New Features and Performance of a Next-Generation SEVEN-Day Continuous Glucose Monitoring System with Short Lag Time

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Abstract

Background: The purpose of this study was to evaluate new features and performance of the SEVEN® PLUS System (DexCom, Inc., San Diego, CA), a real-time continuous glucose monitoring (CGM) device. This study is the first to evaluate the SEVEN PLUS device.

Methods: Fifty-three subjects were enrolled at three U.S. centers; 43 (81%) of the subjects had type 1 diabetes mellitus, and 10 (19%) had insulin-requiring type 2 diabetes mellitus. Subjects inserted and wore either one or two sensors for 7 days. A subgroup (n = 18) wore two sensors to track precision. Subjects participated in one 8-h in-clinic session with blood draws every 15 min on study Day 1, 4, or 7 to collect laboratory reference YSI instrument (YSI, Yellow Springs, OH) and self-measured plasma glucose (SMPG) reference measurements. For the remainder of the week, CGM was used as an adjunct to SMPG during home use.

Results: The overall median absolute relative difference (ARD) versus YSI was 13.0%. Zones A and B of the Clarke Error Grid of CGM measurements were 73.8% and 22.1%, respectively. Precision ARD was 15.3 ± 6.2% (mean ± SD). The median ARD versus SMPG was 12.1%. Sensor life (89% lasted 7 days) was improved compared to the SEVEN device. The lag time obtained with various statistical measures between CGM and YSI were similar and estimated as a median of 8 min (interquartile range, 11 min) using the Pearson correlation coefficient. No serious adverse events or infectious complications were reported.

Conclusions: The performance of this new system compares favorably to the previous SEVEN device in terms of accuracy, precision, lag time, sensor life, and rate of data capture.

Background

To date, several real-time continuous monitoring (CGM) systems have been approved by the Food and Drug Administration and are used for diabetes management. These monitors measure glucose levels and store them in memory at 1–10-min intervals, thereby providing a more complete view of glycemic control over time, as compared to isolated point-in-time self-monitored plasma glucose (SMPG) measurements. Since their introduction, there have been significant technological advances. In addition to improvements in accuracy, there have been additional features, such as the ability to review recent glucose trends, receive hypo- or hyperglycemic alerts, and (“trend”) arrows that indicate velocity and direction of glucose excursions. Data collected from CGM devices can also be downloaded to personal computers for review by diabetes management teams and used as a means to optimize therapy.

We have previously reported¹ that use of a 3-day, subcutaneous, real-time, continuous glucose sensor (STS™ System, DexCom, Inc., San Diego, CA) was well tolerated and resulted in an improvement in glycemic excursions. Clinical research evidence suggests that utilization of CGM data results in reductions of hemoglobin A1c (HbA1c) values²–⁶ and glycemic excursions.⁷ The landmark Juvenile Diabetes Research Foundation (JDRF) CGM trial demonstrated that CGM can be associated with improved glycemic control in adults.⁹ We recognize that CGM provides a unique point from which to view diurnal glucose patterns without time and frequency biases.¹⁰ Continuous glucose readings that supply trend

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Data from this trial were presented, in part, at the 2009 Advanced Technologies & Treatments for Diabetes meeting in Athens, Greece and the 2009 American Diabetes Association meeting in New Orleans, Louisiana.

This study is registered with trial number NCT00722241 at www.clinicaltrials.gov.
information can help identify and prevent unwanted periods of hypo- and hyperglycemia.11 A recent publication from the JDRF group in which patients with diabetes with baseline HbA1c values <7.0% were enrolled demonstrated significant benefit of CGM with regard to lower HbA1c and decreased hypoglycemia.12 In contrast to their prior publication, both rates of CGM adherence and beneficial outcomes were more uniform among all age cohorts.

This clinical study assessed the accuracy, new features, and safety of the SEVEN® PLUS device (DexCom). The reusable components of this device (i.e., transmitter, and receiver) have been modified from the prior SEVEN device; the 7-day sensor remains unchanged. SEVEN PLUS updates include enhancements to the signal processing algorithm, a menu-driven user interface, the addition of glucose rate-of-change arrows and alerts, and the ability to log events in the receiver (e.g., insulin boluses, exercise, carbohydrate intake, illness, etc.). In a secondary analysis time lag between the subcutaneous (interstitial fluid) sensor glucose and the laboratory reference YSI instrument (YSI, Yellow Springs, OH)-measured blood glucose (BG) in a controlled in-clinic setting was also evaluated.

Materials and Methods

Study population

Fifty-three subjects with diabetes mellitus were enrolled at three centers within the United States. Forty-three subjects (81%) had type 1 diabetes mellitus, and 10 subjects (19%) had type 2 diabetes mellitus. Thirty-one (58.5%) subjects were male. Fifty-two subjects (98.1%) were white, one subject (1.9%) was Asian, and seven subjects (13.2%) were Latino. Subjects were 47.3 ± 12.4 (mean ± SD) years old at the time of enrollment with a diagnosis of diabetes mellitus for 20.8 ± 12.4 years. Twenty-six subjects (49.1%) delivered insulin via continuous subcutaneous infusion pumps, 26 subjects (49.1%) used multiple daily injections, and one subject (1.9%) with type 2 diabetes was not on insulin. Height was 173.5 ± 11.7 cm, body mass was 84.9 ± 28.3 kg, and body mass index was 27.9 ± 7.7 kg/m². At baseline, subjects performed SMPG 5.7 ± 3.1 times daily and had an HbA1c level of 7.4 ± 1.3%. The study protocol was approved by the institutional review boards of all participating centers, and all subjects provided witnessed, written informed consent prior to enrollment.

Study procedures and data collection

This study was prospective, open-labeled, and non-randomized and enrolled subjects during May and June 2008. Baseline HbA1c was measured within 30 days of study participation at the enrolling institution. Throughout this study, subjects underwent continuous glucose monitoring with a system comprising a 7-day transcutaneous sensor, a transmitter, and a receiver. The glucose oxidase-based sensor pod remained adhered to the skin following insertion of the sensor probe into abdominal subcutaneous tissue by means of an introducer needle and applicator. Post-insertion, the sensor continuously measured glucose in the surrounding interstitial fluid. The transmitter snapped into the sensor pod and wirelessly sent an averaged electrical current reading (proportional to the glucose concentration) to the receiver at 5-min intervals. The receiver, a pager-like device, converted the transmitter’s raw data into a glucose value after SMPG-based calibration 2 h post-sensor insertion. The receiver provided the real-time glucose value in mg/dL (updated at 5-min intervals), glucose trend graphs of the preceding 1, 3, 6, 12, and 24 h, rate-of-change arrows, alerts for high glucose (>200 mg/dL) and low glucose (<80 mg/dL), and alarms for hypoglycemia (<55 mg/dL). When blinded (one of two receivers for subjects wearing two devices), the receiver did not provide any of this information. The SEVEN PLUS receiver also permitted entry of additional diabetes care-related information including bolus insulin dosages, carbohydrate intake, activity levels, and illness events.

All subjects were provided with a SMPG meter (One-Touch® Ultra®, LifeScan, Inc., Milpitas, CA) and test strips. This plasma-calibrated meter was used for BG measurements performed throughout the study for receiver calibration and diabetes self-management purposes; capillary samples were obtained from fingersticks (alternative site testing was not allowed). Subjects manually entered all SMPG values to their respective receivers. Meters and test strip lots passed quality control testing with the manufacturer’s control solution before assignment to study subjects.

This study was conducted over a 7-day sensor wear period. Aside from clinic visits for sensor insertions, replacements, or removals, subjects wore the study device during normal daily activities while at home, work, or school. At the beginning of each 8-h in-clinic session, subjects performed control testing with the manufacturer’s control solution before assignment to study subjects.

Subjects returned to the clinic and participated in one 8-h in-clinic session on study days 1, 4, or 7 of sensor wear. Subjects underwent peripheral intravenous catheterization of the dorsal hand, lower arm, or antecubital region to obtain blood samples for YSI plasma glucose determination. Meals and insulin doses were manipulated to obtain a full range of glucose values during the in-clinic session.

Adverse event screening and sensor insertion site assessments were performed at each clinic visit. Digital data from all study receivers and SMPG meters were downloaded via personal computer for analysis. At all times, subjects were instructed to use SMPG values in conjunction with sequential sensor readings over time to guide diabetes management decisions.

Evaluation of time lag

The data collected under a controlled in-clinic setting from 49 study subjects were utilized to evaluate the lag time between reference intravenous BG and the interstitial fluid CGM readings. In order to do so, we first interpolated the CGM glucose values (about every 5 min) to readings every minute by linear approximation. YSI reading timestamps (about every 15 min) were then matched with the CGM timestamps to create multiple matched pairs for every minute of lag time between BG and CGM of each subject within a time window of ±60 min from YSI timestamps. The statistical measures of
the Pearson correlation coefficient ($\rho$), regression root mean squared error (RMSE), root mean squared coefficient of variation (RMSCV), and $R^2$ of a specific log form normalized transformed linear regression, defined as agreement criteria, were then calculated within these matched pairs (with different lag times) within a subject. The by-minute time shift that resulted in the optimum statistic within a subject was then identified as the time lag estimate for the subject based on each specific measure. Essentially the lag was the difference in time that CGM data (curve) shifted to optimize (minimize or maximize) each statistic relative to the YSI data (curve).14

### Data analysis

Descriptive statistics for continuous variables were summarized using mean, SD, median, minimum, and maximum for the matched pair data. Categorical variables such as diabetes history and baseline characteristics were summarized using counts and percentages. Clarke error grid analysis (EGA) and continuous glucose EGA (CG-EGA) were used to quantify the clinical accuracy of CGM in reference to laboratory standard YSI. The combined point and rate CG-EGA collapses the error grid zone into three groups—accurate readings, benign errors, and clinical inaccurate readings—and stratifies them by reference BG zone based on both glucose data points in time and the rate of change of glucose. The system performance was also evaluated in terms of the percentage of the CGM system values that are within ±20% of the relative difference (RD) of reference value at glucose levels >80 mg/dL and ±20 mg/dL of absolute difference at glucose levels ≤80 mg/dL (hereafter referred to as %20/20 mg/dL).

### Results

**SEVEN PLUS accuracy**

The SEVEN PLUS accuracy was assessed by analyzing the difference in the glucose measurements from the CGM system real-time display to subjects when compared to the laboratory standard results from YSI. A total of 1,827 CGM–YSI paired points that fell within the 40–400 mg/dL range of the device were analyzed for sensor accuracy. A Pearson correlation coefficient of 0.93 indicated a highly statistically significant linear relationship between CGM and YSI measurements. The overall median absolute RD (ARD) was 13% with a mean ± SD of 15.9 ± 14.5%. The total percentage points within 20 mg/dL or 20% of YSI reference values was 76.1%, and the percentage within 30 mg/dL or 30% of the YSI reference was 90.4%. Clarke EGA analysis showed 1,752 (95.9%) points falling within clinically acceptable zones A or B, with 1,348 (73.8%) in zone A (clinically accurate, sensor values deviate from YSI by <20%) and 404 (22.1%) in zone B (errors leading to benign or no treatment), three (0.2%) points were in zone C (errors resulting in overcorrection of acceptable glucose levels), 72 (3.9%) were in zone D (errors representing failure to detect unacceptable glucose levels), and none (0.0%) was in zone E (errors leading to erroneous treatment decisions). The CG-EGA results indicated that 61% of the SEVEN PLUS

### Table 1. SEVEN PLUS System Overall Accuracy

<table>
<thead>
<tr>
<th>Accuracy versus</th>
<th>YSI</th>
<th>SMPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (number)$^a$</td>
<td>49</td>
<td>53</td>
</tr>
<tr>
<td>Paired points (number), overall</td>
<td>1,827</td>
<td>3,438</td>
</tr>
<tr>
<td>Pearson correlation coefficient</td>
<td>0.93</td>
<td>0.93</td>
</tr>
<tr>
<td>Median ARD</td>
<td>13.0%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Percentage of points within</td>
<td>20%/20 mg/dL of reference$^b$</td>
<td>76.1%</td>
</tr>
<tr>
<td>Zone B</td>
<td>90.4%</td>
<td>89.3%</td>
</tr>
<tr>
<td>Clarke Error Grid</td>
<td>95.9%</td>
<td>96.7%</td>
</tr>
<tr>
<td>Zone A</td>
<td>73.8%</td>
<td>73.6%</td>
</tr>
<tr>
<td>Zone B</td>
<td>22.1%</td>
<td>23.2%</td>
</tr>
</tbody>
</table>

$^a$Four YSI sample were missing because of failed intravenous access attempts or sensor Failures.

$^b$20% or 30% for reference >80 mg/dL and 20 mg/dL or 30 mg/dL for reference ≤80 mg/dL.

### Table 2. CGM to YSI Agreement by Sensor Wear Day

<table>
<thead>
<tr>
<th>Sensor day of wear$^a$</th>
<th>Subjects (N)$^b$</th>
<th>Paired points (n)$^b$</th>
<th>RD (%)</th>
<th>ARD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median</td>
<td>Min, Max</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td>637</td>
<td>−1.7 (22.7)</td>
<td>−5.5</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>635</td>
<td>−1.4 (18.3)</td>
<td>−2.4</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>533</td>
<td>0.9 (23.8)</td>
<td>−1.0</td>
</tr>
</tbody>
</table>

Max, maximum; Min, minimum.

$^a$YSI sessions occurred on Days 1, 4, and 7 of sensor wear; 22 matched pairs fell outside of the per protocol time windows for these sessions.

$^b$N = number of subjects contributing data, n = number of matched pairs.
readings were accurate within the hypoglycemia range (BG ≤70 mg/dL), 97% were accurate within the euglycemia range (70 < BG ≤180 mg/dL), and 94% were accurate within the hyperglycemia range (BG ≥180 mg/dL). Similar results were observed for the CGM–SMPG matched pair data. Overall, the accuracy results of CGM in reference to the laboratory standard YSI or SMPG meter were similar (Table 1).

Sensor stability and reliability

After the 2-h initial calibration period, the SEVEN PLUS device provides glucose information for up to 166 h (i.e., 7 days). Performance of the SEVEN PLUS device was evaluated according to length of time from sensor insertion. Sensor accuracy and stability were assessed by comparing the bias RD and ARD of the paired YSI value on Days 1, 4, and 7 of sensor wear (days of YSI in-clinic sessions) (Table 2). These statistics were relatively consistent at different sensor wear days, although a non-parametric Kruskal-Wallis test statistic had a \( P \) value of 0.01, indicating that the median ARD was slightly better (12.1%) on Day 4 compared with Day 1 (13.2%) or Day 7 (14.1%) and that the median ARD was better on Day 7 (−1.0 mg/dL) compared with Day 1 (−2.4 mg/dL) or Day 7 (−5.5 mg/dL) \( (P = 0.03) \). The SEVEN PLUS device was designed to be used for up to 7 days. Table 3 displays the estimated survival rate of the sensor; 89% of the sensors lasted up to 7 days. Furthermore, 87% of the sensors provided at least 75–100% of expected readings.

Sensor precision

A subgroup of 18 subjects simultaneously wore two SEVEN PLUS devices (one device was blinded) for the purpose of evaluating the precision of the system. Of the total 29,270 matched data pairs, the percentage median paired ARD was 14%, and the median of the coefficient of variation was 10%.

<table>
<thead>
<tr>
<th>Sensor wear day</th>
<th>Percentage (number sensor survival rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>98.6% (70)</td>
</tr>
<tr>
<td>2</td>
<td>97.1% (69)</td>
</tr>
<tr>
<td>3</td>
<td>91.5% (65)</td>
</tr>
<tr>
<td>4</td>
<td>91.5% (65)</td>
</tr>
<tr>
<td>5</td>
<td>91.5% (65)</td>
</tr>
<tr>
<td>6</td>
<td>88.7% (63)</td>
</tr>
<tr>
<td>7</td>
<td>88.7% (63)</td>
</tr>
</tbody>
</table>

Table 3. Estimated Sensor Life

<table>
<thead>
<tr>
<th>YSI glucose rate of change (mg/dL/min)</th>
<th>ARD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N(^a)</td>
</tr>
<tr>
<td>Less than −1</td>
<td>214</td>
</tr>
<tr>
<td>−1 to 1</td>
<td>1,103</td>
</tr>
<tr>
<td>Greater than 1</td>
<td>441</td>
</tr>
</tbody>
</table>

\(^a\)N refers to the number of matched pairs of YSI–sensor data.
New receiver features

The SEVEN PLUS device was designed to provide the user with additional tools to manage his or her diabetes care, which includes the algorithm-estimated glucose rate-of-change trend arrows and user event input logs. The trend arrows provided real-time glucose trending (rising or falling) information and were classified into different glucose rates of change groupings. The SEVEN PLUS device accuracy was evaluated at different rates of change of YSI BG (Table 4). The system bias to YSI reference, the ARD, was consistent at these different glucose rates of change (non-parametric Kruskal-Wallis test, $P = 0.126$). The SEVEN PLUS device allowed the user to log diabetes-related events, such as meals, insulin, health, and activity information. Analysis of device usage demonstrated $44 \pm 21$ (mean $\pm$ SD) screen views per day, consistent with frequent interaction with the CGM device.

Time lag

From the in-clinic controlled setting data, the average overall time delay between reference BG and sensor readings had a time lag median of 8 min (interquartile range, 11 min) using correlation coefficient estimates. The time lag estimates were independently estimated for each subject using multiple statistical measures, such as RMSE, RMSCV, and Pearson correlation coefficients. These time lag estimates between SEVEN PLUS and YSI glucose readings were short and similar using all four measures (Table 5), with the YSI readings shortly preceding the SEVEN PLUS readings. Figure 2 shows the estimated time lag for the same subject shown in Figure 1.

Figure 1 illustrates a case study of the SEVEN PLUS device, which tracked glucose and diabetes-related events well.

### Table 5. Lag Time Estimates (in Min) and Their Confidence Intervals

<table>
<thead>
<tr>
<th>Statistical measure</th>
<th>Study sample</th>
<th>1,000 boot-strapped resampling with replacements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Pearson correlation</td>
<td>7.0</td>
<td>11.3</td>
</tr>
<tr>
<td>RMSE</td>
<td>4.0</td>
<td>16.1</td>
</tr>
<tr>
<td>RMSCV</td>
<td>5.8</td>
<td>11.0</td>
</tr>
<tr>
<td>$R^2$ on transformed data (AC)</td>
<td>6.5</td>
<td>10.4</td>
</tr>
</tbody>
</table>

AC, agreement criteria; IQR, interquartile range.

**FIG. 2.** Lag time estimate of the case sample subject shown in Figure 1.
To explore the possibility that these differences were the result of sensor algorithms or study settings and to support the robustness of this study’s estimates, a resampling bootstrapping method with 1,000 samples was performed. The results provided consistent confidence intervals of the lag time. The bootstrapped resampling for the lag time using different estimators was similar in the median and 95% confidence intervals as well. These are consistent with a short lag time that may be estimated by commonly accessible correlation statistics.

**Safety**

One adverse device effect of a broken sensor probe was reported. This event was neither serious nor unanticipated, and the affected subject was asymptomatic during and after the incident. Adhesive and sensor needle insertion site irritation was mild and infrequent. No severe serious adverse events were reported during this study.

**Discussion**

This is the first report of a clinical study involving use of the SEVEN PLUS CGM device. In this study, the overall RD between SEVEN PLUS measurements of interstitial glucose concentrations (calibrated to plasma glucose) and YSI reference BG levels was small (13%). A strong linear relationship between sensor and YSI reference BG levels was found (indicated by a statistically significant correlation coefficient of 0.93). The clinical applicability of CGM in Clarke EGA showed a satisfactory 96% of paired sensor–YSI points falling within zones A and B of the Clarke Error Grid. These results are better than accuracy measures observed in our previous report of 3-day use of the continuous glucose sensor. Moreover, the present study demonstrated that sensor accuracy was consistent across 7 days of wear.

A recent multicenter randomized study reported that the adult cohort that used CGM more frequently (83% used at least 6 days per week) showed substantially greater improvement in glycemic control without a significant increase in hypoglycemia. The ability of this new SEVEN PLUS device to be worn longer may increase adherence with CGM devices and facilitate such improvements in metabolic control.

The unique data capture feature that tracked how often the subjects viewed the trend screen on the SEVEN PLUS indicated that subjects elected to check and view the glucose trend screens quite frequently while wearing the device. All statistics in sensor stability indicated a reliable sensor performance over the wear period and a high data capture and sensor survival rate.

The SEVEN PLUS device provided users a rate-of-change trend arrow. The study data indicated that the accuracy rate is consistent at different rates of change, which is important for showing glucose trending information. This feature, which is present in other real-time CGM devices, may simplify self-management decisions, for example, the guidelines used during the JDRF CGM trial. Event markers displayed on CGM profiles may also provide patients and caregivers additional insights into the effects of insulin, carbohydrate intake, illness, and exercise on metabolic control.

Multiple studies have investigated the possible lag time between the BG fluctuations and the interstitial glucose CGM measurements. Because such a lag time could greatly influence the accuracy of CGM, a better understanding of the lag time for different CGM devices is important for its use in managing diabetes care. This study utilized various methods in estimating the time lag of the SEVEN PLUS device and concluded that the time lag is approximately 6–8 min, which is considerably shorter than the estimates from other CGM device studies (which showed lag times in excess of 10 min). These observations suggest that this device may simplify CGM device usage for persons with diabetes as, with appropriate calibration, the lag time is negligible.

We conclude that use of this new generation of a 7-day CGM device was safe and well tolerated. The performance of the system compares favorably to the previous SEVEN device in terms of accuracy, precision, sensor life, and rate of data capture. Data provided in the form of real-time glucose values, trend graphs, hyper-/hypoglycemia alerts, and trend arrows may enable users to significantly improve both high and low glucose excursions and to better manage their diabetes.

**Acknowledgments**

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**Author Disclosure Statement**

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