DIABETES TECHNOLOGY & THERAPEUTICS
Volume 27, Number 5, 2025
© Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2024.0592

Open camera or QR reader and scan code to access this article and other resources online.

BRIEF REPORT

Evaluation of Accuracy and Safety of the 365-Day Implantable Eversense Continuous Glucose Monitoring System: The ENHANCE Study

Timothy S. Bailey, MD,[1] David R. Liljenquist, MD,[2] Douglas S. Denham, DO,[3] Ronald L. Brazg, MD,[4] Sorin Ioacara, MD, PhD,[5,6] James Masciotti,[7] Samanwoy Ghosh-Dastidar, PhD,[7] Katherine S. Tweden, PhD,[7] and Francine R. Kaufman, MD[7]

Abstract

The implanted Eversense Continuous Glucose Monitoring (CGM) System transitioned from 90- to 180- to 365-day durations marketed today. This report summarizes the 365-day clinical study. ENHANCE was a prospective, multicenter study evaluating the accuracy and safety of the Eversense 365 CGM system through 1 year in adults with diabetes. Accuracy and adverse events (AEs) were assessed during 14 in-clinic visits comparing CGM and Yellow Springs Instrument reference glucose measurements, including during hyperglycemia and hypoglycemia challenges. In total, 110 participants were implanted with the Eversense 365 CGM System. The overall mean absolute relative difference was 8.8% with primarily one calibration per week. The confirmed alert detection rate at 70 mg/dL was 96.6%, and at 180 mg/dL, it was 97.9%. Ninety percent of the sensors survived 365 days. Interoperable CGM special controls were met. No related serious AEs were reported. The Eversense 365 CGM was shown to be safe and accurate through 1 year with primarily one calibration per week.

Keywords: CGM, implantable sensor, iCGM, eversense.

Introduction

The Eversense E3 Continuous Glucose Monitoring (CGM) System, the previous generation implantable Eversense CGM system in the United States, had up to a 180-day duration with a mean absolute relative difference (MARD) of 8.7%.[1,2] The Eversense AP CGM System met interoperable CGM (iCGM) special controls, enabling it to become part of an automated insulin delivery (AID) device.[3]

In September 2024, the Food and Drug Administration cleared the Eversense 365 CGM System that was redesigned with multiple glucose and oxidation sensing areas to extend

[1]Headlands Research California—AMCR Institute, Escondido, California, USA.
[2]Rocky Mountain Research Center, Idaho Falls, Idaho, USA.
[3]Flourish Inc, San Antonio, Texas, USA.
[4]Rainer Clinical Research Center, Renton, Washington, USA.
[5]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania.
[6]Elias Emergency University Hospital, Bucharest, Romania.
[7]Senseonics, Incorporated, Germantown, Maryland, USA.

sensor life to up to 1 year and also reduce the frequency of required calibrations for iCGM designation. This article describes the performance and safety of the Eversense 365 CGM System in adults with diabetes achieved in the ENHANCE clinical study after feasibility studies showed promise in sensor longevity and performance with primarily weekly calibrations.[4]

Methods

The ENHANCE clinical study (clinicaltrials.gov: NCT 05131139) was a prospective, multicenter, nonrandomized 1-year study involving study participants with diabetes ≥18 years of age at four clinical sites in the United States. The study was conducted between June 2022 and February 2024. Eligibility criteria were identical to those previously described with the exception of baseline hematocrit ≥38%.[1] Study performance was in accordance with the Declaration of Helsinki and was approved by the Food and Drug Administration and Advarra, a centralized internal review board, prior to any study activities. All participants provided both verbal and written informed consent.

The device consists of three components: a fluorescence-based optical glucose sensor (3.5 mm by 18.3 mm cylinder), a smart transmitter, and a medical mobile application (app).[1,5–7] The sensor is inserted into the upper arm by trained health care providers.[1,5–7] The transmitter is placed on the skin over the sensor using a silicone-based adhesive patch. It can be removed without disturbing the sensor and is rechargeable. It wirelessly powers the sensor, calculates the glucose values, provides programmable on-body vibratory alerts for hypoglycemia and hyperglycemia, and relays the information directly to the smartphone app.

Study visits occurred for baseline screening (during which a physical examination, medical history, demographics, HbA1c and hematocrit measurements, and urine pregnancy test in female participants were conducted), sensor insertion (day 0), and 14 total accuracy visits on days 1, 7, or 14 or 22, 30, and then every 30 days until day 365. Sensors were removed following the 365-day visit with a safety visit 10 days postsensor removal.

The in-clinic accuracy visit involved assessing the occurrence of any adverse events (AEs) including serious AEs (SAEs), sensor insertion site integrity, hematocrit levels, pregnancy status, illness (such as fever), and changes in medications since baseline collection. Accuracy of the Eversense 365 CGM System was evaluated by comparing CGM glucose values and venous plasma glucose values measured using the Yellow Springs Instrument (YSI 2300 Stat Plus Glucose and Lactate Analyzer; Yellow Springs, OH) bedside glucose analyzer, as previously described.[1,5–7] Venous plasma sampling via the antecubital vein was performed for 8 h for all accuracy visits except for day one (12 h) and day 180 (10 h) at a frequency of every 15 min (min), unless the glucose was ≤70 mg/dL, during which time sampling was every 5 min. Either hyperglycemic or hypoglycemic challenges were performed in eligible participants on insulin in each clinic session to test the performance of the sensor across the range of glucose measured by the sensor (40–400 mg/dL). Mixed meals with 30%–40% carbohydrate content were used to raise glucose over 300 mg/dL for approximately 75 min for the hyperglycemic challenge, and subcutaneous insulin, based on each individual's insulin sensitivity, was administered to lower glucose levels to <70 mg/dL for no more than 1 h duration for the hypoglycemic challenge.

The CONTOUR NEXT ONE blood glucose (BG) monitoring system (Ascensia Diabetes Care, New Jersey) and respective test strips were used to perform fingerstick BG measurements during the system use. Data from the BG meters and transmitters were downloaded at all study visits to provide calibration values for the glucose calculation algorithm and to use for final accuracy assessment against the collected YSI value. Participants were blinded to CGM values and were instructed to make all diabetes care decisions based on current clinical standards of care. HbA1c was measured at day 90, 180, and 365 visits. Participants were also counseled to report all SAEs and related AEs in between clinic visits during the study.

The Eversense 365 glucose calculation algorithm was applied to the raw sensor data obtained during this study. This updated algorithm prompted for one calibration per day (after initialization 24 h after insertion when four calibrations are requested) through day 13, after which it prompted for one calibration per week in order to generate CGM readings. Descriptive analyses were used to evaluate the accuracy of the CGM compared with YSI over time across glucose ranges of 40–400 mg/dL, the concurrence of CGM and YSI readings, and alert performances as described previously.[1] MARD was calculated using all available YSI–CGM pairs where the YSI reading was paired with the closest CGM reading in the following 5 min. For the 36 participants with two Eversense 365 sensors inserted, CGM measurement data from both sensors were used to evaluate sensor precision as described previously.[1] The secondary sensor did not contribute to any other accuracy analyses. The percent of sensor readings within 15, 20, and 40 mg/dL for YSI values ≤70 mg/dL and within 15%, 20%, and 40% for YSI values >70 mg/dL was used to calculate all 15/15%, 20/20%, and 40/40% agreement rates.

The accuracy data were also evaluated against the iCGM special controls (1)(v)(A)–(K) standards.[3] Special controls (1)(v) (A)–(F) define the acceptable lower bound (LB) of the 95% confidence interval (CI) of the percentages of readings within ±15/15% of YSI reference values or ±40/40% of YSI reference values by iCGM glucose ranges <70, 70–180, and >180 mg/dL. Special controls (1)(v) (G) define the acceptable LB of the 95% CI of the percentage of readings within ±20% of YSI reference values for the overall 40–400 mg/dL iCGM range. Finally, iCGM special controls (1)(v)(H)–(K) are the following: (1) no BG value >180 mg/dL when iCGM glucose is <70 mg/dL, (2) no BG value <70 mg/dL when iCGM glucose is >180 mg/dL, (3) and (4) no more than 1% of iCGM values indicate a positive rate of change >1 mg/dL/min when the true negative rate of change is <–2 mg/dL/min and vice versa.

The proportion of patients experiencing device-related or insertion/removal procedure-related SAEs (95% CI) was calculated, and related AEs were tabulated.

Results

In total, 127 participants were enrolled, 6 participants withdrew prior to insertion after enrollment, and 11

Table 1. System Agreement to YSI within YSI Ranges

YSI glucose range (mg/dL)	N *pairs*	*Percent within 15 mg/dL or 15% of YSI*	*Percent within 20 mg/dL or 20% of YSI*	*Percent within 40 mg/dL or 40% of YSI*	*MARD (%)*
Overall	40,497	85.6	93.4	99.6	8.8
<54	358	90.2	95.0	99.4	7.7[a]
54–69	2446	89.8	96.7	99.6	7.8[a]
70–180	23,130	82.4	91.4	99.4	9.0
181–250	7997	87.1	94.5	99.9	7.8
>250	6566	89.5	95.9	100.0	7.5

[a]For YSI glucose values <70 mg/dL, mean absolute difference was calculated.
MARD, mean absolute relative difference; YSI, Yellow Springs Instrument.

participants were documented as screen failures to result in 110 participants inserted with sensors, of which 36 were inserted with two sensors, one in each arm. The mean age of the study cohort was 47.2 years; 63% were male, 93% self-identified as white, 60% had type 1 diabetes, with a mean duration of 17.4 ± 11.7 years, and the majority were on intensive insulin therapy (78%). The mean baseline HbA1c was 7.7 ± 1.5%, and the mean body mass index was 32 ± 6.8 kg/m^2.

The overall accuracy with 40,497 matched CGM and YSI glucose pairs is provided in Table 1. The overall MARD was 8.8% through 365 days, while the 15/15% metric was 85.6%, and the 20/20% was 93.4%. Detection rates confirming a hypoglycemic or hyperglycemic event showed the confirmed event detection rate at the threshold and predictive alert setting of 60 and 70 mg/dL were 90.5% and 96.6%, respectively, and at 180 and 250 mg/dL were 97.9% and 95.6%, respectively.

Calibration stability assessment of the 365 sensors showed that the 15/15% metric ranged from 85% in the first 12 h after calibration to 85.8% at 168 h after calibration. Similarly, the 20/20% metric ranged from 92.7% at 12 h to 93.8% at 168 h after calibration, allowing for a 7-day calibration scheme. MARDs and the 15/15%, 20/20%, and 40/40% metrics throughout sensor life in 30-day successive intervals are shown in Table 2. MARDs and 15/15% metrics from the beginning, middle, and end of sensor life were as follows: 9.7% and 81.5% days 1–30, 7.8% and 89.0% days 121–150, 7.9% and 88.7% days 181–210, 7.9% and 88.3% days 271–300, and 8.8% and 86.9% days 331–365, respectively. Among the 36 participants who had two sensor insertions, there were a total of 82,731 matched pairs generated during clinic sessions, which resulted in a paired absolute relative difference (ARD) of 8.0% and percent coefficient of variation of 5.7%. Finally, the rate of change accuracy is shown in Table 3, demonstrating the system remained accurate across all CGM system rate of change categories.

iCGM special controls A–K were met,[3] as shown in Table 4. Specifically, the lower bound of the 95% confidence interval (LBCI) of rule A was 86.3%, rule B was 81.5%, rule C was 88.9%, rule D was 98.7%, rule E was 99.3%, rule F was 99.7%, and rule G was 91.8%. Rule H calculation showed 0 values >180 mg/dL, rule I showed 0 values <70 mg/dL, rule J was 0.5%, and rule K was 0.4%.

The Kaplan–Meier survival analysis was completed for the 110 primary sensors in the 110 participants. The sensor survival was 96% at day 90, 96% at day 180, 93% at day 270, 92% at day 330, and 90% at day 365.

There were no SAEs related to the device or insertion/removal procedures. There were no unanticipated AEs and no unanticipated adverse device effects. Most of the device- or insertion/removal procedure-related AEs were mild in severity.

Twenty-three related AEs were reported in 17 participants (15.5%). These included transient dermatological events of mild skin infection ($n = 4$, insertion procedure related), prolonged wound healing ($n = 3$, two removal procedure related and one insertion procedure related), and skin irritation to

Table 2. System Stability in Successive Intervals

Wear period	*Matched pairs (*N*)*	*Percent within 15 mg/dL or 15% of YSI*	*Percent within 20 mg/dL or 20% of YSI*	*Percent within 40 mg/dL or 40% of YSI*	*MARD (%)*
Days 1–30	9129	81.5	90.6	99.3	9.7
Days 31–60	3283	84.0	93.4	99.7	9.0
Days 61–90	2858	82.7	90.9	99.4	9.9
Days 91–120	3561	88.1	95.1	99.6	8.4
Days 121–150	2745	89.0	96.0	99.7	7.8
Days 151–180	2727	86.2	93.7	100.0	8.1
Days 181–210	3076	88.7	95.5	100.0	7.9
Days 211–240	2855	88.2	95.0	99.6	8.2
Days 241–270	1951	82.7	91.3	99.9	9.4
Days 271–300	2718	88.3	95.4	99.9	7.9
Days 301–330	2257	89.0	94.9	99.9	8.1
Days 331–end	3337	86.9	94.8	99.8	8.8

Table 3. Effect of CGM System ROC on CGM System and YSI Agreement

CGM ROC mg/dL/min	N *pairs*	*Percent of CGM system readings within YSI*		
		15/15% of Reference	*20/20% of Reference*	*40/40% of Reference*
<–2	748	80.9	90.9	99.6
[–2, –1)	3181	84.8	92.8	99.2
[–1, 1]	31,594	86.7	94.3	99.7
(1, 2]	3364	80.2	89.7	99.6
>2	1422	78.3	87.3	98.9

CGM, continuous glucose monitoring; ROC, rate of change.

the adhesive patch and transient skin changes such as atrophy and discoloration ($n = 8$, device related) affecting 11.8% of participants (15 events in 13 participants). Neurological events of pain (three insertion procedure related) and vasovagal episode (two insertion procedure related and one removal procedure related) occurred in 3.6% of participants (six events in four participants) and nausea (removal procedure related) and bleeding (removal procedure related) occurred with one event each in 0.9% of the participants. Ultrasound imaging was used to aid in the removal of 2 of the 146 total sensors. All related AEs were resolved by study participant completion. The mean HbA1c was 7.3 ± 1.2%, 7.3 ± 1.2%, and 7.4 ± 1.3% by 90, 180, and 365 days, respectively, compared with the baseline of 7.7 ± 1.5, with participants blinded to CGM data.

Discussion

The ENHANCE study was designed to evaluate the accuracy and safety of the Eversense 365 CGM System over a 365-day period across the glucose range of 40–400 mg/dL.

Based on 40,497 matched pairs, the study demonstrated 85.6% of the CGM readings were within 15/15% of the YSI values, and 93.4% of the CGM readings were within 20/20% of the YSI values across all glucose ranges, including hypoglycemia and hyperglycemia. The overall MARD was 8.8%, with a mean absolute difference (MAD) of 7.7 mg/dL for glucose levels <54 mg/dL and 7.8 for values 54–69 mg/dL. CGM system stability assessment showed MARDs <10% and percent of CGM readings within 15/15% of YSI no less than 81.5% during all wear periods from the first 30 days to the last 30 days of the 365-day wear period. The evaluation of CGM accuracy from high to low rates of change demonstrated approximately 80% of CGM readings were within 15/15% of the YSI values during even the highest rates of CGM system change of <2 or >2 mg/dL/min. iCGM special controls were met, allowing Eversense to be used in AIDs. The detection of hypoglycemia (at 70 mg/dL) and hyperglycemia (at 180 mg/dL) with confirmed events was 96.6% and 97.9%, respectively. These results are similar to measurements reported for other commercially available CGM systems[8–10]; however, they were achieved for a full year duration compared with 7, 10, and 14/15 days for the transcutaneous devices.[8–10]

Two advancements in the Eversense 365 sensor enabled accurate glucose sensing for 365 days with fewer calibrations.[11] First, an analyte indicator was added to the hydrogel to directly measure oxidative deboronation of the glucose indicator molecule induced by interstitial fluid reactive oxygen species, which enabled a reduction in calibration frequency. Second, the sensor electronics were expanded to include an array of four glucose and oxidation sensing areas allowing for mitigation of both local oxidation and immune-mediated degradation (both temporary and permanent). With the sensing array, calculation of glucose uses weighted averaging across the sensing areas.

The performance of the Eversense 365 system in the ENHANCE study demonstrated that the calibration frequency could be reduced to once per week beginning on day 14, further reducing the burden of implantable CGM usage.

Table 4. iCGM Special Control Results

iCGM special control	*iCGM glucose range (mg/dL)*	*Matched pairs* (N)	*Eversense 365 CGM system performance*	
			Point estimate	*95% LB*
(1)(v)(A)	<70	3040	87.2	86.3%
(1)(v)(B)	70–180	23,049	81.9%	81.5%
(1)(v)(C)	>180	14,408	89.3%	88.9%
(1)(v)(D)	<70	3040	99.0%	98.7%
(1)(v)(E)	70–180	23,049	99.4%	99.3%
(1)(v)(F)	>180	14,408	99.8%	99.7%
(1)(v)(G)	40–400	40,497	92.0%	91.8%
(1)(v)(H)	<70	40,497	0 values >180 mg/dL	
(1)(v)(I)	>180	40,497	0 values <70 mg/dL	
(1)(v)(J)	40–400	210	0.5%	
(1)(v)(K)	40–400	806	0.4%	

iCGM, interoperable continuous glucose monitoring; LB, lower bound.

There were no unanticipated related AEs and no device- or insertion/removal procedure-related SAEs in the study overall. Many of the AEs associated with the Eversense 365 CGM System are common to all CGM systems. The procedure-related AEs observed in the ENHANCE study are as expected from a minor office-based procedure that is used to insert and remove the sensor in the subcutaneous tissue; however, they were mostly mild in nature and transient and no different from those reported in prior studies of the Eversense CGM system.[1,5–7]

Conclusions

The ENHANCE study demonstrated that the long-term implantable Eversense 365 CGM System with four sensing and oxidation areas was safe and accurate, lasting up to 365 days. Moreover, it was shown that the Eversense 365 CGM System was able to maintain good accuracy, including meeting iCGM special controls, with a calibration frequency of primarily once per week during the 365 days of system wear.

Acknowledgments

The authors wish to give thanks to the clinical study site teams (Headlands Research California—AMCR Institute in Escondido, CA, USA; Rocky Mountain Research Center in Idaho Falls, Idaho, USA; Rainer Clinical Research Center in Renton, WA, USA; Flourish Inc, San Antonio, TX, USA) and to the study participants.

Authors' Contributions

T.S.B., D.R.L., D.L.D., and R.L.B. contributed to study participant recruiting, data acquisition, and critical review of the article. S.G.D. and K.S.T. were involved in design and analysis. J.M. was involved in conception of the device evaluated. K.S.T. and F.R.K. wrote the first draft of the article, and all authors edited, reviewed, and approved the final version of the article. S.I., J.M., and S.G.D. contributed to critical review of the article. K.S.T. is the guarantor of this work and, as such, 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. Senseonics Inc., the manufacturer of the Eversense 365 CGM System funded the study.

Author Disclosure Statement

T.S.B. has received research support from or has acted as a consultant for Abbott Rapid Diagnostics, Biolinq, Corcept, Dexcom, Eli Lilly, Medtronic, Medtrum, Novo Nordisk, Senseonics, vTv Therapeutics, Abbott Diabetes, ACON, CeQur, HagarTech, i-sense, Eye Sense, Mannkind, Novo, Perspirion, Sanofi, Sequel Med Tech, and Ypsomed. D.L. has received research support from Senseonics. D.D. has received research support from Senseonics. S.I. has received research support from Senseonics and Medtronic. R.L.B. has received research support from Senseonics. J.M., S.G.D., K.S.T., and F.R.K. are employees of Senseonics Inc., the manufacturer of Eversense.

Funding Information

No funding was received for this article.

References

1. Garg SK, Liljenquist D, Bode B, et al. Evaluation of accuracy and safety of the next-generation up to 180-day long-term implantable eversense continuous glucose monitoring system: The PROMISE Study. Diabetes Technol Ther 2022;24(2):84–92; doi: 10.1089/dia.2021.0182
2. Eversense E3 CGM User Guide. Available from: https://www.eversensediabetes.com/wp content/uploads/LBL-6002-01-001-Rev D_Eversense E3 User Guide_mgdL_R3_web.pdf [Last accessed: January 22, 2025].
3. Code of Federal Regulations. 862.1355 Integrated continuous glucose monitoring system. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-862/subpart-B/section-862.1355 [Last accessed: September 19, 2024].
4. Sanchez P, Al-Khawi L, Masciotti J, et al. Interim 365-day performance of a long term implantable continuous glucose monitoring system with reduced calibration. Diabetes Technol Ther 2023;25(S2):EP180; doi: 10.1089/dia.2023.2525.abstracts
5. Kropff J, Choudhary P, Neupane S, et al. Accuracy and longevity of an implantable continuous glucose sensor in the PRECISE study: A 180-day, prospective, multicenter, pivotal trial. Diabetes Care 2017;40(1):63–68.
6. Christiansen MP, Klaff LJ, Brazg R, et al. A prospective multicenter evaluation of the accuracy of a novel implanted continuous glucose sensor: PRECISE II. Diabetes Technol Ther 2018;20(3):197–206.
7. Christiansen MP, Klaff LJ, Bailey TS, et al. A prospective multicenter evaluation of the accuracy and safety of an implanted continuous glucose sensor: The PRECISION Study. Diabetes Technol Ther 2019;21(5):231–237.
8. Garg SK, Kipnes M, Castorino K, et al. Accuracy and safety of the dexcom G7 continuous glucose monitoring in adults with diabetes. Diabetes Technol Ther 2022;24(6):373–380.
9. Alva S, Brazg R, Castorino K, et al. Accuracy of the third generation of a 14-day continuous glucose monitoring system. Diabetes Ther 2023;14(4):767–776.
10. Christiansen MP, Garg SK, Brazg R, et al. Accuracy of a fourth-generation subcutaneous continuous glucose sensor. Diabetes Technol Ther 2017;19(8):446–456.
11. Velvadapu VN, Masciotti JM, Dehennis AD, et al. Evaluation of an implantable CGM system using a multiple-analyte indicator hydrogel for calibration reduction. Diabetes 2022;71(Supplement_1):691.

Address correspondence to:
Katherine S. Tweden, PhD
Senseonics
Incorporated
20451 Seneca Meadows Pkwy
Germantown
MD 20876
USA

E-mail: Katherine.tweden@senseonics.com