. WHO-5
2. EQ-5D-5L
3. Health Service Utilization Form
4. Diabetes Distress Scale (DDS)
5. Hypoglycemic Fear Survey, Worry Subscale (HFS-W)
6. Hypoglycemia Confidence
7. Bolus Insulin Questionnaire
8. Clarke Hypoglycemia Scale
9. CGM Attitudes*

10. CGM Satisfaction*

**Only administered to CGM Group*

15.1.16 Month 12 PROs*:*

1. WHO-5
2. EQ-5D-5L
3. Health Service Utilization Form
4. Diabetes Distress Scale (DDS)
5. Hypoglycemic Fear Survey, Worry Subscale (HFS-W)
6. Hypoglycemia Confidence
7. Bolus Insulin Questionnaire
8. Clarke Hypoglycemia Scale
9. CGM Satisfaction Scale
10. CGM Attitudes

16. DATA COLLECTION AND DATA MANAGEMENT

Data collected during this study will be documented on electronic case report forms (e-CRFs). The Investigator or designee is responsible for completing the Case Report Forms (CRFs). The EDC system will be validated prior to study commencement. Sites will be trained on use of the EDC system by sponsor or designee. Good Documentation Practices principles will be required. Subjects who fail the Run-In Phase will not undergo randomization and thus will be withdrawn from the study, with documentation provided on a termination CRF.

A database system, Part 11 compliant, will be created using Jaeb Center's custom built electronic data capture system for data entry and verification of the data inputted by site personnel.

17. STATISTICAL ANALYSIS

As this is an intent-to- treat (ITT) study, analysis will be conducted on all subjects enrolled at Months 6 and 12. A second analysis will also be conducted at Months 6 and 12 on the sub-group of compliant subjects, using an *a priori* definition for subject compliance to CGM. Compliance is defined as use of CGM on average a minimum of 6 days during a 7-day wear period (at least 85% of the days).

17.1 Randomization

For Phase 1, the two diabetes cohorts (T1DM and T2DM) will undergo randomization separately between Group 1-CGM and Group 2-SMBG and will be stratified by A1C result (<8.5% and ≥ 8.5%). Randomization will be performed using a 2:1 randomization scheme for the T1DM cohort and a 1:1 randomization scheme will be used for the T2DM cohort.

A combination of permuted blocks randomization and stratified randomization will be used. A SAS program will be written to generate the randomization schedule. For Phase 2, randomization will be stratified between Group 1a-CGM/MDI and Group 1b-CGM/CSII to ensure equal distribution for subjects with A1C result ≤ 7%, >7% to <7.5% and ≥7.5%.

17.2 Data Analysis

For **Phase 1**, the primary endpoint for this study is change in A1C from baseline to six months between groups. This will be evaluated in the total population and in the T1DM and T2DM cohorts.

The study hypothesis is:

H_o = A1C $_{delta}$ between Group 1-CGM and Group 2-SMBG = 0

H_1 = A1C $_{delta}$ between Group 1-CGM and Group 2-SMBG ≠ 0

It is anticipated that subjects with T1DM or T2DM who are sub-optimally controlled will show an improvement in glycemic control with the use of RT-CGM in Group 1-CGM, over and above any improvement in subjects using SMBG in Group 2-SMBG. Improvement in glycemic control will be based on the evaluation of the A1C from baseline to 6 months. The magnitude of the change will be compared between the Group 1-CGM to Group 2-SMBG, using repeated measure of mean variance analysis.

For **Phase 2**, the primary endpoint is change in %Time-in-range (70 to 180 mg/dl) as determined by CGM from month 6 between groups.

Secondary analyses will involve descriptive comparisons and specific health economics modeling of the following at month 6 and 12 (unless otherwise stated), as applicable:

Month 6 (within and between group analyses) endpoints:

- Percent A1C ≤7%
- %Time-in-Range (70 to 180 mg/dL)
- %Time-in-Hypoglycemia
- %Time-in-Hyperglycemia
- QoL changes
- Cost effectiveness
- Incidence of severe hypoglycemia
- Change in hypoglycemia awareness
- Changes in glucose variability
- Change in SMBG frequency over time

Month 12 (within and between group analyses) endpoints:

- Percent A1C ≤ 7% from month 6
- Change in A1C from month 6 to month 12
- %Time-in-Hypoglycemia
- %Time-in-Hyperglycemia
- Incidence of severe hypoglycemia
- QoL Changes
- Change in hypoglycemia awareness
- Changes in glucose variability

Data analysis will be conducted at the completion of the data collection period for all subjects.

Baseline demographic factors will be summarized. For continuous variables, such as age, the mean, standard deviation, median, and range will be presented. For categorical variables, such as gender, the proportion of subjects in each category will be presented.

Summary statistics will include the mean, standard deviation, median, and range. 95% confidence level will be used, when applicable.

Changes in continuous parameters (e.g. A1C, SMBG measurements per day, glucose distribution) from baseline to follow-up will be analyzed using repeated measures ANOVA, adjusted for the baseline value and the variables by which the randomization was stratified. Chi-squared tests or Fisher's Exact test will be used to analyze categorical data. All null hypotheses will be tested against two-sided alternatives at the 5% significance level.

Event analysis will be conducted by comparing results experienced by SMBG arm to CGM arm. Any device-related adverse events (AEs) will be tabulated and reported.

Missing data will be handled as follows:

For HbA1c data, if the laboratory value is unavailable then the XX value will be used. If neither measurement is available then the value will be imputed based on available previous lab and/or XX HbA1c measurements using Rubin's method.

For CGM data, analyses will include all data available during the randomized trial. Therefore, there will not be imputation for missing data.

Final analysis of results will be generated using SAS software 9.2 or higher.

17.3 Cost-effectiveness Analysis**:**

In addition to the data analysis focused on clinical outcomes there will also be a companion analysis of the economic impact and cost effectiveness of the intervention. The cost-effectiveness analysis will be detailed in a separate document and is summarized below.

The analyses will address the following objectives:

- To collect utilities for diabetes-related health states for patients and to measure health care utilization and economic consequences attributable to the Group 1-CGM compared to Group 2- SMBG
- To evaluate the within-trial cost-effectiveness of the intervention provided to Group 1-CGM group compared to Group 2-SMBG
- To estimate the lifetime cost-effectiveness of CGM use utilizing a Monte Carlo– based Markov simulation model to project the course of the natural history of the disease and the associated spending in both the Group 1-CGM and Group 2-SMBG

For all analyses, the effectiveness parameter will be expressed in terms of quality-adjusted life-years (QALY) and incremental cost effectiveness ratios (ICER). Cost accounting will vary according to the time-frame and perspective of the analysis. The within-trial health system perspective will include all the direct costs associated with the program and all direct and indirect medical costs accrued by the subjects during the course of the trial. On the other hand, the societal perspective for the within-trial analysis will also account for the time costs subjects enrolled in the study.

For the lifetime analysis, investigators will use the Huang, O'Grady and Basu model that was used in the JDRF CGM trial. The model will be modified to incorporate recent changes in our understanding of the impact of glucose control on the development of complications, as well as spending associated with the treatment of diabetes and its complications.

Data to be collected from study subjects at baseline and during the study will include utilities information for current health, complication related to health states, treatment-related experiences, medical care utilization and spending, household income, employment, and caregiver time.

Utilities can be directly elicited using three standard methods: the time trade-off (TTO), standard gamble (SG), and rating scale (RS) or visual-analog scale (VAS). TTO is the most commonly used for both its ease of understanding and ease of administration. However, it also has drawn some concern because it asks patients if they would be willing to trade off time at the end of their lives to be disease free.

Further details will be provided in the detailed Statistical Analysis Plan.

17.4 Sample Size Justification

Phase 1 will be 90% powered to show a difference if the true population value is a difference of 0.4% between the two groups in Phase 1, using a SD of 0.7.

Phase 2 there will be 80% power to show a difference if the true population value is a difference of 7.5% in Time-in-Range between groups, assuming a standard deviation of 8.0% and a minimum of 50 participants entering and completing phase 2.

A maximum of 338 subjects will be randomized. A sample size of 147 for each diabetes cohort (total n=294) will allow for both study phases and cohorts to be powered to 90%. Assuming a 15% drop-rate a total of 169 subjects for each diabetes cohort is required in Phase 1 (T1DM cohort: 113 subjects in Group 1-CGM, and 56 subjects in Group 2-SMBG; T2DM cohort: 85 in Group1-CGM and 85 in Group 2-SMBG). To achieve randomization sample size, up to 500 subjects may be enrolled into the Run-in phase of the study.

A 2:1 CGM: SMBG unbalanced randomization scheme will be used in Phase 1 for the T1DM cohort to ensure that an adequate sample size for Group 1a (CGM/MDI) and Group 1b (CGM/CSII) will be available to enter Phase 2.

18. STUDY PROCEDURES (Run-in Period)

18.1 Visit S1 –Screening, Consenting, and Blinded CGM Initiated (Time = 0-14)

Potential subjects will be asked to voluntarily provide consent by signing an IRB-approved informed consent document (**Appendix A: Informed Consent**). The investigator or designee will explain the nature, purpose, expected duration, and risks associated with study participation. Potential subjects will have the opportunity to ask questions and receive answers from study staff. All subjects will be provided a copy of the signed informed consent document.

Subjects who have indicated willingness to participate by signing the informed consent document and who meet the inclusion and exclusion criteria are eligible to participate in the study. Subjects in each diabetes cohort (T1DM and T2DM) will be given different informed consent documents to reflect that Phase 2 of the study is only applicable to subjects having T1DM.

All subjects will be **considered enrolled** in the screening phase of the study once subjects' sign the informed consent. Regarding study entry A1C confirmation, if the most recent historical A1C is outside the 1 month window from study entry sites will need to draw a POC or local lab A1C for eligibility confirmation ***(Sites that do not have a POC or on-site lab, may split this visit.)***

Eligible subjects who sign the informed consent document will have the following tests/exams, devices and training provided during this visit:

- Screening A1C (POC or local lab), *confirm* ≥7.7% and ≤10% (POC or local lab results may be historical if results available 1 month prior to consent date.) **If yes, then continue collection of remaining visit labs and data.**
- Pregnancy test (urine) will be completed for women of childbearing potential (test conducted within 72 hours of sensor insertion).
- Labs:
  - Central Lab –
    - A1C; **Note**: via a method approved by the National Glycohemoglobin Standardization Program (NGSP)[29]
  - Local Labs –
    - Complete Metabolic Panel (CMP) which includes liver and kidney function fasting or non-fasting (if obtained within 3 months, may use historical)
    - C-peptide, fasting or non-fasting (may use historical if obtained within the last 6 months)
    - CBC (if obtained within 3 months may use historical)

- Total cholesterol, fasting or non-fasting (if obtained within the last 12 months may use historical)
- Vital Signs
- Basic demographic information
- Height & Weight (for BMI)
- Download current blood glucose meter(s) (if possible) to assess baseline SMBG frequency. If the meter(s) is not available, it can be brought to the next visit.
- Study-assigned blood glucose meter, strips, and training as needed
- Initial CGM training/core tasks:
  - Insertion steps
  - Calibration
  - Troubleshooting
- Blinded CGM insertion and initial calibration (CGM receiver blinded using SweetSpot. Ensure receiver is blinded – receiver screen will read "Display Off" if properly blinded.)
- Home use instructions, such as CGM basic troubleshooting

Subjects will be provided a blood glucose meter and test strips to use for all SMBG testing. Test strips will be allocated at each study visit. Instruction on blood glucose meter use will be provided.

Subjects will be advised that MRIs, diathermy, and CT scans are not compatible with the CGM sensor. In the event a subject needs to have an MRI or CT scan during course of the study, their current sensor will to be discontinued prior to any of these tests per the IFU.

18.2 Visit S2 – Week 1 – Blinded CGM Use (Time = 0- 7 days; Window ± 2 days)

All subjects return after one week of initiation of the blinded-CGM wear to identify any challenges with wearing or using the CGM device. Subjects will be guided how to self-deploy a second device for a second week of data collection, or if preferred by the subject, study staff may deploy at this visit.

Study staff will-

- Obtain CGM and Blood Glucose Meter (BGM) data, per usual practice
- Assess any AEs or device issues
- Upload devices to SweetSpot, and assess CGM and BGM compliance using the utilization reports. Subjects will be terminated if non-compliant. The investigator and team will assess subject's eligibility to continue in the study based on adherence to CGM and study procedures. Compliance definition for continuing on in the study is established as:
  - CGM Adherent - 85% of days with wearing CGM sensor , carrying the receiver AND calibrating 2 times/ calendar day (approximating the 12-hour calibration scheme)
  - SMBG Adherent - Minimum of 3 or more fingersticks daily for BG monitoring (inclusive of calibration measurements) for **Type 1**; minimum of 2 or more fingersticks daily for BG monitoring (inclusive of calibration measurements) for **Type 2**
  - Medications: Avoidance of acetaminophen-containing medications
- Inform subject that they must be able to self-deploy sensor by Screening Visit 3 (required if randomized to CGM group).

18.3 Visit S3 – Week 2 - Run-In Completion, Subject Compliance Assessment, & Randomization (Time = 0; Window ± 2 days)

Study staff will -

- Upload meter and CGM data to SweetSpot

  Note: In the event the subject was unable to collect a minimum of 12 days of CGM data during the 2 weeks of baseline blinded CGM data *due to device issues, not compliance issues* (i.e., adhesive or sensor failures) they may have their Run-in period extended for 1 additional week in order to collect this baseline data. This extension would be at the discretion of the investigator.

- Assess any AEs or device issues that may have occurred since the last study visit
- Assess compliance using SweetSpot utilization report. Subjects will be terminated if non-compliant. The investigator and team will assess subject's eligibility to continue in the study based on adherence to CGM and study procedures. Compliance definition for continuing on in the study is established as:
  - CGM Adherent - 85% of days (e.g. 12 out of 14 days in a 2 week period). Includes wearing CGM sensor ,carrying the receiver AND calibrating 2 times/calendar day (approximating the 12-hour calibration scheme)
  - SMBG Adherent - Minimum of 3 or more fingersticks daily for BG monitoring (inclusive of calibration measurements) for **Type 1**; minimum of 2 or more fingersticks daily for BG monitoring (inclusive of calibration measurements) for **Type 2**
  - Medications: Avoidance of acetaminophen-containing medications
- Assess subject's ability to self-deploy sensor (required if randomized to CGM group)
- Subjects are eligible to continue in the study if:
  - Willing and compliant with CGM and BGM during the Run-in period
  - Central lab A1C result is confirmed within eligibility range: ≥7.5% to ≤10% Note: site is blinded to actual central lab result; however, site will be notified whether subject's central lab was *within range* for study eligibility.
- Obtain concomitant medications (not vitamins/minerals) including dose and frequency, and if subject takes as needed (p.r.n.). Assess for addition or modification of any GLP-1 agonists, pramlintide, and SGLT-2 inhibitors.
- If these medications are added *prior to randomization*, the subjects will be withdrawn from the study. Administer baseline PROs to all eligible subjects:

  1. WHO-5 Well-Being Index
  2. EQ-5D-5L
  3. Health Service Utilization Form
  4. Diabetes Distress Scale (DDS)
  5. Hypoglycemic Fear Survey, Worry Subscale (HFS-W
  6. Hypoglycemia Confidence
  7. Bolus Insulin Questionnaire
  8. Diabetes Numeracy Test (DNT5)
  9. Clarke Hypoglycemia Scale
  10. CGM Expectations Questionnaire

- **Randomize** per EDC procedures on the study website:
  - RT-CGM (Group 1-CGM)

- SMBG (Group 2-SMBG)

- Retrieve CGM Systems from subjects randomized to Group 2-SMBG and maintain systems with proper identification for future study use with same subject
- Un-blind CGM receiver for subjects in Group 1-CGM
    - Train RT-CGM group on the use of the Dexcom G4 System in real-time mode, which includes:
        - Sensor insertion
        - CGM calibration
        - Focused instruction about alerts
        - Using the direction and rate of glucose change for diabetes management
        - Troubleshooting
        - Provide and review the "**Diabetes Management Guidelines Using CGM**" (**Appendix F**)
- Obtain abbreviated medical and diabetes history
- Schedule or provide general diabetes self-management education with clinician (see **Appendix C, Clinician Guidelines: General Diabetes Education**)
- Establish and review glucose targets with each subject (clinician)
- Inform each subject's treating physician and/or primary care physician regarding their patient's involvement in the study
- Set initial alerts settings for subjects in the CGM group (clinician)
- Download CGM and Blood Glucose Meter (BGM) data, per usual practice for diabetes management (clinician)

19. STUDY PROCEDURES (PHASE 1)

19.1 Visit 1 – Week 1 – CGM Troubleshooting - *CGM Group Only* (Window ± 2 days)

This visit is scheduled one week after randomization to perform the following:

- Upload meter and CGM data to SweetSpot
- Modify subject's CGM alerts based on their experience (clinician)
- Assess for any AEs or device issues
- Subject will deploy a new CGM sensor, or staff will guide subject to deploy a new CGM sensor (if the subject is unable to deploy on their own)
- Provide each subject with additional sensors to deploy at home until they return for *Week 4* visit
- Teach and encourage subjects with home PCs to download their CGM devices (clinician)

- Dispense test strips
- Provide and review the "**Diabetes Management Guidelines Using CGM**" (**Appendix F**) (clinician)
- Download and review CGM with subjects to assess calibration, reinforce the need to calibrate, and for diabetes management (clinician)

Study staff will train subjects who are willing and able to download CGM data on Dexcom CGM software. From here, subjects can view their glucose trends which will give them their personal data for review. If desired, subjects may send their data via email (PDF) or print their results to share with their clinician.

Ad hoc follow-up phone calls and/or visits may be performed to address any questions on CGM use from the subject.

19.2 Phone Visits (Week 2 Phone & Week 3 Phone): Window ± 2 days)

All subjects will receive a follow-up phone call at Week 2 and Week 3 to assess their overall feedback, ability to deploy sensors and set-up system (for those in the CGM group), and to answer any questions the subject may have.

Glucose data may be reviewed (if the subject is able to download at home) and therapy adjusted.

Ad hoc visits may be added as needed, that may include device downloads.

19.3 Visit 2 – Week 4 – Follow-Up (Window ± 4 days)

Study staff will -

- Upload meter and CGM data to SweetSpot database
- Troubleshoot CGM and/or SMBG issues
- Assess any AEs or device issues
- Obtain concomitant medications including dose and frequency (not vitamins/minerals), and if subject takes as needed (p.r.n.). Assess for addition or modification of any GLP-1 agonists, pramlintide, and SGLT-2 inhibitors.
    - In the event the subject begins GLP-1 agonists, pramlintide, or SGLT-2 inhibitors during the study, those subjects will still be allowed to participate in future study visits.
- Provide additional education to either group if required per clinical assessment (clinician)
- Review and assess subject per Appendix D: *Clinician Guidelines for Follow-Up Visits* (clinician)
- Make adjustments to diabetes therapy, if indicated (clinician)
- Dispense test strips
- Download CGM and BGM data, per usual practice for diabetes management (clinician)

<u>For the CGM group</u>-

- Provide and review the "Diabetes Management Guidelines Using CGM" (Appendix F) (clinician)
- Dispense additional sensors to deploy at home for weekly insertions until they return for their Week 12 visit

19.4 Visit 3 – Week 11 – Blinded CGM - *SMBG Group only* (Window ± 5 days)

The purpose of this visit is to have subjects wear blinded CGM for one sensor session. Subjects will return the CGM at Week 12 Visit.

At this visit the following will be done:

- Assess any AEs or device issues
- A CGM sensor will be inserted in blinded mode (self-deployed or assisted by study staff) and subjects will be provided CGM training and core tasks to include calibration, and troubleshooting. (Subjects are asked to contact the site if any sensor/adhesive issues arise within the first 3 days of wear for sensor replacement.)

19.5 Visit 4 – Week 12 – (Month 3) – Mid Phase 1 Assessment (Window ± 1 days – SMBG; ± 7 days – CGM)

Study staff will -

- Upload meter and CGM data to SweetSpot database
- Troubleshoot CGM and/or SMBG issues
- Assess any AEs or device issues
- Obtain concomitant medications (not vitamins/minerals). Assess if subject takes as needed (p.r.n). Assess for addition or modification of any GLP-1 agonists, pramlintide, and SGLT-2 inhibitors.
    - In the event the subject begins GLP-1 agonists, pramlintide, or SGLT-2 inhibitors during the study, those subjects will still be allowed to participate in future study visits.
- Provide additional education to either group, if required per clinical assessment (clinician)
- Review and assess subject per Appendix D: *Clinician Guidelines and Follow-Up Visits* (clinician)
- Make adjustments to diabetes therapy, if indicated (clinician)
- Dispense test strips
- Complete POC A1C (via POC or local lab); these results may be shared with the subject
- Draw blood for A1C assessment. **Note:** Results of central lab A1C will not be shared with the subject
- Record Height and weight (for BMI)
- Retrieve blinded-CGM from *Group 2-SMBG*. (NOTE: If subject's sensor/adhesive failed within the first 3 days during this one week of blinded wear, they were instructed to contact the site for a new sensor to be inserted.)
- *CGM group subjects*, provide additional sensors to self-deploy weekly until they return for Week 24 visit
- *CGM group subjects*, provide and review Appendix F: *Diabetes Management Guidelines Using CGM* (clinician)
- Download CGM and BGM data, per usual practice for diabetes management (clinician)

19.6 Visit 5 – Week 23 – Blinded CGM - *SMBG Group Only* (Window ± 5 days)

The purpose of this visit is to have subjects wear blinded CGM for one sensor session. Subjects will return their blinded-CGM at Week 24 Visit.

At this visit the following will be done:

- Assess any AEs or device issues
- A CGM sensor will be inserted in blinded mode (self-deployed or assisted by study staff) and subjects will be provided CGM training on core tasks to include calibration, and troubleshooting. (Subjects are asked to contact the site if any sensor/adhesive issues occur within the first 3 days of wear for sensor replacement.)

19.7 Visit 6 -- Week 24 (Month 6) – Phase 1 Final Assessments (Window ± 1 days – SMBG; ± 7 days – CGM) & Commencement of Phase 2

Follow-up assessments for eligibility to continue onto Phase 2 for Group 1-CGM, and end-of-study tasks will occur during this visit. The following subjects complete the study at the end of Phase 1:

- Subjects who have T2DM
- Group 1-CGM subjects who are using ≥100 units/day of insulin
- Group 2-SMBG subjects

Study staff will -

- Upload meter and CGM data to SweetSpot database
- Assess any AEs or device issues
- Obtain concomitant medications including dose and frequency (not vitamins/minerals), and if subject takes as needed (p.r.n.). Assess for addition or modification of any GLP-1 agonists, pramlintide, and SGLT-2 inhibitors.
    - In the event the subject begins GLP-1 agonists, pramlintide, or SGLT-2 inhibitors during the study, those subjects will still be allowed to participate in future study visits.
- Provide additional education to either group if required per clinical assessment (clinician)
- Draw blood for A1C assessment. **Note:** Results of central lab A1C will not be shared with the subject
- Complete POC A1C (via POC or local lab); these results may be shared with the subject
- Record height and weight (for BMI)
- *CGM group subjects*, provide and review Appendix F: *Diabetes Management Guidelines Using CGM* (clinician)
- Administer PROs:
    1. WHO-5
    2. EQ-5D-5L
    3. Health Service Utilization Form
    4. Diabetes Distress Scale (DDS)
    5. Hypoglycemic Fear Survey – Worry subscale (HFS-W)
    6. Hypoglycemia Confidence

7. Bolus Insulin Questionnaire
8. Clarke Hypoglycemia Scale
9. CGM Attitudes*
10. CGM Satisfaction Scale*

**NOTE: CGM Satisfaction and CGM Attitudes are administered only to Group 1- CGM.*

- Retrieve blinded-CGM from Group 2-SMBG (NOTE: If subject's sensor/adhesive failed within the first 3 days during this one week of blinded wear, they were instructed to contact the site for a new sensor to be inserted.)
- Download CGM and BGM data, per usual practice for diabetes management (clinician)
- Complete Care Management Form to assess clinic visits unrelated to study visits (See Section 10)

For subjects *not* continuing on to Phase 2:

Subjects in Group 2-SMBG will be offered a trial of real-time CGM (using a FDA-approved CGM System) and, if interested, will be trained on basic RT-CGM. Follow-up will be provided after the 2-week trial is complete, according to site's standard-of-care with CGM follow-up.

If the subject desires to continue with CGM and the investigator believes CGM is clinically warranted for the particular subject, a prescription will be written for sensors and follow-up communication with their treating physician will be made. Their prescription will be communicated with the subject's treating physician.

Subjects in Group 1-CGM *not* continuing onto Phase 2 will have a review of Diabetes Management Guidelines. They will be provided a prescription for CGM, if desired and the investigator believes CGM is clinically warranted for the particular subject. Their prescription will be communicated with the subject's treating physician.

For subjects continuing on to Phase 2:

Eligible subjects with T1DM in Group 1-CGM, using <100 units/day of insulin and who used CGM 21 out of 28 days within the last month, will be asked if they are willing to participate in Phase 2. If eligible and willing to continue, subjects will be **randomized** to one of the following groups:

- MDI with CGM (Group 1a-CGM/MDI)
- CSII with CGM (Group 1b-CGM/CSII)

For all subjects who enter Phase 2:

- Offer carbohydrate counting instruction (individual or group training)
- Group 1a-CGM/MDI subjects will meet with a clinician to discuss any further questions they have regarding diabetes management
- Group 1b-CGM/CSII subjects will be provided a study-assigned pump, PDM, and will receive insulin pump-related training on device set-up and use
  - Initial pump settings will be determined and discussed
  - Additional visits for pump training can be scheduled as needed
- Subjects will be provided sensors and strips to cover the weeks between visits.
- Insulin pods are provided to subjects randomized to Group 1b-CGM/CSII

Randomization in this phase will be stratified between Groups 1a and 1b to ensure even distribution for subjects with A1C result ≤ 7%, >7% to <7.5% and ≥7.5%

20. STUDY PROCEDURES (PHASE 2 – Follow-up Study)

20.1 Visit 1 - Week 26 – Follow-up – *CGM/CSII Group Only* (Window ± 4 days)

Study staff will-

- Upload CGM and BGM to SweetSpot database
- Download OmniPod data onto a centrally-located computer
- Troubleshoot any pump/device issues
- Assess any AEs or device issues, specifically related to the pump
- Obtain concomitant medications including dose and frequency (not vitamins/minerals), and if subject takes as needed (p.r.n.). Assess for addition or modification of any GLP-1 agonists, pramlintide, and SGLT-2 inhibitors.
    - In the event the subject begins GLP-1 agonists, pramlintide, or SGLT-2 inhibitors during the study, those subjects will still be allowed to participate in future study visits.
- Provide and review Appendix D *Clinical Guidelines for Follow-up Visits*; and Appendix F: *Diabetes Management Guidelines Using CGM* (clinician)
- Make pump adjustments. **Note:** pump adjustments may require frequent visits, and follow-up phone calls. These ad hoc visits will be documented as part of pump training. (clinician)
- Dispense diabetes supplies – pods (Group 1b only), test strips, sensors to deploy at home until they return for their *Week 30* visit
- Download CGM and BGM data, per usual practice for diabetes management (clinician)

20.2 Visit 2 – Week 30 - Follow-Up (Window ± 4 days)

Study staff will -

- Upload meter, CGM, to SweetSpot database
- Download OmniPod data onto a centrally-located computer
- Troubleshoot any CGM, BGM or pump issues
- Assess any AEs or device issues
- Provide additional education to either group if required per clinical assessment (clinician)
- Make adjustments to diabetes therapy, if indicated (clinician)
- Provide and review **Appendix D** *Clinical Guidelines for Follow-up Visits*; and **Appendix F**: *Diabetes Management Guidelines Using CGM* Dispense diabetes supplies – pods (Group 1b only), strips and additional sensors to deploy at home until they return for their *Week 38* visit (clinician)
- Download CGM, BGM and pump data, per usual practice for diabetes management (clinician)

20.3 Visit 3 – Week 38 (Month 9) –Follow-Up (Window ± 7 days)

Study staff will-

- Upload BGM, CGM, and OmniPod PDM data to SweetSpot database
- Download OmniPod data onto a centrally-located computer
- Troubleshoot any CGM, BGM or pump issue
- Assess any AEs or device issues

- Obtain concomitant medications including dose and frequency (not vitamins/minerals), and if subject takes as needed (p.r.n.). Assess for addition or modification of any GLP-1 agonists, pramlintide, and SGLT-2 inhibitors.
    - In the event the subject begins GLP-1 agonists, pramlintide, or SGLT-2 inhibitors during the study, those subjects will still be allowed to participate in future study visits.
- Obtain CGM, BGM and pump data, per usual practice Provide additional education to either group if required per clinical assessment (clinician)
- Make adjustments to diabetes therapy, if indicated (clinician)
- Provide and review Appendix D *Clinical Guidelines for Follow-up Visits*; and Appendix F: *Diabetes Management Guidelines Using CGM* (clinician)
- Draw blood for A1C assessment. **Note:** Results of central lab A1C will not be shared with the subject
- Complete POC A1C (via POC or local lab); these results may be shared with the subject
- Dispense diabetes supplies – pods (Group 1b only), strips and additional sensors to deploy at home until they return for their *Week 52* visit
- Download CGM, BGM and pump data, per usual practice for diabetes management (clinician)

20.4 Visit 4 – Week 52 (Month 12) – Final Assessment (Window ± 7 days)

This visit signifies Phase 2 completion.

Study staff will -

- Upload meter, and CGM, to SweetSpot database
- Download OmniPod data onto a centrally-located computer
- Assess any AEs or device issues
- Obtain concomitant medications including dose and frequency (not vitamins/minerals), and if subject takes as needed (p.r.n.). Assess for addition or modification of any GLP-1 agonists, pramlintide, and SGLT-2 inhibitors.
- Assess compliance (SC), and make final evaluation of subjects' diabetes management decisions (clinician).
- Draw final blood for A1C assessment. **Note:** Results of central lab A1C will not be shared with the subject.
- Complete POC A1C (via POC or local lab); these results may be shared with the subject
- Administer PRO surveys
- Collect OmniPod PDM, collect CGM if not clinically warranted/desired. . **Note: S**ubject may be prescribed the CGM System and pump per Investigator's assessment, if requested by the subject.
- Download CGM, BGM and pump data, per usual practice for diabetes management (clinician)
- Complete Care Management Form to assess clinic visits unrelated to study visits (See Section 10)

PROs to be administered at Month 12 include:

1. WHO-5
2. EQ-5D-5L
3. Health Service Utilization Form
4. Diabetes Distress Scale (DDS)
5. Hypoglycemic Fear Survey – Worry subscale (HFS-W)
6. Hypoglycemia Confidence
7. Bolus Insulin Questionnaire
8. Clarke Hypoglycemia Scale
9. CGM Satisfaction Scale
10. CGM Attitudes

20.5 Device Replacements

Dexcom G4 PLATINUM components that malfunction or are lost during the course of the study may be replaced at any time at the discretion of the Investigator and Sponsor.

21. RISKS

21.1 Sensor Insertion/Use/Removal

Insertion of the sensors into the skin may result in pain, erythema, and/or edema at the insertion sites. Infection, excessive bleeding, or hematoma are also possible side effects of device use; however, the expected frequency of these events is low based on data obtained from similar devices and adverse event information from more than five previous Dexcom studies where the device was inserted from 12 hours to 15 days.

After removal of the sensors, subjects may experience irritation due to the medical adhesive used to apply the sensor pod and any bandages that may be placed over the device. This reaction is self-limiting and should resolve within hours and not more than a week post-removal. Subjects may experience some itching in the area during the healing process, which is normal.

Rarely, subjects may develop an allergic reaction to one or more of the components of the sensor and/or transmitter. This is similar to allergies that can occur due to contact with medical tape.

Sensors may fracture in situ on rare occasions. In these rare instances when this has occurred in the past, consulting physicians and surgeons have recommended not to remove the wire fragment from beneath the skin as long as there are no symptoms of infection or inflammation. In the event that signs and/or symptoms of infection or inflammation arise such as redness, swelling, and pain subjects should consult with the investigator or prescribing physician for the best course of action. If there is no portion of the broken sensor wire fragment visible above the skin, attempts to remove it without medical guidance are not advised.

A thermal burn due to the electrical components of the device is not a risk as the circuit designed and verified to limit the intra-electrode current to a maximum of 20 µAmps. Given that any level less than 1 µAmp is considered safe, per ISO 14708-1 and EN45502-1, the device's maximum current output is 2 percent of the 1 µAmp limit.

21.2 Hypoglycemia

Treatment of diabetes is associated with increased risk of severe hypoglycemia. Hypoglycemia may be associated with reduced cognitive function, diaphoresis, tachycardia, coma, and seizure. These complications are an inherent risk of having diabetes. Subjects will be required to use blood glucose meter (not CGM) values to guide all diabetes-related therapeutic decisions (e.g. insulin dosing modifications) to minimize the risk of treatment errors.

Severe hypoglycemia will be captured as a serious adverse event if the event required assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that the subject was unable to treat his or herself, was unable to verbalize his or her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. If these criteria are not met but emergency evaluation or treatment was obtained from a health care provider the event will be captured as an Adverse Event and not a Serious Adverse Event unless one of the criteria for SAE is met.

21.3 Diabetic Ketoacidosis (DKA)

Subjects may also be randomized to use a currently-marketed insulin pump during Phase 2. Due to the use of insulin, there are risks of hypoglycemia and associated symptoms related to the infusion of insulin.

Diabetic ketoacidosis is a serious complication of diabetes that occurs when the liver produces high levels of ketones, which are an acid. Diabetic ketoacidosis develops when there is insulin deficiency; in response the body switches to burning fatty acids and producing acidic ketone bodies that cause most of the symptoms and complications. Vomiting, dehydration, tachypnea, confusion and occasionally coma are symptoms.

DKA will be captured as a serious adverse event if confirmed and treated. Hyperglycemia that does not meet criteria for definite or probable DKA is reported as an Adverse Event if emergency evaluation or treatment was obtained from a health care provider; these events are considered Adverse Events and not Serious Adverse Events unless one of the criteria for SAE is met.

Subjects may also be randomized to use a currently-marketed insulin pump during Phase 2. Due to the use of insulin, there are risks of hyperglycemia and associated symptoms related to potential interruptions of insulin delivery.

22. Non-Significant Risk Rationale

The Dexcom Continuous Glucose Monitoring System described in this protocol is considered by the Sponsor to be of non-significant risk as it does not meet the definition of a significant risk device per 21 CFR 812.3(m), in that:

- It is not an implant nor presents a potential for serious risk to the health, safety or welfare of a subject;
- CGM devices are not purported or represented to be for use in supporting or sustaining human life and thus do not present a potential for serious risk to the health, safety, or welfare of a subject; or
- Use of CGM devices does not present a potential for serious risk to the health, safety or welfare of a subject.

The following information supports a non-significant risk determination for the device that will be used in this protocol:

- FDA-approved Dexcom CGM Systems have been considered a non-significant risk device;
- The CGM device and insulin pump used in this study are being used on label in intended population;
- The Medtronic-Minimed Guardian RT® CGMS, a FDA approved device using similar technology, has been considered a non-significant risk device;
- The FreeStyle Navigator® CGMS, a FDA-approved device using similar technology, has been considered a non-significant risk device;

- The insertion needle thickness used in the device is not significantly thicker than the needles used in syringes for insulin injection and the needle insertion depth is less than 0.5 inches;
- None of the expected device-related adverse events as defined in the protocol and associated documents (e.g. Instructions for Use) would be life-threatening or would result in any permanent impairment of a body function or permanent damage to a body structure;
- There are no expected electrical safety risks as the device has passed the electrical safety tests as per EN45502-1 and EN60601;
- If the subject feels any discomfort during the course of the study, he/she will be able to remove the device immediately (the device is not permanent);
- The device is being used to complement, not replace, self-monitoring of blood glucose meter information and readings are not intended to be used alone to make diabetes self-management decisions. As with the currently approved device and per intended use of similar technologies, subjects in the study will be instructed not to use the device for diabetes therapy or management;
- Subjects will be instructed to monitor their blood glucose levels as per their usual practice.
- A recently completed Dexcom-sponsored study, conducted for regulatory purposes (FDA), concluded that the safety profile of the System is comparable to the initial Dexcom G4 Platinum CGM System for adults.

23. ADVERSE EVENTS

At all study visits, study staff will determine if any device or study-related adverse events (AEs) have occurred. Disease related events that are *chronic in nature and occur as part of the progression of the diabetes disease state* (i.e. diagnoses of retinopathy, nephropathy, neuropathy) *will not* be captured as adverse events in this study.

Confirmed DKA and *severe* hypoglycemic events will be captured as adverse events, as well as captured on separate event CRFs - a DKA Event Form, or a Severe Hypoglycemic Event Form, respectively. These event-specific forms will be utilized to capture additional details surrounding each event, if known. All confirmed DKA and severe hypoglycemic events, per protocol definition (see Section 1. Abbreviations and Definitions), will be considered Serious Adverse Events (SAEs). Therefore, a SAE form will always be completed for any confirmed DKAs and severe hypoglycemic events which occur during the course of this study.

Hypoglycemic events are also considered reportable adverse events if the criteria for severe hypoglycemia are *not* met but emergency evaluation or treatment was obtained from a health care provider; these events are considered Adverse Events and not Serious Adverse Events unless one of the criteria for SAE is met.

Hyperglycemia that does *not* meet criteria for definite or probable DKA is reported as an Adverse Event if emergency evaluation or treatment was obtained from a health care provider; these events are considered Adverse Events and not Serious Adverse Events unless one of the criteria for SAE is met.

All study or device-related AEs will be monitored until adequately resolved or stable.

For purpose of this protocol, AEs will be captured on the AE CRF form if causality is related to the study, or device. *AEs are categorized as follows*:

23.1 Adverse Event (AE)

Any clinically significant undesirable experience (sign, symptom, illness, or other medical event) meeting the causality definition above that appears or worsens in a subject during a clinical study. A clinically significant event is any event (sign, symptom, lab/imaging abnormality, or diagnosis) that is noteworthy enough to merit documentation in standard medical records (e.g. history and physical, progress notes, clinic visit notes, etc.). Other non-clinically significant events (e.g. colds, minor headaches, etc.) *may* be documented on source documents only.

23.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as any AE that is fatal, life-threatening, results in persistent or significant disability or incapacity, requires medical or surgical intervention to prevent permanent impairment or damage, or results in initial (in-patient) hospitalization or prolongation of hospitalization. Life-threatening is defined as the substantial risk of dying at the time of the adverse event or suspicion that continued use of the device would result in a subject's death.

Any SAE, including death, due to any cause (related or unrelated to the device), that may occur during a clinical study must be reported immediately (within 2 working days of learning of the event). Details of the SAE submitted via eCRF will result in an automatic email generated and forwarded to the Sponsor. The Sponsor contact for SAE review:

David Price, MD
Vice President, Medical Affairs
Dexcom, Inc.
6340 Sequence Drive
San Diego, CA 92121
Telephone: (858) 875-9525
Fax: (858) 332-0200
Email: dprice@dexcom.com

Dexcom Clinical Affairs personnel will document SAE details and assessment by Clinical Affairs management in a timely manner.

23.3 Severity of Adverse Events

The following definitions may be used to rate severity of AEs:

23.3.1 Mild

Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms are transient.
Example: hypoglycemia with at home treatment by subject or friend/family member.

23.3.2 Moderate

Discomfort severe enough to cause interference with usual activities, requiring treatment but not extended hospitalization or intensive care for the subject.

Example: hypoglycemia with seizure involvement, requiring treatment with glucagon and/or an emergency room visit.

23.3.3 Severe

Incapacitating, causing inability to do work or usual activities; signs and symptoms may be of systemic nature or require medical evaluation and/or treatment, requiring additional hospitalization or intensive care (prolonged hospitalization).

Example: hypoglycemia with seizure involvement, requiring hospitalization.

23.4 Relationship of Adverse Event to the Study, Disease, or Device

The investigator will categorize the relationship of the event to the study, disease, or study device as follows:

23.4.1 Not Related

AE is due to an underlying disease state or concomitant medication or therapy not related to the device, disease or study.

23.4.2 Probably Not Related

AE has minimum or no temporal relationship to the device, disease or study participation and/or a more likely alternative etiology exists.

23.4.3 Possibly Related

AE has a strong temporal relationship to the device, disease or study procedures and alternative etiology is equally or less likely compared to the potential relationship to the device, disease or study.

23.4.4 Probably Related

AE has a strong temporal relationship to the device, disease or study and another etiology is unlikely.

23.5 Anticipated Adverse Device Effects

The following events have been identified as possible device-related adverse events of **sensor insertion and wear**:

- Excessive pain or discomfort from system deployment (8 or greater on a 10-point Likert scale)
- Excessive bleeding
- Hematoma (slight ecchymosis is a known consequence of needle skin puncture and will not be captured as an AE)
- Excessive edema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- Excessive erythema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- Local infection
- Sensor or introducer needle fracture during insertion/wear/removal

Degrees of edema, erythema, or infection that may occur at the sensor insertion or adhesive tape site will be assessed by the subject and documented for review by study staff. An AE will be recorded as severe in intensity if skin appearance indicates significant edema or erythema (per definition above) and/**or** if infection, defined as the presence of pus, at the sensor insertion or adhesive tape site occurs.

The following events have been identified as possible device-related AEs of **insulin pump** use, **infusion of insulin and potential interruptions of insulin delivery**:

- Localized infection
- Skin irritation/erythema /rash (slight irritation/ erythema will not be captured as an AE)
- Hematoma (Slight ecchymosis is a known consequence of needle skin puncture and will not be captured as an AE)
- Discomfort/pain deployment (8 or greater on a 10-point Likert scale)
- Bleeding, excessive
- Diabetic Ketoacidosis (DKA)
- Severe hypoglycemia

Information regarding device-related AEs that occur during the study will be entered into appropriate CRFs. Such information will include, at a minimum:

- Date of event
- Severity
- Outcome
- Resolution of event
- Causality to study devices and procedures

23.6 Unanticipated Adverse Device Effects

An unanticipated adverse device effect (UADE) is not expected to occur. An UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by – or associated with – the device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (including documents such as the protocol, the informed consent document, other study-related documents), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

During the review of a reported SAE, if Clinical Affairs management with the Investigator input determines the severity or extent of the event was not cited in this protocol or associated protocol materials, and the event was classified as, 'possibly related' to the device, the event will be documented as an UADE. If the event is classified as an UADE, the Investigator must notify the IRB and Dexcom will notify the FDA within ten (10) working days of the original SAE notification.

If determined that the UADE presents an unreasonable risk to subjects, Dexcom will terminate all investigations or parts of investigations presenting that risk as soon as possible, but not later than 5 working days after such determination is made and not later than 15 working days after Dexcom first receives notice of the original SAE. Dexcom will not resume a terminated study without IRB and FDA approval.

23.7 MDR Reportable Events/MDR Reporting

For purposes of this protocol, the CGM devices are either currently marketed or similar to devices currently marketed in the US. Therefore, the sponsor will follow the required reporting regulations if a MDR reportable event were to occur according to Sponsor SOP and FDA guidelines. (SOP-300024 US MDR Reporting; Code of Federal Regulations Title 21 Part 803; Medical Device Reporting; Draft Guidance for Industry and Food and Drug Administration Staff Medical Device Reporting for Manufacturers: July 9, 2013, 19-21).

MDR reportable events are events that manufacturers become aware of that reasonably suggest one of their marketed devices may have caused or contributed to a death or serious injury, or has malfunctioned and the malfunction of the device would likely cause or contribute to a death or serious injury if the malfunction were to recur (21 CFR 803.3).

24. ETHICAL CONSIDERATIONS

24.1 Informed Consent

Informed consent will be obtained in accordance with the Code of Federal Regulations (CFR) Title 21, Part 50. Subjects will be asked to sign state specific forms, such as Subject's Bill of Rights, or equivalent, (if applicable) and HIPAA authorization form, if not included in the site's consent template. Subjects will be provided the opportunity to review these documents prior to

coming to the clinical site. The Investigator or designee will explain the purpose and duration of the study, the study procedures and subject requirements, and the potential risks and benefits. Study staff will attempt to answer all questions the subject may have. Consenting process will be documented in the subject's source documents. A copy of the consent will be provided to the subject.

The study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the 1983 amendment per FDA's Guidance for Industry: Acceptance of Foreign Clinical Studies written in March, 2001.

Subjects will receive a stipend for their participation in the study and a CGM system at the end of Phase 1 if clinically warranted, subject was compliant with study protocol and requested by subject.

24.2 Institutional Review Board

The protocol, informed consent document, and subject training materials for this study will be reviewed and approved by a duly constituted Institutional Review Board (IRB) before subjects are screened.

The Investigator will ensure that all aspects of the IRB review are conducted in accordance with current institutional, local, and national regulations. An IRB approval letter will be provided to the Sponsor prior to study initiation. Protocol amendments must adhere to the same requirements as the original protocol. The Investigator will submit all IRB-required reports and updates, including any continuing review and/or final closeout reports. The Investigator will inform the IRB of any reportable AEs as per the IRB reporting rules.

25. DATA COLLECTION

This study will use electronic data capture (EDC). The Investigator or designee is responsible for completing the CRFs. Good Documentation Practices principles will be required.

26. DEVICE ACCOUNTABILITY

The Investigator(s) will store devices in a secure location at the clinical site. An accurate and current accounting of the dispensing for the Dexcom and other device components will be maintained by a member of the study site staff on the "Device Accountability Log". All used and unused devices must be returned to the Dexcom Clinical Affairs department (or accounted for if lost) upon completion of enrollment or upon request of the Sponsor.

27. MONITORING

Monitoring will be conducted by trained and experienced Clinical Research Associates (CRAs) in accordance with Dexcom's standard operating procedures. CRAs will evaluate study conduct and documentation on an ongoing basis. Assessment of site performance will be reviewed with Clinical Affairs management to determine the level of monitoring required. All informed consent documents will be source verified along with key data fields related to safety and performance indicators. All CRF data will be collected via the EDC system designated for the study for analysis. A risk-based monitoring plan will be developed consistent with the Food and Drug Administration (FDA) Guidance for Industry: Oversight of Clinical Investigations—A Risk-based Approach to Monitoring (August 2013). This approach focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study. Monitoring is separated into Central (remote) monitoring and On-Site monitoring (site visits). Considerable focus is placed on real-time centralized monitoring methods.

28. STUDY TERMINATION

Subject participation in the clinical study will be terminated following the last visit or when all AEs have been resolved or considered ongoing but stable. Prior to this time, subjects may voluntarily withdraw at any point in the study or the Investigator and/or Sponsor may determine that it is in the best interest of the subject to be terminated from the study. Reasons for withdrawal of subject from the study include, but are not limited, to the following:

a) In the opinion of the Investigator, the subject's health or safety would be compromised by continuing in the study
b) In the opinion of the Investigator, it is in the subject's best interest to discontinue participation in the study
c) During the study, (female) subject becomes pregnant.

However, discontinuation of the study intervention (CGM) does not equate with discontinuation from the study and every effort will be made to retain subjects in the study for the primary outcome assessment, even if CGM is discontinued.

The clinical study in its entirety will be considered complete upon receipt of reports from study monitoring activities, completion of site closeout visits, and issuance of a clinical study report. The clinical study report will include all safety and efficacy data.

Any early termination of the study will be reported to the IRB.

29. INVESTIGATOR RESPONSIBILITIES

The Investigator's signature(s) on this protocol confirms that the Investigator is familiar with all sections of the protocol and agrees to conduct this study in accordance with the provisions of the protocol and applicable regulations. The Investigator(s) must sign this protocol prior to commencement of any study-related activities (e.g. screening).

The Investigator(s) are responsible for protecting the rights, safety, and welfare of subjects under their care. The Investigator(s) are also responsible for obtaining IRB approval prior to study start and the written informed consent of each subject before participation in this study. The informed consent must comply with FDA regulations (21 CFR 50) and be approved by the IRB.

The Investigator(s) are responsible for ensuring completion of the CRFs per the study timelines discussed in the site initiation visit and subsequent monitoring visits.

Dexcom and/or the IRB retain the right to disqualify an Investigational Site and remove all study materials at any time. Specific instances, which may precipitate clinical site disqualification, include but are not limited to:

a) Unsatisfactory subject enrollment with regard to quality and quantity.
b) Persistent non-compliance related to protocol procedures by the Investigator/Investigational Center.
c) Inaccurate, incomplete, and/or untimely data recording on a recurrent basis.
d) The incidence and/or severity of adverse experiences in this or other studies indicating inadequate oversight
e) Unsatisfactory accountability of study devices.

30. SPONSOR RESPONSIBILITIES

The Sponsor is responsible for selecting qualified Investigators and providing them with the information needed to properly conduct the study. The Sponsor will ensure proper monitoring of the study and that IRB approval has been obtained prior to the Investigator commencing study-related activities. The Sponsor is also responsible for ensuring that the reviewing IRB(s) and FDA, if applicable, are promptly informed of significant new information.

31. CONFIDENTIALITY OF RECORDS

All records and documents pertaining to this study will be retained for a period of no less than 2 years by Dexcom, Inc. and will be available for inspection by FDA or other regulatory agencies at any time. All records containing personal identification or information that identifies a study subject will be handled confidentially within the law. These records will be coded and kept in locked files. No individual identities will be used in any reports or publications resulting from this study.

Neither the site nor subjects will disclose, share, or use any information gathered during the course of the clinical study. All information about the study, including the study product and study procedures, is confidential. Any publication about the products or the study by print or electronic format (e.g. blogging) is strictly prohibited.

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33. APPENDICES

Appendix A: Informed Consent

Appendix B: Study Flowchart

Appendix C: Clinician Guidelines: General Diabetes Education

Appendix D: Clinician Guidelines for Follow-Up Visits

Appendix E: Visit Flowchart

Appendix F: Diabetes Management Guidelines Using CGM

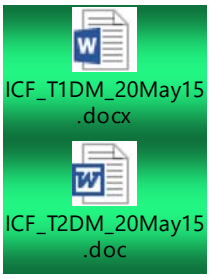
Appendix G: Patient Reported Outcome (PRO) Measures

Appendix H: Test and Exam Table

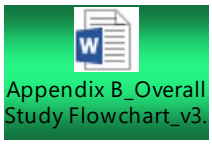
Appendix I: Sample CGM Information Guide

Appendix J: OmniPod Guidance Documents

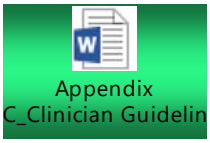
Appendix A: Informed Consent



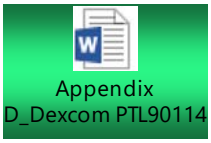
Appendix B: Overall Study Flowchart



Appendix C: Clinician Guidelines: General Diabetes Education

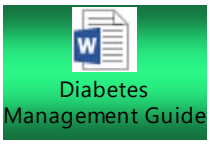


Appendix D: Clinician Guidelines for Follow-Up Visits

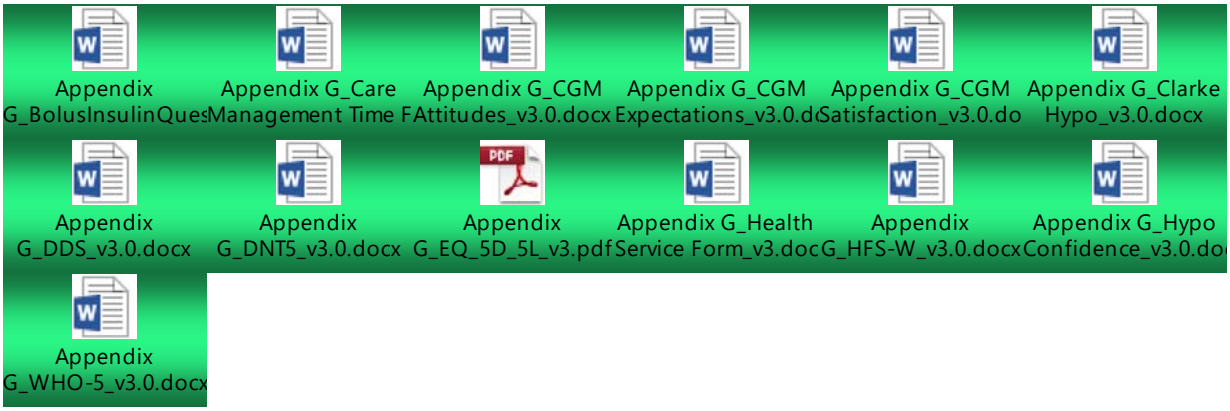


Appendix E: Visit Flowchart

Appendix F: Diabetes Management Guidelines Using CGM



Appendix G: Patient Reported Outcome (PRO) Measures



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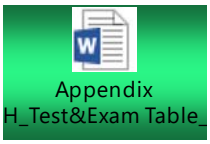
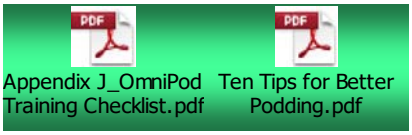
Appendix H: Test and Exam Table



Appendix I: Sample CGM Information Guide

This is a sample of CGM information and training that may be used by clinicians at the study site:

Appendix J: OmniPod Guidance Documents



Supplementary Online Content

Beck RW, Riddlesworth T, Ruedy K, et al, for the DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes who using use injections for insulin delivery: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2016.19975

eTable 1 Inclusion and Exclusion Criteria
eTable 2 Participant Education and Guidelines for Clinicians – Both Groups
eTable 3 Continuous Glucose Monitoring Use in CGM Group
eTable 4 Change in HbA1c from Baseline to 24 Weeks According to Baseline Factors
eTable 5 Continuous Glucose Monitoring Metrics at 12 Weeks and 24 Weeks
eTable 6 Nighttime Continuous Glucose Monitoring Metrics
eTable 7 Daytime Continuous Glucose Monitoring Metrics
eTable 8 Insulin Use, Body Weight and Hypoglycemia Unawareness
eTable 9 Severe Hypoglycemia, Diabetic Ketoacidosis, and Other Serious Adverse Events
eTable 10 CGM Satisfaction Questionnaire at 24 Weeks

This supplementary material has been provided by the authors to give readers additional information about their work.

SUPPLEMENT 2

eTable 1. Inclusion and Exclusion Criteria

Inclusion Criteria

1. Age 25 years of age and older
2. Diagnosis of type 1 diabetes
3. Followed regularly by a physician or diabetes educator for their diabetes management – with at least 2 office visits in last year as documented by clinical history
4. Using multiple daily injections of insulin for at least 12 months prior to study entry
5. Sub-optimal glycemic control, defined as persistent hyperglycemia, confirmed initially by historical or local lab (POC or site's lab) A1C of ≥7.7% to ≤10%, then followed with a confirmatory result by central lab of ≥7.5% to ≤10%
6. Desire to lower A1C such as a goal of 7%
7. Stable control of diabetes, as determined per investigator assessment
8. Stable diabetes medication regimen for 3 months prior to study entry
9. Stable weight maintained 3 months prior to study entry, per investigator's assessment, and not planning any structured weight reduction interventions such as prescription weight loss medications, bariatric surgery, or protein sparing modified fast during the course of the study.
10. Willing to wear a device (CGM)
11. Willing to avoid use of acetaminophen medications throughout the study
12. Currently performing self-monitoring blood glucose testing (by history) an average of ≥3 times per day
13. Able to speak, read, and write English

Exclusion Criteria

1. Use of *personal* RT-CGM 3 months prior to study entry (professional CGM use, blinded or un-blinded, is acceptable)
2. Use of CSII 3 months prior to study entry (including patch pumps)
3. Plan to use personal CGM and/or pump during the course of the study
4. Addition of any new oral or injectable hypoglycemic agents (including GLP-1 analogues, Pramlintide, and SGLT-2 inhibitors – these agents are *only* for T2DM participants) within 3 months prior to study entry. (Use of these agents does not affect eligibility if used 3 or more months prior to study entry.) For GLP-1 medications, must be on stable dose and the GLP-1 medication will be maintained throughout the study.
   Note: These agents should not be added or modified during course of the study. If use of this class medication is planned, the patient is not eligible.
5. Use of pre-mixed insulin (e.g. 70/30 or 50/50) 6 months prior to study entry
6. Current or anticipated *acute* uses of glucocorticoids (oral, injectable, or IV), that will affect glycemic control and impact A1C – such as frequent steroid bursts required for inflammatory arthritis or inflammatory bowel disease, recurrent lumbar epidural steroid injections, etc. (Long-term stable glucocorticoid doses are allowed, such as when used for the treatment of rheumatoid arthritis or Addison's disease).
7. Pregnancy (as demonstrated by a positive test at study entry) at time of screening or are planning to become pregnant during the study
8. Medical conditions that, per investigator determination, make it *inappropriate or unsafe* to target an A1C of <7%. Conditions *may* include but are not limited to:
   - Unstable. recent cardiovascular disease,
   - Recent myocardial infarction
   - Significant heart failure
   - Ventricular rhythm disturbances
   - Recent transient ischemic attack, or cerebrovascular accident
   - Significant malignancy
   - Other conditions resulting in physical or cognitive decline
   - Recurrent severe hypoglycemia

eTable 1. Inclusion and Exclusion Criteria (continued)

9. History of visual impairment which would hinder participant's participation in the study and perform all study procedures safely, as determined by investigator
10. History of psychiatric, psychological disorder, or psycho-social issues that could limit adherence to the required study tasks
11. Renal disease defined as estimated Glomerular Filtration Rate eGFR <45
12. Extensive skin changes/disease that preclude wearing the sensor on normal skin (e.g. extensive psoriasis, recent burns or severe sunburn, extensive eczema, extensive scarring, extensive tattoos, dermatitis herpetiformis)
13. Known allergy to medical-grade adhesives
14. Current participation in another investigational study (must have completed any previous studies at least 30 days prior to being enrolled in this study)
15. Recent hospitalization or emergency room visit in the 6 months prior to screening resulting in a primary diagnosis of uncontrolled diabetes
16. Currently abusing illicit drugs, alcohol, or prescription drugs
17. Any condition, per investigator assessment, that could impact reliability of the A1C measurement, such as (but not limited to) hemoglobinopathy, hemolytic anemia, chronic liver disease; chronic GI blood loss, red blood cell transfusion or erythropoietin administration within 3 months prior to screening

eTable 2. Participant Education and Guidelines for Clinicians – Both Groups

Education and Diabetes Management

<u>One session of general diabetes education</u>

Establish, review, or discuss:

- Glucose targets (individualized)
- Insulin dosing principles
  - Take before, not after each meal
  - Do not skip doses
- Basics of pattern management
- Basics of meal planning
- Hypoglycemia management
- Clinicians were encouraged to review retrospective glucose data with participants and use the data to adjust insulin

Clinician Guidelines

- Review insights from the participants and gleaned from CGM and SMBG downloads
- Make lifestyle and medication/insulin recommendations ***<u>per usual practice</u>***
- CGM Group—adjust alerts (per usual practice) and review CGM diabetes management guidelines

eTable 3. Continuous Glucose Monitoring Use in CGM Group[a]

	Week 4 Visit (N=105 [c])	Week 12 Visit (N=103)	Week 24 Visit (N=102 [c])	Overall (N=102 [d])
	n (%) unless otherwise stated			
Average Number of Days of Usage Per Week				
median (interquartile range)	7.0 (7.0-7.0)	7.0 (7.0-7.0)	7.0 (7.0-7.0)	7.0 (6.9-7.0)
range	3.3-7.0	0.0-7.0	0.0-7.0	2.3-7.0
Zero Use	0	1 (<1%)	2 (2%)	0
<1 day/week	0	0	0	0
1-<2 days/week	0	0	0	0
2-<3 days/week	0	0	0	1 (<1%)
3-<4 days/week	1 (1%)	0	0	0
4-<5 days/week	0	0	1 (1%)	3 (3%)
5-<6 days/week	0	3 (3%)	4 (4%)	2 (2%)
6-<7 days/week	11 (11%)	7 (7%)	12 (12%)	22 (22%)
7 days/week	88 (88%)	92 (89%)	79 (81%)	74 (73%)
<6 days/week	1 (1%)	4 (4%)	7 (7%)	6 (6%)
≥6 days/week	99 (99%)	99 (96%)	91 (93%)	96 (94%)
% of Possible Readings [b] *median (interquartile range)*	98% (95%-99%)	96% (92%-98%)	96% (90%-98%)	96% (92%-98%)

a. Based on most recent 28 days from device download at each visit.
b. Excludes 2 hours after each new sensor insertion.
c. Five participants at Week 4 and 4 participants at Week 24 who used the device but whose download was unavailable were considered to have missing data.
d. Average of Weeks 4, 12 and 24.

eTable 4. Change in HbA1c from Baseline to 24 Weeks According to Baseline Factors

	N	Baseline Mean HbA1c	24-week Mean HbA1c	Mean Change in HbA1c	Mean Adjusted Difference (99% Confidence Interval) [a]	P value for Interaction [a]
	CGM / Control					
Baseline Factor						
HbA1c						0.16
<8.5%	46 / 24	8.0 / 8.0	7.4 / 7.8	-0.6 / -0.2	-0.4 (-0.9 to 0.0)	
≥8.5%	56 / 29	9.1 / 9.0	7.9 / 8.5	-1.3 / -0.5	-0.8 (-1.2 to -0.3)	
Age						0.18
25-<45 years	51 / 16	8.7 / 8.8	7.8 / 8.2	-0.9 / -0.6	-0.3 (-0.8 to +0.2)	
45-<60 years	32 / 23	8.7 / 8.5	7.5 / 8.2	-1.2 / -0.2	-0.8 (-1.3 to -0.3)	
≥60 years	19 / 14	8.4 / 8.6	7.5 / 8.1	-1.0 / -0.4	-0.6 (-1.2 to 0.0)	
Continuous Glucose Monitoring Time <70mg/dL						0.10
<5%	54 / 27	8.7 / 8.6	7.7 / 8.1	-1.0 / -0.6	-0.4 (-0.8 to 0.0)	
≥5%	48 / 26	8.6 / 8.6	7.6 / 8.3	-1.0 / -0.2	-0.8 (-1.2 to -0.3)	
SMBG Frequency						0.44
3 times per day	56 / 25	8.7 / 8.5	7.7 / 8.0	-1.0 / -0.5	-0.5 (-0.9 to 0.0)	
≥4 times per day	46 / 28	8.6 / 8.6	7.7 / 8.3	-0.9 / -0.3	-0.7 (-1.1 to +0.2)	
Education [b]						0.49
<Bachelor's degree	44 / 22	8.7 / 8.6	7.8 / 8.1	-1.0 / -0.5	-0.5 (-0.9 to 0.0)	
≥Bachelor's degree	53 / 29	8.6 / 8.6	7.6 / 8.2	-1.0 / -0.4	-0.6 (-1.1 to +0.2)	
Hypoglycemia Unawareness [c]						0.32
Reduced Awareness or Uncertain (Score ≥3)	37 / 24	8.6 / 8.5	7.5 / 8.2	-1.1 / -0.3	-0.7 (-1.2 to -0.2)	
Aware (Score ≤2)	65 / 29	8.7 / 8.7	7.7 / 8.2	-0.9 / -0.5	-0.5 (-0.9 to -0.1)	
Diabetes Numeracy Score [d]						0.55
≤3 out of 5 correct	29 / 15	8.9 / 8.6	7.8 / 8.1	-1.1 / -0.6	-0.5 (-1.0 to +0.1)	
≥4 out of 5 correct	73 / 38	8.6 / 8.6	7.6 / 8.2	-0.9 / -0.3	-0.6 (-1.0 to -0.3)	
Hypoglycemia Fear Total Score [e]						0.14
0-13	52 / 23	8.7 / 8.4	7.7 / 7.9	-1.0 / -0.5	-0.4 (-0.8 to +0.1)	
14-77	50 / 30	8.6 / 8.7	7.6 / 8.4	-1.0 / -0.3	-0.7 (-1.2 to -0.3)	
Post-hoc analysis [f]						
Type of Clinical Site						0.07
Community	63 / 30	8.6 / 8.5	7.6 / 8.3	-1.0 / -0.2	-0.8 (-1.2 to -0.4)	
Academic	39 / 23	8.7 / 8.7	7.8 / 8.0	-1.0 / -0.7	-0.3 (-0.7 to +0.2)	

a. Treatment group comparisons made by including interaction term in each analysis of covariance model adjusted for baseline HbA1c and clinical site as a random effect. For the type of clinical site, the model contained random site intercepts and fixed effects for the site and the type by treatment group interaction was a fixed effect. For P values, continuous variable used for all outcomes other than education and type of clinical site. P values <0.01 were considered statistically significant.

b. Education missing for 5 participants in the CGM Group and 2 participants in the Control Group.

c. The Hypoglycemia Unawareness questionnaires has 8 items with a total score from 0 to 7. Higher score denotes more unawareness.

d. The Diabetes Numeracy questionnaire has 5 items quizzing the participant's knowledge of calculations related to diabetes management. Missing for 1 in CGM Group.

e. Hypoglycemia Fear questionnaire contains 18 items on what the participant worries about related to their diabetes. Higher score denotes more fear.

f. Post-hoc analysis for clinical site. All of the other subgroups in this table were pre-specified in the statistical analysis plan.

eTable 5. Continuous Glucose Monitoring Metrics at 12 Weeks and 24 Weeks

	Baseline		12 Weeks [a]		24 Weeks [a]	
	CGM Group (N=105)	**Control Group (N=53)**	**CGM Group (N=102)**	**Control Group (N=51)**	**CGM Group (N=99)**	**Control Group (N=53)**
Hours of Data *mean ± SD*	322 ± 50	325 ± 51	154 ± 16	148 ± 15	154 ± 15	157 ± 42
Glucose Variability: Coefficient of Variation *mean ± SD*	42 ± 7%	42 ± 7%	38 ± 6%	41 ± 8%	38 ± 7%	42 ± 7%
Minutes/Day in Range 70-180mg/dL *mean ± SD*	660 ± 179	650 ± 170	727 ± 222	667 ± 224	740 ± 223	639 ± 210
Hypoglycemia *median (interquartile range)*						
Minutes/day <70 mg/dL	65 (33-103)	72 (35-136)	49 (20-69)	65 (29-124)	33 (14-72)	55 (24-116)
Minutes/day <60 mg/dL	32 (15-61)	39 (15-78)	21 (7-36)	27 (9-86)	15 (4-29)	31 (6-72)
Minutes/day <50 mg/dL	13 (5-29)	18 (4-39)	4 (0-13)	13 (0-48)	4 (0-11)	8 (1-33)
Hyperglycemia *median (interquartile range)*						
Minutes/day >180 mg/dL	687 (554-810)	725 (537-798)	663 (486-809)	666 (579-878)	604 (460-814)	734 (626-896)
Minutes/day >250 mg/dL	301 (190-401)	269 (184-383)	226 (135-366)	297 (197-419)	208 (112-352)	352 (230-460)
Minutes/day >300 mg/dL	129 (66-201)	109 (71-204)	70 (28-147)	123 (47-219)	71 (30-140)	171 (75-228)
Mean Glucose (mg/dL) *mean ± SD*	187 ± 27	186 ± 30	180 ± 28	186 ± 31	180 ± 31	191 ± 29
Area Above Curve 70 mg/dL *median (interquartile range)*	0.5 (0.3-1.1)	0.7 (0.2-1.4)	0.4 (0.1-0.6)	0.4 (0.2-1.5)	0.3 (0.1-0.5)	0.6 (0.1-1.1)
Area Under Curve 180 mg/dL *median (interquartile range)*	34 (25-46)	33 (26-45)	29 (18-41)	34 (24-49)	26 (16-42)	41 (27-54)

a. Participants with <72 hours of data were excluded from the analysis (1 CGM and 1 Control at 12 weeks and 3 CGM and 0 Control at 24 weeks; a pre-specified condition).

eTable 6. Nighttime[a] Continuous Glucose Monitoring Metrics

	Baseline		12 Weeks [b]		24 Weeks [b]			
	CGM Group (N=105)	**Control Group (N=53)**	**CGM Group (N=102)**	**Control Group (N=51)**	**CGM Group (N=99)**	**Control Group (N=53)**	**Mean Adjusted Difference (99% Confidence Interval) [c]**	**P value [c]**
Hours of Data *mean ± SD*	108 ± 18	109 ± 17	53 ± 6	48 ± 6	53 ± 5	52 ± 14	–	–
Glucose Variability: Coefficient of Variation *mean ± SD*	42 ± 9%	44 ± 9%	37 ± 9%	41 ± 12%	36 ± 9%	40 ± 9%	-4% (-7% to -1%)	<0.001
% Time in Range 70-180 mg/dL *mean ± SD*	46 ± 15%	45 ± 13%	51 ± 18%	49 ± 20%	50 ± 18%	44 ± 19%	+4% (-2% to +10%)	0.09
Hypoglycemia *median (interquartile range)*								
% time <70 mg/dL	5.5% (2.2%-9.6%)	7.2% (2.3%-11.0%)	3.1% (0.6%-7.6%)	7.6% (0%-12.8%)	1.8% (0.1%-4.9%)	5.2% (0.9%-9.4%)	–	0.003
% time <60 mg/dL	2.9% (1.0%-5.8%)	4.0% (1.7%-8.5%)	1.3% (0%-3.1%)	3.0% (0%-8.9%)	0.6% (0%-2.3%)	2.4% (0%-6.3%)	–	0.002
% time <50 mg/dL	1.1% (0.3%-3.0%)	1.8% (0.2%-4.7%)	0% (0%-1.1%)	0.8% (0%-5.1%)	0% (0%-0.9%)	0.3% (0%-2.4%)	–	0.001
Hyperglycemia *median (interquartile range)*								
% time >180 mg/dL	47% (34%-60%)	47% (33%-56%)	42% (32%-57%)	38% (27%-60%)	44% (32%-56%)	48% (40%-64%)	–	0.49
% time >250 mg/dL	19% (10%-28%)	19% (10%-30%)	15% (8%-25%)	16% (6%-27%)	15% (7%-24%)	19% (11%-30%)	–	0.12
% time >300 mg/dL	8% (3%-15%)	7% (4%-15%)	5% (<1%-10%)	6% (0%-13%)	4% (<1%-10%)	7% (2%-17%)	–	0.02
Mean Glucose (mg/dL) *mean ± SD*	185 ± 34	181 ± 34	180 ± 34	172 ± 37	179 ± 35	186 ± 37	-2 (-14 to +9)	0.61
Area Above Curve 70 mg/dL *median (interquartile range)*	0.7 (0.2-1.5)	1.0 (0.4-2.1)	0.3 (0-0.8)	0.7 (0-2.2)	0.2 (0-0.6)	0.5 (0-1.5)	–	0.002
Area Under Curve 180 mg/dL *median (interquartile range)*	34 (21-47)	33 (21-46)	25 (16-41)	27 (13-41)	27 (14-39)	35 (24-49)	–	0.08

a. Nighttime defined as 10pm to <6am

b. Participants with <24 hours of nighttime data were excluded from the analysis (1 CGM and 1 Control at 12 weeks and 3 CGM and 0 Control at 24 weeks; a pre-specified condition).

c. Treatment group comparisons made using analysis of covariance models, adjusted for the corresponding baseline value, baseline HbA1c and clinical site as a random effect using pooled data from 12 and 24 weeks. Due to skewed distributions for the hypoglycemia and hyperglycemia metrics (including area above curve 70 mg/dL and area below curve 180 mg/dL), these models were based on ranks using van der Waerden scores. P values <0.01 were considered statistically significant (with 99% confidence intervals accordingly provided for the metrics which are approximately normally distributed).

eTable 7. Daytime[a] Continuous Glucose Monitoring Metrics

	Baseline		12 Weeks [b]		24 Weeks [b]			
	CGM Group (N=105)	**Control Group (N=53)**	**CGM Group (N=101)**	**Control Group (N=51)**	**CGM Group (N=99)**	**Control Group (N=53)**	**Mean Adjusted Difference (99% Confidence Interval) [c]**	**P value [c]**
Hours of Data *mean ± SD*	214 ± 33	216 ± 34	102 ± 10	99 ± 10	101 ± 10	105 ± 28	–	–
Glucose Variability: Coefficient of Variation *mean ± SD*	41 ± 6%	40 ± 6%	37 ± 6%	40 ± 6%	37 ± 6%	41 ± 6%	-3% (-5% to -1%)	<0.001
% Time in Range 70-180mg/dL *mean ± SD*	46 ± 13%	45 ± 13%	51 ± 16%	45 ± 16%	52 ± 17%	44 ± 16%	+6% (+1% to +11%)	0.003
Hypoglycemia *median (interquartile range)*								
% time <70 mg/dL	4.1% (1.9%-5.9%)	3.2% (1.9%-7.1%)	2.9% (1.0%-4.9%)	3.2% (1.0%-6.6%)	2.2% (0.8%-4.9%)	3.7% (1.5%-6.1%)	–	0.02
% time <60 mg/dL	1.7% (0.6%-3.3%)	1.6% (0.7%-4.3%)	1.1% (0.2%-2.3%)	1.3% (0.2%-4.1%)	0.9% (0.2%-1.9%)	1.6% (0.3%-3.7%)	–	0.02
% time <50 mg/dL	0.6% (0.1%-1.5%)	0.7% (0.3%-1.7%)	0.2% (0%-0.8%)	0.5% (0%-2.1%)	<0.1% (0%-0.7%)	0.6% (0%-1.4%)	–	0.007
Hyperglycemia *median (interquartile range)*								
% time >180 mg/dL	50% (39%-60%)	51% (39%-59%)	46% (33%-57%)	53% (38%-63%)	42% (31%-57%)	53% (43%-62%)	–	0.009
% time >250 mg/dL	21% (13%-29%)	20% (13%-28%)	15% (9%-24%)	22% (15%-34%)	14% (7%-25%)	25% (16%-35%)	–	<0.001
% time >300 mg/dL	8% (5%-15%)	8% (5%-14%)	5% (2%-10%)	10% (3%-17%)	5% (2%-11%)	11% (4%-17%)	–	<0.001
Mean Glucose (mg/dL) *mean ± SD*	188 ± 28	189 ± 31	180 ± 29	192 ± 34	180 ± 33	194 ± 32	-13 (-24 to -2)	0.002
Area Above Curve 70 mg/dL *median (interquartile range)*	0.5 (0.2-0.8)	0.4 (0.2-1.1)	0.3 (0.1-0.6)	0.3 (0.1-1.0)	0.2 (0.1-0.5)	0.4 (0.1-0.9)	–	0.002
Area Under Curve 180 mg/dL *median (interquartile range)*	34 (24-48)	33 (24-46)	28 (18-40)	38 (24-53)	26 (15-42)	40 (28-54)	–	<0.001

a. Daytime defined as 6am to <10pm

b. Participants with <48 hours of daytime data were excluded from the analysis (2 CGM and 1 Control at 12 weeks and 3 CGM and 0 Control at 24 weeks; a pre-specified condition).

c. Treatment group comparisons made using analysis of covariance models, adjusted for the corresponding baseline value, baseline HbA1c and clinical site as a random effect using pooled data from 12 and 24 weeks. Due to skewed distributions for the hypoglycemia and hyperglycemia metrics (including area above curve 70 mg/dL and area below curve 180 mg/dL), these models were based on ranks using van der Waerden scores. P values <0.01 were considered statistically significant (with 99% confidence intervals accordingly provided for the metrics which are approximately normally distributed).

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eTable 8. Insulin Use, Body Weight and Hypoglycemia Unawareness

	Baseline		24 Weeks			
	CGM Group (N=105)	**Control Group (N=53)**	**CGM Group (N=102)**	**Control Group (N=53)**	**Mean Adjusted Difference (99% Confidence Interval) [c]**	**P value [c]**
Total Daily Insulin Dose [a] *units/kg/day median (IQR)*	0.7 (0.5, 0.9)	0.6 (0.5, 0.9)	0.7 (0.6, 0.9)	0.7 (0.5, 0.8)	–	–
Change in Total Daily Insulin Dose from Baseline to 24 Weeks [a] *median(IQR)*			-0.02 (-0.10, +0.05)	+0.03 (-0.06, +0.09)	–	0.23
Ratio of Long-acting to Rapid-acting Units of Insulin Per Day *median (IQR)*	1.0 (0.8, 1.4)	1.0 (0.7, 1.5)	0.9 (0.7, 1.3)	1.0 (0.6, 1.3)	–	0.54
Number of Rapid-Acting Insulin Injections Per Day *n(%)*					–	–
1	0	0	1 (<1%)	0		
2	0	1 (2%)	0	1 (2%)		
3	71 (68%)	32 (60%)	58 (57%)	29 (55%)		
4	23 (22%)	15 (28%)	26 (25%)	16 (30%)		
≥5	11 (10%)	5 (9%)	17 (17%)	7 (13%)		
Change in Number of Rapid-acting Insulin Injections Per Day from Baseline to 24 Weeks *n(%)*					–	0.90
≤-1			15 (15%)	9 (17%)		
0			60 (59%)	30 (57%)		
≥+1			27 (26%)	14 (26%)		
Body Weight (kg) *mean ± SD*	84.1 ± 19.6	80.8 ± 17.5	86.3 ± 20.2	81.5 ± 17.4	–	–
Change in Body Weight (kg) *mean ± SD*			+1.7 ± 4.2	+0.7 ± 3.1	+1.0 (-0.7 to +2.8)	0.12
Clarke Hypoglycemia Unawareness Questionnaire Total Score [b] *mean ± SD*	2.1 ± 1.8	2.7 ± 2.1	2.0 ± 1.8	2.5 ± 2.1	–	–
Change in Clarke Hypoglycemia Unawareness Questionnaire Total Score [b] *mean ± SD*			-0.2 ± 1.3	-0.3 ± 1.6	-0.1 (-0.7 to +0.5)	0.64

a. Total daily insulin dose missing for 2 participants in the CGM Group at 24 weeks due to unknown weight.

b. Contains 8 items related to hypoglycemia awareness. Total possible score between 0 and 7 with higher scores denoting more unawareness. 2 participants in the CGM Group and 1 in the Control Group did not complete this questionnaire at 24 weeks.

c. Treatment group comparisons for total daily insulin, long-acting to rapid-acting ratio, weight, and Clarke Hypoglycemia Unawareness score made using analysis of covariance models, adjusted for the corresponding baseline value and clinical site as a random effect. Due to skewed distributions for the total daily insulin and long-acting to rapid-acting ratio, these models were based on ranks using van der Waerden scores. Treatment group comparison for the number of rapid-acting injections per day made using a Poisson regression model, adjusted for the baseline value and clinical site as a random effect. P values <0.01 were considered statistically significant (with 99% confidence intervals accordingly provided for the outcomes which are approximately normally distributed).

eTable 9. Severe Hypoglycemia, Diabetic Ketoacidosis, and Other Serious Adverse Events

	CGM Group (N=105)	Control Group (N=53)	P value [c]
Severe Hypoglycemia			
# Events Per Participant			0.67
0	103	51	
1	2 [a]	1	
2	0	1	
24-week Kaplan-Meier Incidence (95% Confidence Interval)	+2% (-4% to +8%)	+4% (-6% to +14%)	0.49
24-week Incidence Rate [b] (per 100 person-years)	4.2	12.2	0.27
Diabetic Ketoacidosis	0	0	
Other Serious Adverse Events (# events/# participants)	3/2 [d]	0/0	

a. During 1 event, the participant was not using continuous glucose monitoring and during the other, the participant did not hear the continuous glucose monitoring device's hypoglycemia alarm.

b. 24-week incidence rate out of 0.45 person-years for CGM Group and 0.46 person-years for Control Group.

c. Proportions of participants experiencing one or more severe hypoglycemic events in each treatment group compared using logistic regression adjusting for history of severe hypoglycemic events in 12 months prior to randomization and clinical site as a random effect. Incidences of hypoglycemic events were compared using Poisson regression adjusting for history of severe hypoglycemic events in 12 months prior to randomization and clinical site as a random effect. P values <0.05 were considered statistically significant.

d. Serious adverse events were inner ear disorder, pulmonary mass, and trigeminal neuralgia

eTable 10. CGM Satisfaction Questionnaire at 24 Weeks (N=101 participants in CGM Group [a])

	Mean Score [b]	Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
Using the continuous glucose monitor…						
1. Causes me to be more worried about controlling blood sugars.	3.3	21 (21%)	13 (13%)	14 (14%)	17 (17%)	36 (36%)
2. ►Makes adjusting insulin easier.	4.4	56 (55%)	36 (36%)	6 (6%)	2 (2%)	1 (1%)
3. ►Helps me to be sure about making diabetes decisions.	4.4	53 (52%)	42 (42%)	5 (5%)	0	1 (1%)
4. Causes others to ask too many questions about diabetes.	3.7	8 (8%)	5 (5%)	23 (23%)	38 (38%)	27 (27%)
5. Makes me think about diabetes too much.	3.9	2 (2%)	6 (6%)	22 (22%)	41 (41%)	29 (29%)
6. ►Helps to keep low blood sugars from happening.	4.2	37 (37%)	49 (49%)	12 (12%)	2 (2%)	0
7. ►Has taught me new things about diabetes that I didn't know before.	4.1	36 (36%)	44 (44%)	15 (15%)	4 (4%)	1 (1%)
8. Causes too many hassles in daily life.	4.2	0	3 (3%)	14 (14%)	43 (43%)	41 (41%)
9. ►Teaches me how eating affects blood sugar.	4.3	46 (46%)	46 (46%)	7 (7%)	1 (1%)	1 (1%)
10. ►Helps me to relax, knowing that unwanted changes in blood sugar will be detected quickly.	4.3	45 (45%)	46 (46%)	9 (9%)	1 (1%)	0
11. ►Has helped me to learn about how exercise affects blood sugar.	3.9	26 (26%)	42 (42%)	29 (29%)	3 (3%)	1 (1%)
12. ►Helps with keeping diabetes under control on sick days.	3.9	20 (20%)	51 (50%)	28 (28%)	2 (2%)	0
13. ►Has shown me that blood sugar is predictable and orderly.	3.2	10 (10%)	32 (32%)	30 (30%)	22 (22%)	7 (7%)
14. Sometimes gives too much information to work with.	4.1	0	4 (4%)	12 (12%)	56 (55%)	28 (28%)
15. ►Has made it easier to accept doing blood sugar tests.	3.9	32 (32%)	37 (37%)	23 (23%)	4 (4%)	2 (2%)
16. Is uncomfortable or painful.	4.2	3 (3%)	3 (3%)	9 (9%)	42 (42%)	43 (43%)
17. ►Has helped me to learn how to treat low sugars better.	4.0	26 (26%)	53 (52%)	17 (17%)	5 (5%)	0
18. Is more trouble than it is worth.	4.6	0	1 (1%)	3 (3%)	33 (33%)	64 (63%)
19. ►Has helped my family to get along better about diabetes.	3.7	25 (25%)	30 (30%)	35 (35%)	7 (7%)	3 (3%)
20. ►Shows patterns in blood sugars that we didn't see before.	4.4	47 (47%)	48 (48%)	3 (3%)	2 (2%)	0
21. ►Helps prevent problems rather than fixing them after they've happened.	4.2	36 (36%)	53 (52%)	9 (9%)	2 (2%)	1 (1%)
22. ►Allows more freedom in daily life.	4.2	42 (42%)	36 (36%)	22 (22%)	1 (1%)	0
23. ►Makes it clearer how some everyday habits affect blood sugar levels.	4.4	41 (41%)	54 (53%)	5 (5%)	0	0
24. ►Makes it easier to complete other diabetes self care duties.	4.0	30 (30%)	49 (49%)	18 (18%)	4 (4%)	0

eTable 10. CGM Satisfaction Questionnaire at 24 Weeks (N=101 participants in CGM Group [a])--continued

	Mean Score [b]	Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
25. Has caused more family arguments.	4.6	0	2 (2%)	6 (6%)	24 (24%)	69 (68%)
26. Is too hard to get it to work right.	4.5	1 (1%)	1 (1%)	5 (5%)	33 (33%)	60 (59%)
27. Has been harder or more complicated than expected.	4.5	0	2 (2%)	7 (7%)	35 (35%)	57 (56%)
28. ►Has helped to control diabetes better even when not wearing it.	3.6	16 (16%)	42 (42%)	31 (31%)	8 (8%)	4 (4%)
29. Causes our family to talk about blood sugars too much.	4.3	0	2 (2%)	8 (8%)	52 (51%)	39 (39%)
30. Makes it harder for me to sleep.	4.2	0	9 (9%)	7 (7%)	39 (39%)	45 (45%)
31. Causes more embarrassment about feeling different from others.	4.4	0	2 (2%)	6 (6%)	38 (38%)	55 (54%)
32. Shows more “glitches” and “bugs” than it should.	4.2	1 (1%)	6 (6%)	11 (11%)	41 (41%)	42 (42%)
33. Interferes a lot with sports, outdoor activities, etc.	4.2	0	6 (6%)	8 (8%)	49 (49%)	38 (38%)
34. Skips too many readings to be useful.	4.4	1 (1%)	2 (2%)	6 (6%)	42 (42%)	50 (50%)
35. Gives a lot of results that don’t make sense.	4.2	0	4 (4%)	8 (8%)	49 (49%)	40 (40%)
36. Causes too many interruptions during the day.	4.4	0	1 (1%)	6 (6%)	50 (50%)	44 (44%)
37. Alarms too often for no good reason.	4.3	0	5 (5%)	8 (8%)	44 (44%)	44 (44%)
38. ►Has helped to adjust pre-meal insulin doses.	4.2	35 (35%)	57 (56%)	6 (6%)	3 (3%)	0
39. The feedback from the device is not easy to understand or useful.	4.4	2 (2%)	0	10 (10%)	36 (36%)	53 (52%)
40. I don’t recommend this for others with diabetes.	4.7	0	0	3 (3%)	21 (21%)	76 (75%)
41. ►Has made me worry less about having low blood sugars.	4.2	40 (40%)	47 (47%)	7 (7%)	5 (5%)	1 (1%)
42. ►If possible, I want to use this device when the research study is over.	4.7	78 (77%)	20 (20%)	3 (3%)	0	0
43. ►Helps in adjusting doses of insulin needed through the night.	4.1	31 (31%)	51 (50%)	14 (14%)	3 (3%)	1 (1%)
44. ►Makes me feel safer knowing that I will be warned about low blood sugar before it happens.	4.6	67 (66%)	29 (29%)	5 (5%)	0	0

Overall mean ± SD score 4.2 ± 0.4.
‘Benefits’ subscale mean ± SD score 4.2 ± 0.5 (item numbers 2, 3, 6, 7, 9, 10, 11, 12, 17, 20, 21, 22, 23, 24, 38, 41, 42, 43, 44)
‘Lack of Hassles’ subscale mean ± SD score 4.3 ± 0.5 (item numbers 4, 5, 8, 14, 16, 18, 25, 26, 27, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 40)

a. One participant did not complete this questionnaire. Responses were missing from 1 participant for items #5,6,7,14,16,19,20,23,26,30,40,41,43 and missing from 3 participants for item #15.
b. Items with a “►” symbol are positively worded (agreeing corresponds to more satisfaction) and those without the symbol are negatively worded (agreeing corresponds to less satisfaction). To calculate the means, the scores for the positively worded items were reversed so that a higher score always corresponds to greater satisfaction. For example, a value of 5 corresponds to “Agree Strongly” with a positively worded item, or “Disagree Strongly” with a negatively worded item.