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ORIGINAL ARTICLE

Evaluation of a Novel Continuous Glucose Measurement Device in Patients with Diabetes Mellitus across the Glycemic Range

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Abstract

Background:

This glucose clamp study assessed the performance of an electrochemical continuous glucose monitoring (CGM) system for monitoring levels of interstitial glucose. This novel system does not require use of a trocar or needle for sensor insertion.

Method:

Continuous glucose monitoring sensors were inserted subcutaneously into the abdominal tissue of 14 adults with type 1 or type 2 diabetes. Subjects underwent an automated glucose clamp procedure with four consecutive post-steady-state glucose plateau periods (40 min each): (a) hypoglycemic (50 mg/dl), (b) hyperglycemic (250 mg/dl), (c) second hypoglycemic (50 mg/dl), and (d) euglycemic (90 mg/dl). Plasma glucose results obtained with YSI glucose analyzers were used for sensor calibration. Accuracy was assessed retrospectively for plateau periods and transition states, when glucose levels were changing rapidly (approximately 2 mg/dl/min).

Results:

Mean absolute percent difference (APD) was lowest during hypoglycemic plateaus (11.68%, 14.15%) and the euglycemic-to-hypoglycemic transition (14.21%). Mean APD during the hyperglycemic plateau was 17.11%; mean APDs were 18.12% and 19.25% during the hypoglycemic-to-hyperglycemic and hyperglycemic-to-hypoglycemic transitions, respectively. Parkes (consensus) error grid analysis (EGA) and rate EGA of the plateaus and transition periods, respectively, yielded 86.8% and 68.6% accurate results (zone A) and 12.1% and 20.0% benign errors (zone B). Continuous EGA yielded 88.5%, 75.4%, and 79.3% accurate results and 8.3%, 14.3%, and 2.4% benign errors for the euglycemic, hyperglycemic, and hypoglycemic transition periods, respectively. Adverse events were mild and unlikely to be device related.

Conclusion:

This novel CGM system was safe and accurate across the clinically relevant glucose range.

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Abbreviations: (APD) absolute percent difference, (ARD) absolute rate difference, (CGM) continuous glucose monitoring, (CI) confidence interval, (EGA) error grid analysis, (HbA1c) hemoglobin A1c, (SD) standard deviation, (YSI) Yellow Springs Instruments

Keywords: blood glucose, continuous glucose monitoring, glucose clamp method, hyperglycemia, hypoglycemia

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Introduction

The invention of minimally invasive glucose sensors with subcutaneous placement has allowed people with diabetes to continuously monitor changes in glucose levels. Continuous glucose monitoring (CGM) provides the opportunity to obtain and maintain good glycemic control by limiting the frequency and intensity of glucose excursions. Of particular importance, CGM may limit hypoglycemia over the long term;[1–3] hypoglycemia has been identified as a major barrier to attaining optimal glucose control among insulin-treated patients with diabetes.[1,4–6] In addition, warning alarms can help individuals to be aware of impending periods of hyperglycemia or hypoglycemia prior to the onset of major symptoms.[3] However, CGM is still an emerging field, and the accuracy of approved CGM systems has been reported to be suboptimal;[7–9] thus there remains a need for the continued development and improvement in CGM technology.

A CGM system with a novel sensor insertion device is currently under development. This system employs electrochemical sensor technology by generating an electrical signal proportional to the interstitial glucose concentration using glucose oxidase. The system is intended to be portable and has three main components: a sensor that is inserted subcutaneously without the use of a trocar or needle, a transmitter that adheres to the skin and relays the electrical signals from the sensor, and a receiver that can be worn on a belt or placed nearby (within 10 ft) that records the electrical data and can convert the signals to glucose concentrations. This study evaluated the performance of a prototype of this CGM system for measuring glucose during different glycemic levels, with an emphasis on hypoglycemia through the induction of two hypoglycemic states in each subject.

Methods

Subjects

Adults aged 18 to 65 years with type 1 or type 2 diabetes were screened for study eligibility. Subjects were required to be otherwise healthy and to have a body mass index of 19 to 35 kg/m^2 and a hemoglobin A1c (HbA1c) less than or equal to 12%. Exclusion criteria included any acute diseases, chronic diseases other than diabetes; skin disorders; or current use or recent exposure to topical medications at the sensor insertion site or to medications that, in the opinion of the investigator, might interfere with the investigational device or the subject's ability to participate in the study; pregnancy; or current or recent alcohol or drug abuse. In addition, ingesting acetaminophen within 24 h of the study procedure was a criterion for rescheduling. The study protocol was approved by an institutional review board (Schulman Associates IRB, Inc., Cincinnati, OH), and all subjects completed the informed consent process.

Study Design

This was a single-center, glucose clamp study consisting of hypoglycemic, euglycemic, and hyperglycemic plateaus as well as transition periods of rapidly changing glucose levels. The main components of the CGM system used in this study included the sensor module with sterile electrodes, an attached transmitter, and a receiver. The CGM sensors were near-final design; however, other parts of the system were early prototype and not representative of the final product design.

The sensors have electrodes made from platinum and silver/silver chloride with an outer membrane composed of polyurethane and are 0.33 mm in diameter. The sensors were inserted into the subcutaneous tissue on each side of the subject's abdomen (two sensors per subject) on the evening prior to the glucose clamp procedure. A length of approximately 12 mm of the sensor was inserted at approximately a 30° angle and a depth of 5 to 6 mm beneath the skin. Two sensors were inserted for each subject in order to maximize the amount of data collected per subject; comparison between sensors was not a prespecified end point in this early feasibility study, and the results from each sensor were analyzed independently. Subjects were allowed to consume water throughout the study but were to remain fasting after the provided evening meal.

On the study day (i.e., morning after sensor insertion), the subject's current insulin treatment was stopped, and blood glucose was established and maintained at the target level (90 mg/dl) by an automated glucose clamp device (Biostator CGIIS®, MTB Medizintechnik, Amstetten, Germany). In addition to the glucose infusion provided by the Biostator, a variable intravenous insulin infusion was applied in order to clamp glucose at four 40 min plateau periods: first hypoglycemic period (50 mg/dl), hyperglycemic period (250 mg/dl), second hypoglycemic period (50 mg/dl), and euglycemic period (90 mg/dl).

Transition periods between each plateau were managed such that blood glucose was rapidly changing at an approximate rate of 2 mg/dl/min (**Figure 1**). Glucose and/or insulin were infused to achieve and maintain each plateau period. At the conclusion of the testing period and after the subject was stable at a euglycemic glucose level of 90 mg/dl for at least 40 min, both sensors were removed.

Data Collection

Raw electrical current values were collected once every minute from the CGM system and converted to values representative of sensor interstitial fluid glucose concentrations. The conversion was done retrospectively, after the study was completed, using a predetermined algorithm. A Yellow Springs Instruments (YSI) glucose analyzer (YSI Life Sciences, Inc., Yellow Springs, OH) was used for the measurement of venous plasma samples collected every 5 min, and results were regarded as reference measurements. The CGM system was calibrated once per CGM sensor, just prior to the initiation of the clamp procedure (i.e., just before the transition from "steady state" to the first hypoglycemic plateau). Calibration was done retrospectively using a YSI plasma glucose measurement in conjunction with a preset algorithm that was determined prior to study initiation.

Accuracy

The absolute percent difference (APD) from the YSI reference value, which describes the point accuracy of the CGM, was calculated as

$$\text{APD} = \left|\frac{\text{CGM} - \text{YSI}}{\text{YSI}}\right| \times 100,$$

where CGM represents a glucose reading from the investigational CGM device and YSI is the corresponding reference value. In order to compensate for the delay between blood and interstitial fluid glucose, the algorithm compares a YSI value with a CGM value obtained 4 min later.[10–14] The absolute rate difference (ARD), which describes the rate-of-change accuracy of the CGM device, was calculated as

$$\text{ARD} = \left|\text{CGM}'_t - \text{YSI}'_t\right|,$$

where CGM'_t and YSI'_t are the glucose rates of change of the CGM and YSI devices, respectively, over 5 min.

Three types of error grid analysis (EGA) were performed, including point-wise EGA [Parkes (consensus)[15] and Clarke[16] EGA classify results based on the clinical significance of data from a single point in time], rate EGA (classifies results based on the clinical significance of differences in glucose rates of change between devices), and continuous EGA (combines rate EGA and Clarke EGA and takes into account where the CGM result would be on the grid at a later time, calculated from the rate of change of CGM glucose).

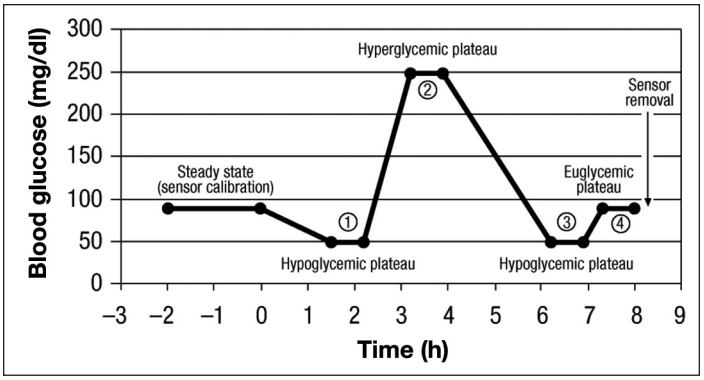

Figure 1. Study design. Representative glucose levels achieved during the clamp procedure with a targeted rate of change of 2 mg/dl/min; the actual rate of glucose change varied among subjects depending on each individual's status, including insulin sensitivity and difficulties in changing glucose levels between glycemic states (e.g., hypoglycemic to hyperglycemic).

Safety

Adverse events were recorded throughout the study. Subjects underwent physical examination and vital sign measurements (blood pressure, pulse, aural temperature) after sensor removal. The sensor explant sites were evaluated for edema and erythema using the Draize scoring system[17,18] approximately 5 min following removal of the two sensors. Follow-up assessments were conducted 3 to 7 days after the procedure, including an assessment of adverse event reporting, a review of concomitant medications, and an examination of the sensor explant sites.

Results

Subjects

Of 23 screened subjects, 15 met the inclusion and exclusion criteria and 14 completed the study; 1 subject who qualified for enrollment served as a backup and did not complete the study. One subject withdrew consent, and 3 subjects did not meet inclusion criteria (no evidence of diabetes, $n = 1$; HbA1c ≥12%, $n = 2$). The remaining reasons for exclusion were based on safety of the clamp procedure (retinopathy and hypertension, $n = 1$; history of epilepsy, $n = 1$; high uric acid, $n = 1$; low hemoglobin and hematocrit, $n = 1$). Subject demographic and baseline characteristics are shown in **Table 1**. Half of the subjects had type 1 diabetes, and half had type 2 diabetes.

Sensor Insertion

Sensor insertion into the abdomen was successful on the first attempt for 25 of 28 sensors (89.3%). For the remaining three sensors, a repeated attempt to insert the sensor was required.

Accuracy of the CGM Sensor

The smallest APDs for the plateau periods were observed during the hypoglycemic plateaus (**Table 2**). The smallest APDs and ARDs for the transition periods were observed during the euglycemic to hypoglycemic transition (steady state to first plateau; **Table 3**).

Parkes (consensus) EGA for the four plateau periods combined (n = 873 paired data sets) showed that 86.8% of results were in zone A (accurate) compared with YSI reference glucose values (**Figure 2**). The grouped outlier shown at the 100 mg/dl level was data collected from a single sensor. An additional 12.1% of results were in zone B, indicating that they differed from the YSI values but were associated with benign or no treatment error. Only 1% of results were in zone C (associated with clinically significant error), and no results were within zones D or E (associated with increasing clinically significant error). Similar results were observed with the Clarke EGA (zone A, 79.8%; zone B, 14.9%; zone D, 5.3%).

Rate EGA showed that the majority (88.6%) of the transition period results were in zones A (68.6%) and B (20.0%) and categorized as accurate or benign compared with YSI reference values, while 11.5% were in zones C (3.8%), D (5.3%), or E (2.4%; **Figure 3** and **Table 4**).

Table 1.
Subject Demographic and Baseline Characteristics

Characteristic	*N* = 14
Median age (range), years	40 (24–64)
Gender, *n* (%)	
Female	5 (36)
Male	9 (64)
Race, *n* (%)[a]	
Caucasian	8 (57)
Black or African American	3 (21)
Hispanic or Latino	3 (21)
Type of diabetes, *n* (%)	
Type 1	7 (50)
Type 2	7 (50)
Median body mass index (range), kg/m^2	27.5 (21.9–34.3)

[a] Percentages may not total 100% because of rounding.

Table 2.
Absolute Percent Difference by Plateau Period

Plateau period	*n*	Mean (95% CI) APD, %	Median (SD) APD, %
Hypoglycemic plateau 1 (1st)	232	11.68 (10.18–13.18)	8.91 (11.58)
Hyperglycemic plateau (2nd)	220	17.11 (15.34–18.88)	15.33 (13.32)
Hypoglycemic plateau 2 (3rd)	212	14.15 (12.64–15.65)	11.87 (11.10)
Euglycemic plateau (4th)	209	18.55 (15.74–21.36)	14.87 (20.61)
All plateau periods	873	15.29 (14.31–16.27)	12.09 (14.78)

Table 3.
Absolute Percent Difference and Absolute Rate Difference by Transition Period

Transition period	APD, %			ARD, mg/dl/min		
	n	Mean (95% CI)	Median (SD)	*n*	Mean (95% CI)	Median (SD)
Euglycemic-to-hypoglycemic transition (steady state to 1st plateau)	351	14.21 (12.89–15.53)	10.61 (12.59)	314	0.62 (0.55–0.69)	0.46 (0.63)
Hypoglycemic-to-hyperglycemic transition (1st to 2nd plateau)	396	18.12 (16.89–19.35)	15.43 (12.48)	365	1.29 (1.17–1.41)	0.96 (1.18)
Hyperglycemic-to-hypoglycemic transition (2nd to 3rd plateau)	703	19.25 (18.02–20.47)	15.63 (16.52)	671	0.90 (0.83–0.97)	0.64 (0.90)
Hypoglycemic-to-euglycemic transition (3rd to 4th plateau)	139	17.54 (14.85–20.23)	11.77 (16.04)	116	1.14 (0.93–1.35)	0.81 (1.14)
All transition periods	1589	17.70 (16.97–18.43)	14.19 (14.85)	1466	0.96 (0.91–1.01)	0.67 (0.98)

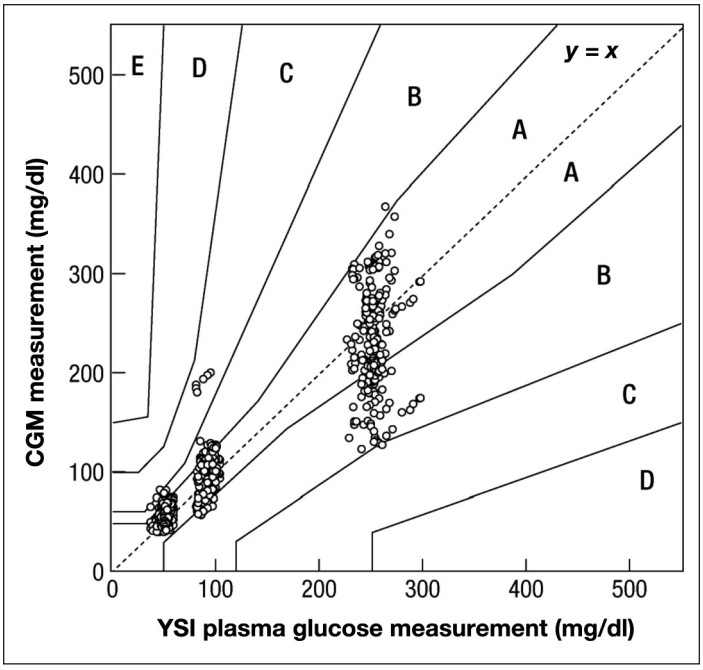

Figure 2. Parkes (consensus) EGA (plateau periods). Results were classified based on the clinical significance of data from a single point in time relative to YSI reference values (zone A, accurate; zone B, benign or no treatment error; zones C–E, increasing clinically significant error).

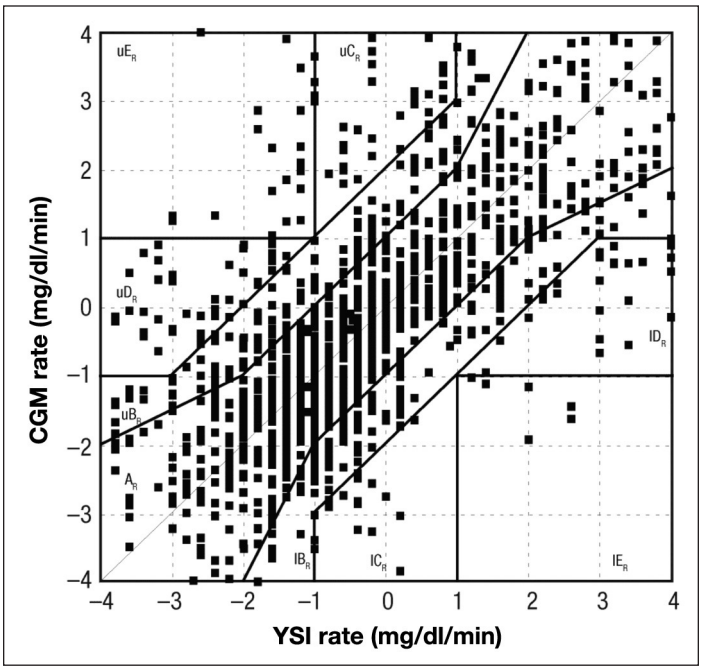

Figure 3. Rate EGA (transition periods). Results were classified based on the clinical significance of the differences in glucose rates of change between the CGM and YSI devices (zone A_R, accurate; zones lB_R and uB_R, benign or no treatment error; zones lC_R, uC_R, lD_R, uD_R, lE_R, and uE_R, increasing clinically significant error). u, upper; l, lower.

Continuous EGA indicated that 91.0% of CGM results were associated with accurate (83.2%) or benign (7.8%) errors, and the CGM system was most accurate in the euglycemic and hyperglycemic ranges, with 96.8% and 89.8% of results, respectively, in the accurate (88.5% and 75.4%) or benign (8.3% and 14.3%) error zones (**Figure 4**). During the hypoglycemic transition period, 81.7% of CGM results were in the accurate (79.3%) or benign (2.4%) error zones, whereas 18.3% were associated with erroneous results.

Table 4.
Rate Error Grid Analysis (Transition Periods)[a]

Zone	A	B	uC	lC	uD	lD	uE	lE
n	1006	293	38	17	48	29	28	7
%	68.6	20.0	2.6	1.2	3.3	2.0	1.9	0.5

[a] u, upper; l, lower.

Data Loss

The algorithm used for CGM data analysis was designed to withhold or cease data transmission under certain predefined circumstances, such as high or low current values outside the physiologic range or unrecoverable changes (e.g., dislodged or unstable sensor, electrical short). No data were lost because of reception failures. Data withheld because of the algorithm resulted in a loss of 3.9% of total minutes (recording time). An additional 5.0% of total minutes were lost because the algorithm indicated that two sensors required replacement during the study. The first sensor replacement was triggered because of low current during the first hypoglycemic period, and the second sensor replacement was triggered because of a high current during the hyperglycemic period.

		Point error grid zones									
		Hypoglycemia BG ≤ 70 mg/dl N = 425 (29.0%)			Euglycemia 70 < BG ≤ 180 mg/dl N = 748 (51.0%)			Hyperglycemia BG > 180 mg/dl N = 293 (20.0%)			
		A	D	E	A	B	C	A	B	C	D	E
Rate error grid zones	A	67.3%	11.8%	0%	57.5%	10.8%	0%	37.5%	15.0%	0%	1.7%	0%
	B	12.0%	4.9%	0%	14.0%	6.1%	0%	16.7%	6.1%	0%	1.0%	0%
	uC	1.2%	0.5%	0%	1.2%	1.5%	0%	3.1%	0.7%	0%	0%	0%
	lC	0.5%	0.2%	0%	0.4%	0.7%	0%	2.0%	0%	0%	0%	0%
	uD	0%	0.5%	0%	2.7%	0.1%	0%	5.5%	3.1%	0%	0%	0%
	lD	0.5%	0%	0%	1.2%	0.5%	0%	2.4%	2.4%	0%	0%	0%
	uE	0.2%	0%	0%	1.2%	1.6%	0%	1.7%	0.3%	0%	0%	0%
	lE	0.2%	0.2%	0%	0.4%	0%	0%	0.7%	0%	0%	0%	0%

Accurate readings Benign errors Erroneous results

Figure 4. Continuous EGA (transition periods). Results were classified based on the clinical significance of combined rate and Clarke EGAs (zone A, accurate; zone B, benign or no treatment error; zones C–E, increasing clinically significant error). BG, blood glucose; u, upper; l, lower.

Safety

Five subjects experienced a total of six adverse events during the study (**Table 5**). All six events were classified as nonserious, mild, and unlikely to be related to the CGM device. There were no sensor fractures during the study. Based on skin assessments, one subject experienced erythema at the sensor explant sites, with a score of 2 (well-defined erythema) on the day of sensor explant; all other cases were scored as 0 (no erythema) or 1 (very slight erythema). At the follow-up visit 3 to 7 days after sensor explant, all scores for erythema were 0. No subjects experienced edema during the study.

Table 5.
Classification of Adverse Events

Adverse event	Intensity	Action taken	Outcome	Relationship to drug/ device
Minor facial puffiness	Mild	None	Recovered	Unlikely
Vomiting	Mild	None	Recovered	Unlikely
Toothache	Mild	Medication	Recovered	Unlikely
Left forearm erythema	Mild	None	Recovered	Unlikely
Ecchymosis at infusion site	Mild	None	Not recovered[a]	Unlikely
Headache	Mild	Medication	Recovered	Unlikely

[a] Recovery status not documented at the follow-up visit.

Discussion

Application of CGM technology to diabetes care is still a relatively new field, and currently available CGM systems must overcome several challenges.[9,19,20] There are accuracy concerns specific to CGM systems that are related to measuring glucose concentration in the interstitial fluid.[9,19,20] Given the time delay of glucose transport from blood to the interstitial space (lag time) and the difference in circulating versus interstitial glucose concentrations, CGM systems require proper calibration using direct blood glucose measurements.[9,19,20] Additionally, the CGM system must have a broad range of performance, including excellent performance at both the lower and upper limits of the glycemic range.

In this study, a prototype, investigational CGM system was associated with a high degree of accuracy with a glucose clamp during hypoglycemic, euglycemic, and hyperglycemic plateaus. The point accuracy of the CGM system was very good during the plateau periods, especially during the hypoglycemic plateaus (mean APDs of 12% and 14%). Dynamic accuracy during the transition periods was also good, with an overall mean ARD of 1.1 mg/dl/min. Point-wise, rate, and continuous EGA classified a high proportion of results as accurate or benign/no treatment error (98.9%, 88.6%, and 91.0%, respectively).

The high level of accuracy in the hypoglycemic range observed with this CGM system is of interest, considering some of the accuracy limitations of currently available CGM devices, particularly at low glycemic levels.[7–9,21] In an early comparative study evaluating the accuracy (based on continuous EGA) of two CGM devices, the Medtronic MiniMed CGM system and Abbott FreeStyle Navigator® had similar accuracy over the euglycemic range (89.3% and 88.8%, respectively) but not during hypoglycemia, with the latter CGM device having significantly greater accuracy in this state (61.6% and 82.4%, respectively; $p < .0005$).[21] Later, a study of the Medtronic Guardian® REAL-time CGM system in an intensive care unit setting found that less than 50% of readings in the hypoglycemic range were accurate.[7] In another study, the clinical utility of self-monitoring of blood glucose in the hypoglycemic range significantly exceeded that of CGM using the FreeStyle Navigator; based on continuous EGA, 83.5%, 6.4%, and 10.1% of self-monitoring of blood glucose readings and 57.1%, 8.4%, and 34.5% of CGM results were classified as "clinically accurate," "benign errors," and "clinical errors," respectively (all $p < .0001$).[8] Finally, in a study assessing the accuracy of the DexCom SEVEN® CGM system, the mean APD was shown to be 16.7% across all glucose concentrations and 24.3% in the hypoglycemic range, with continuous EGA showing a reduction in accuracy from 97.5% in the euglycemic range to 75.0% in the hypoglycemic range.[22]

The investigational CGM system assessed in this study was safe and well tolerated, with only mild non-device-related adverse events reported during the study. The long-term safety and tolerability of this CGM system remain to be established.

Because of the retrospective nature of this early feasibility study, additional studies are needed to evaluate the accuracy of this CGM system in the clinical setting. Also, since CGM devices are intended to be routinely worn by patients in their daily lives, it will also be important for future analyses to determine the accuracy of the CGM sensors after several days of continuous use and under a wide variety of conditions.

Conclusions

The results of this study showed that the investigational CGM prototype has a high degree of accuracy across hypoglycemic, euglycemic, and hyperglycemic plateaus and transition periods and was not associated with safety or tolerability concerns. Further development of this investigational CGM device is ongoing.

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Disclosure:

Ann Tideman, Jennifer Matson, Nancy Dunne, Scott Pardo, Joan Parkes, Holly Schachner, and David Simmons are full-time employees of Bayer HealthCare LLC. Linda Morrow and Marcus Hompesch are employees and stockholders of Profil Institute for Clinical Research, Inc., which received funding from Bayer HealthCare LLC, to conduct this study.

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References:

1. Hay LC, Wilmshurst EG, Fulcher G. Unrecognized hypo- and hyperglycemia in well-controlled patients with type 2 diabetes mellitus: the results of continuous glucose monitoring. Diabetes Technol Ther. 2003;5(1):19–26.
2. Garg SK, Schwartz S, Edelman SV. Improved glucose excursions using an implantable real-time continuous glucose sensor in adults with type 1 diabetes. Diabetes Care. 2004;27(3):734–8.
3. Klonoff DC. Continuous glucose monitoring: roadmap for 21st century diabetes therapy. Diabetes Care. 2005;28(5):1231–9.
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837–53.
5. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–86.
6. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes mellitus. Arch Intern Med. 2001;161(13):1653–9.
7. Jacobs B, Phan K, Bertheau L, Dogbey G, Schwartz F, Shubrook J. Continuous glucose monitoring system in a rural intensive care unit: a pilot study evaluating accuracy and acceptance. J Diabetes Sci Technol. 2010;4(3):636–44.
8. McGarraugh GV, Clarke WL, Kovatchev BP. Comparison of the clinical information provided by the FreeStyle Navigator continuous interstitial glucose monitor versus traditional blood glucose readings. Diabetes Technol Ther. 2010;12(5):365–71.
9. Mazze RS, Strock E, Borgman S, Wesley D, Stout P, Racchini J. Evaluating the accuracy, reliability, and clinical applicability of continuous glucose monitoring (CGM): Is CGM ready for real time? Diabetes Technol Ther. 2009;11(1):11–8.
10. Rebrin K, Steil GM. Can interstitial glucose assessment replace blood glucose measurements? Diabetes Technol Ther. 2000;2(3):461–72.
11. Dexcom STS-7 Continuous Glucose Monitoring System summary of safety and effectiveness data. http://www.accessdata.fda.gov/cdrh_docs/pdf5/P050012S001b.pdf. Accessed April 13, 2011.
12. Steil GM, Rebrin K, Hariri F, Jinagonda S, Tadros S, Darwin C, Saad MF. Interstitial fluid glucose dynamics during insulin-induced hypoglycaemia. Diabetologia. 2005;48(9):1833–40.
13. Garg SK, Smith J, Beatson C, Lopez-Baca B, Voelmle M, Gottlieb PA. Comparison of accuracy and safety of the SEVEN and the Navigator continuous glucose monitoring systems. Diabetes Technol Ther. 2009;11(2):65–72.
14. Ichimori S, Nishida K, Shimoda S, Sekigami T, Matsuo Y, Ichinose K, Shichiri M, Sakakida M, Araki E. Development of a highly responsive needle-type glucose sensor using polyimide for a wearable artificial endocrine pancreas. J Artif Organs. 2006;9(2):105–13.
15. Parkes JL, Slatin SL, Pardo S, Ginsberg BH. A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose. Diabetes Care. 2000;23(8):1143–8.
16. Clarke WL. The original Clarke Error Grid Analysis (EGA). Diabetes Technol Ther. 2005;7(5):776–9.
17. Draize JH. Dermal toxicity. In: Staff of the Division of Pharmacology, Food and Drug Administration, Department of Health, Education and Welfare, eds. Appraisal of the safety of chemicals in foods, drugs and cosmetics. Austin: Association of Food and Drug Officials of the United States Business Office, Bureau of Food and Drugs, Texas State Department of Health; 1959, 46–59.
18. Johnson AW, Goodwin BF. The Draize test and modifications. Curr Probl Dermatol. 1985;14:31–8.
19. Hirsch IB. Clinical review: realistic expectations and practical use of continuous glucose monitoring for the endocrinologist. J Clin Endocrinol Metab. 2009;94(7):2232–8.
20. Keenan DB, Mastrototaro JJ, Voskanyan G, Steil GM. Delays in minimally invasive continuous glucose monitoring devices: a review of current technology. J Diabetes Sci Technol. 2009;3(5):1207–14.
21. Clarke WL, Anderson S, Farhy L, Breton M, Gonder-Frederick L, Cox D, Kovatchev B. Evaluating the clinical accuracy of two continuous glucose sensors using continuous glucose-error grid analysis. Diabetes Care. 2005;28(10):2412–7.
22. Zisser HC, Bailey TS, Schwartz S, Ratner RE, Wise J. Accuracy of the SEVEN continuous glucose monitoring system: comparison with frequently sampled venous glucose measurements. J Diabetes Sci Technol. 2009;3(5):1146–54.