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Research Article

Implantable CGM Use Improves Glycemic Control in CGM Naive Patients

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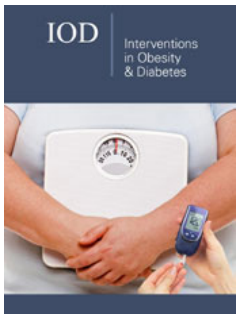

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Abstract

Background: Multiple studies have confirmed the safety and accuracy of implantable Eversense CGM Systems.

Methods: A prospective, multicenter one-year post-market study comparing SMBG to CGM in adults with diabetes naive to CGM was initiated in the US. Following screening, patients used SMBG for 6 months followed by Eversense for 6 months. Visits occurred every 90 days to collect SMBG/CGM and safety data. HbA1c was measured at baseline, 6 and 12 months. Glucometrics were calculated.

Result: One-hundred users have completed the study (9% type 1 diabetes, 57 years age). Mean HbA1c was <7% by end of study. Time In Range(70-180mg/dL), Time Below Range(<70mg/dL) and Time Above Range (>180mg/dL, >250mg/dL) improved with CGM compared to SMBG.

Conclusion: CGM naïve patients met mean HbA1c target by study end. TIR (70-180mg/dL) increased and both TBR(<70mg/dL) and TAR (>180, >250mg/dL) decreased with CGM use. These data suggest that Eversense CGM improves glucose management compared to SMBG.

Keywords: CGM naive; Continuous glucose monitoring; Glucometrics; Implantable sensor; Type 1 diabetes; Type 2 diabetes

Abbreviations: CGM: Continuous Glucose Monitoring: HbA1c: Glycated Hemoglobin; SMBG: Self-Monitoring of Blood Glucose; TIR: Time in Range; TBR: Time Below Range; TAR: Time Above Range; MARD: Mean Absolute Relative Deviation; T1D: Type 1 Diabetes; T2D: Type 2 Diabetes; AE: Adverse Event; BG: Blood Glucose; SAEs: Serious Adverse Events; SD: Standard Deviation; CV: Coefficient of Variation; GMI: Glucose Management Indicator

Introduction

The initial CGMs required confirmation of a CGM interstitial glucose value with a fingerstick blood glucose level (Self-Monitoring of Blood Glucose [SMBG]) before administering a prandial or correction insulin bolus, i.e., adjunctive use. As CGM systems evolved and achieved lower MARD values, adjunctive use of CGM was no longer required, allowing patients to dose insulin with the CGM glucose value alone. The main supportive study for the non-adjunctive use of CGM was the REPLACE-BG study which demonstrated that there was no difference in time in range (glucose 70-180mg/dL) and in the occurrence of severe hypoglycemic events over a 26-week period in adults with diabetes when comparing CGM alone versus CGM with a confirmatory SMBG reading [1].

In June 2019, the FDA approved Eversense 90-day CGM system for management of diabetes without a confirmatory SMBG value. A post approval study was designed to assess the safety and glycemic outcomes of this non-adjunctive use of the implanted sensor system. This manuscript describes the results of an interim analysis comparing glycemic outcomes when using SMBG to those while using the Eversense CGM System in the first 100 CGM naive adults with type 1 or type 2 diabetes (T1D or T2D, respectively) who completed the study to determine if glycemic management improved during Eversense CGM System use compared to SMBG use in this patient population.

Materials and Methods

The study design is a prospective, multicenter, one year comparison of SMBG to Eversense in CGM naive adults with either T1D or T2D diabetes in the United States in an estimated 925

users. Individuals are eligible for participation in the study if they are ≥18 years old, have a clinically confirmed diagnosis of T1D or T2D and have a smart phone. Patients are not study candidates if they have prior use of CGM, have serious illness or complications, have a known contradiction to dexamethasone or dexamethasone acetate, require intravenous mannitol or sorbitol solutions, or are pregnant or planning pregnancy. The study was performed in accordance with the Declaration of Helsinki and was approved by a centralized internal review board. All participants provided both verbal and written informed consent.

This study has two Phases: use of SMBG for 6 months (SMBG Phase) followed by use of Eversense for 6 months (CGM Phase), with Eversense sensors inserted at the start of the CGM Phase. The 90-day Eversense CGM System was used in the CGM Phase initially and transitioned to the 180-day Eversense E3 CGM System following FDA approval in February 2022. Therefore, during the CGM Phase, participants could have either two 90-day duration sensors inserted sequentially, a combination of one 90-day and one 180-day sensor, or 180-day only. The study consists of the following activities: 1) baseline screening and start of the SMBG Phase with visits every 90 day for BG meter download, Adverse Event (AE) assessment, and diary collection for 6 months, 2) start of the CGM Phase with visits every 90 days for CGM replacement (90-day sensor only), BG meter download, AE assessment, diary collection and 3) final sensor removal (performed at the final clinic visit followed by a follow-up assessment phone call). Participants with one 90-day sensor followed by one 180-day sensor had a 12 month visit for endpoint assessment. CGM data are collected continuously using the Eversense Data Management System (DMS).

At the baseline screening visit, investigators obtained participant demographics and medical history, performed a physical examination, and obtained a blood sample for hemoglobin A1c measurement. Hemoglobin A1c was measured using a central laboratory (MedPace Reference Laboratory, Cincinnati, Ohio). Urine pregnancy testing was also conducted in female participants of childbearing potential. During the CGM phase, sensors are inserted into the upper arm as described previously [2]. Patients are administered the Diabetes Distress Scale at baseline and 6- and 12-month visits and the CGM Satisfaction Scale 3 months after the start of the CGM Phase (9-month visit) and end of the CGM Phase (12-month visit). AEs, including Serious Adverse Events (SAEs) are recorded at each visit and between visits during periodic phone calls. The primary study outcome is safety comparing moderate and severe hypoglycemic and DKA events in both phases. Secondary outcomes include changes in HbA1C from baseline after the SMBG Phase completion at 6 months, and after the CGM Phase completion at 12 months. Changes in glucometrics from the end of the SMBG Phase to the end of the CGM Phase are also evaluated. Safety and quality of life measures will be addressed in subsequent publications.

Study participants are supplied with a Blood Glucose (BG) meter and test strips (CONTOUR Next One, Ascensia Diabetes Care, Basel, Switzerland). During the SMBG Phase, participants are instructed to make diabetes care decisions based on BG meter values and obtain at least 4 SMBG measurements per day. During the CGM Phase, diabetes care decisions are based on the Eversense CGM system values. CGM calibration values were entered into the mobile application as prompted daily. Study participants are instructed to keep a diary of moderate and severe hypoglycemic and diabetic ketoacidosis events and to contact their clinical site when severe AEs or SAEs occur during the study. An interim analysis was conducted comparing glycemic outcomes when using SMBG to that while using the Eversense CGM System including all participants who had completed the study as of March 9, 2023.

Statistical analysis

Confidence intervals and p-values were calculated using a paired samples t-test with appropriate degrees of freedom. All metrics were calculated by subject. Descriptive statistics for glucometrics were calculated by participants using all available SMBG values in the SMBG Phase and all available Sensor Glucose (SG) values in the CGM Phase. Differences between the SMBG Phase and CGM Phase glucometrics were also calculated.

These calculations included mean glucose, Standard Deviation (SD), Coefficient of Variation (CV), and Glucose Management Indicator (GMI). The percent of SMBG values through the SMBG Phase and SG values through the CGM Phase, and time in minutes each participant had readings in each of the following glucose ranges over the 24-hour period were calculated: <54mg/dL, <70mg/dL, 70-180mg/dL, >180mg/dL, and >250mg/dL. In addition, the percentage of participants who had reached at least 70% time in range (70-180mg/dL) through each phase was calculated. Lastly, changes in HbA1c from baseline to the end of each phase and percent of participants who had an HbA1c <7% during each phase were calculated.

Result and Discussion

One hundred study participants have completed the study across 21 sites in the United States since first study enrollment on April 13, 2021, to March 9, 2023. Enrollment is ongoing as of this report. Demographics show the cohort was 50% male, mean age was 57±11 years, mean duration of diabetes 14.6±9.2 years and 9% reported type 1 diabetes. Forty-nine percent of participants used an intensive insulin regimen (Multiple Daily Injections [MDI] or Continuous Subcutaneous Insulin Infusion [CSII]) and 51% were on oral medications, non-insulin injectable agents (e.g., GLP-1) or reported no diabetes medications.

Overall, HbA1c was reduced 0.69±1.15% (Mean±SD) from baseline through the end of the study (Table 1). The HbA1c at baseline was 7.66±1.63%, and at the end of the SMBG Phase had decreased to 7.17±1.27% (Table 1). There was a significant further decrease in HbA1c after the CGM Phase to 6.93±1.08%. The change from baseline HbA1c to the end of the SMBG Phase was -0.48±1.03% [-0.68, -0.27, p<0.0001] and the change from the end of the SMBG Phase to the end of the CGM Phase was -0.25±0.79% [-0.41, -0.09, p=0.003]. The percentage of users with HbA1c <7%, the target value [3], at baseline was 36%, at the end of the SMBG

Phase was 46%, and at the end of the CGM Phase was 57%. Table 1 shows the results of the glucometric analysis through each phase including between phase differences. There was a significant reduction in mean glucose levels between SMBG and CGM Phases. In addition, the measures of glycemic variability (SD and CV) were both significantly reduced between the study phases. The GMI value was 7.14% at the end of the SMBG Phase and 6.95% at the end of the CGM Phase. While time in hypoglycemia <54mg/dL was not different between SMBG and CGM Phases, time <70mg/dL was significantly lower after CGM compared to SMBG. TIR showed a significant mean increase of 5.04% (p<0.001) between SMBG and CGM Phases which translated to a mean increase of 74.73 additional minutes (~1 hour and 15 minutes) in range. In addition, the percent of study participants who had achieved >70% TIR increased from 60.2% at the end of SMBG Phase to 68% at the end of CGM Phase. Time above range (time>180mg/dL and >250mg/dL) were also significantly reduced in the CGM Phase compared to SMBG Phase.

Table 1: Glucometric and HbA1c Changes by SMBG Phase and CGM Phase. Abbreviations: SD, Standard Deviation; SG, Sensor Glucose; CV, Coefficient of Variation; GMI, Glucose Management Indicator; SMBG, Self-Monitoring of Blood Glucose; CGM, Continuous Glucose Monitoring; HbA1c, Glycated Hemoglobin; CI, Confidence Interval.

End of Phase	End of SMBG Phase(n=98)		End of CGM Phase (n=100)		Change SMBG vs CGM (n=98)
Parameters	**Mean (SD)**		**Mean (SD)**		**Mean (SD) [95% CI] p value**
Mean Glucose, mg/dL	159.99 (43.55)		152.24 (32.77)		-7.67 (26.17) [-12.91, -2.42] p<0.005
SD, mg/dL	48.57 (22.52)		42.68 (16.35)		-5.75 (11.32) [-8.02, -3.48] p<0.0001
SG CV%	29.58 (8.55)		27.53 (7.16)		-1.97 (5.46) [-3.07, -0.88] p<0.001
GMI, %	7.14 (1.04)		6.95 (0.78)		-0.18 (0.63) [-0.31, -0.06] p =0.005
Time in Glucose Range, %	**Mean (SD)**	**Time (min)**	**Mean (SD)**	**Time (min)**	**Mean (SD) [95% CI] p value**
<54mg/dL	0.40 (1.34)	5.76	0.29 (0.63)	4.18	-0.11 (1.10) [-0.33, +0.11] p=0.34
<70mg/dL	2.11 (4.09)	30.38	1.40 (2.02)	20.16	-1.44 (4.15) [-2.54, -0.34] p=0.01
[70-180]mg/dL	69.02 (24.96)	993.89	74.21 (22.12)	1068.62	+5.04 (13.65) [+2.31, +7.78] p<0.001
>180mg/dL	28.87 (24.75)	415.73	24.40 (22.10)	351.36	-4.49 (14.42) [-7.41, -1.56] p=0.003
>250mg/dL	9.92 (15.13)	142.85	6.82 (11.45)	98.21	-3.00 (9.12) [-4.83, -1.17] p=0.002
HbA1c	**Mean (SD) %**				**Change [95% CI] p value**
Baseline (n=100)	7.66 (1.63)				
6 months (before sensor use) (n=99)	7.17 (1.27)				
12 months (after sensor use) (n=96)	6.93 (1.08)				
Change from baseline through 12 months (SMBG Phase and CGM Phase) (n=96)	-0.69 (1.15)				[-0.92, -0.46] p<0.0001
Change from baseline to 6 months (SMBG Phase) (n=99)	-0.48 (1.03)				[-0.68, -0.27] p<0.0001
Change from 6 to 12 months (CGM Phase) (n=95)	-0.25 (0.79)				[-0.41, -0.09] p=0.003

This post approval study was designed to assess the safety of the non-adjunctive Eversense CGM systems. Two 6-month time periods are compared; during the first 6 months SMBG was used to manage diabetes while during the second 6 months the Eversense CGM System was used. Two different generations of Eversense were used by the subjects in this interim analysis: the original Eversense 90-day system with a MARD of 8.5% for one or both sensor cycles or the Eversense E3 180-day CGM System (MARD of 8.5%) for the only or second sensor cycle after FDA approval in February 2022.

While participants with either type 1 or type 2 diabetes had reductions in their HbA1c after the first 6- months using SMBG only, there was a further significant decrease in HbA1c after 6-months of CGM use with Eversense CGM System. The mean HbA1c value achieved after the CGM time-period was below the target of 7%. In addition, glucometrics showed CGM was able to result in significantly more TIR and significantly less TAR for both >180mg/dL and >250mg/dL, with significantly less time spent <70mg/dL. Mean glucose, SD, CV and calculated GMI were also all significantly improved during the CGM time-period compared to the SMBG time-period. There have been numerous, large, randomized clinical trials performed that support the glycemic benefits of CGM over SMBG in patients with type 1 and type 2 diabetes [4-8]. Numerous meta-analyses have confirmed this finding [9,10]. The benefits of CGM compared to SMBG included a significant reduction in HbA1C and time spent in hypoglycemia [4-8], reduction in hypoglycemia unawareness [11,12], improved patient- reported outcomes [5], and reduction in rates of DKA and severe hypoglycemia [13]. In the early 2000s, these studies were done with adjunctive CGM systems that required confirmation of glucose levels with SMBG prior to adjusting insulin doses for meals and high glucose corrections. However, as CGM accuracy improved, CGM systems were approved for non-adjunctive use, i.e., without SMBG glucose confirmation. The REPLACE- BG study demonstrated that CGM data could be used to safely make insulin treatment decisions, showing no difference in those using CGM alone versus those using a confirmatory SMBG

reading [1]. Of note, the use of continuous glucose monitoring (such as the Eversense CGM Systems) may further enhance glycemic control in patients by facilitating the activation of the anti-aging gene Sirutin 1 with relevance to glucose regulation and insulin secretion. Plasma Sirutin 1 levels may improve with the use of the CGM systems [14-16].

Limitations of this report include that it is an interim analysis, and that the study has predominately enrolled adults with type 2 diabetes. The differential in recruitment of participants with T1D versus T2D was due to the requirement that study participants be CGM naive; an increasingly difficult criterion to achieve in the type 1 population. An additional limitation is that blinded CGM was not used to assess glucometrics in the SMBG Phase. However, a total of 52,537 SMBG values were obtained during the SMBG phase and the changes between phases were statistically significant in all categories except for time <54mg/dL.

Conclusion

This interim analysis of 100 patients who completed the 1-year study confirms that the 6-month period when patients managed their glucose levels with the Eversense CGM system allowed for superior glucose outcomes compared to the initial 6-month period where management was achieved with SMBG only.

Acknowledgment

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Conflict of Interest Statement

KST, BR, CM and FRK are employees of Senseonics, Incorporated, the manufacturer of the CGM System evaluated.

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