Accuracy and Longevity of an Implantable Continuous Glucose Sensor in the PRECISE Study: A 180-Day, Prospective, Multicenter, Pivotal Trial

Jort Kropff,[1] Pratik Choudhary,[2] Sankalpa Neupane,[3] Katharine Barnard,[4] Steve C. Bain,[5] Christoph Kapitza,[6] Thomas Forst,[7] Manuela Link,[8] Andrew Dehennis,[9] and J. Hans DeVries[1]

Diabetes Care 2017;40:63–68 | DOI: 10.2337/dc16-1525

OBJECTIVE

It is known that continuous glucose monitoring (CGM) systems can lower mean glucose compared with episodic self-monitoring of blood glucose. Implantable CGM systems may provide additional benefits.

RESEARCH DESIGN AND METHODS

We studied the Eversense (Senseonics Inc.) implantable CGM sensor in 71 participants aged 18 years and older with type 1 and type 2 diabetes in a 180-day multinational, multicenter pivotal trial. Participants used the CGM system at home and in the clinic. CGM accuracy was assessed during eight in-clinic visits with the mean absolute relative difference (MARD) for venous reference glucose values >4.2 mmol/L as the primary end point. Secondary end points included Clarke Error Grid Analysis and alarm performance. The primary safety outcome was device-related serious adverse events. This trial is registered with ClinicalTrials .gov, number NCT02154126.

RESULTS

The MARD value against reference glucose values >4.2 mmol/L was 11.1% (95% CI 10.5, 11.7). Clarke Error Grid Analysis showed 99.2% of samples in the clinically acceptable error zones A and B. Eighty-one percent of hypoglycemic events were detected by the CGM system within 30 min. No device-related serious adverse events occurred during the study.

CONCLUSIONS

Our results indicate the safety and accuracy of this new type of implantable CGM system and support it as an alternative for transcutaneous CGM.

People with diabetes frequently use fingerstick capillary glucose measurements to guide their dosing decisions (1). Continuous glucose monitoring (CGM) systems can provide glucose data in real time and reduce the need for fingerstick testing (2). Additionally, people with diabetes can receive temporal information, trend information, and alarms for impending hypoglycemic and hyperglycemic events (2). When used regularly, CGM can effectively lower mean glucose compared with fingerstick glucose measurements only (3). Unfortunately, wear time of current transcutaneous CGM is low in some populations, which might partially be explained

[1]Department of Endocrinology, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands
[2]King's College London, London, U.K.
[3]Cambridge University Hospitals NHS Foundation Trust, Cambridge, U.K.
[4]Bournemouth University, Bournemouth, U.K.
[5]Joint Clinical Research Facility, Swansea University, Swansea, U.K.
[6]Profil, Neuss, Germany
[7]Profil, Mainz, Germany
[8]Institut für Diabetes-Technologie Forschungs- und Entwicklungsgesellschaft mbH an der Universität Ulm, Ulm, Germany
[9]Research, Senseonics Inc., Germantown, MD

Corresponding author: Jort Kropff, j.kropff@amc.nl.

Received 14 July 2016 and accepted 17 October 2016.

Clinical trial reg. no. NCT02154126, clinicaltrials .gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-1525/-/DC1.

by usability issues (4,5). The accuracy of CGM systems has improved over the years but could be improved further, especially in the hypoglycemic range (2). Transcutaneous CGM systems consist of a wired sensor containing glucose-sensing enzymes, a transmitter, and a display device. The wired sensor is placed just below the skin in the subcutaneous fat and is continuous with the transmitter base. The transmitter is placed in the transmitter base and sends data wirelessly to a display device such as a dedicated receiver or a smartphone. Several transcutaneous CGM systems are currently on the market (6–8). Implantable CGM systems may provide additional ease of use over transcutaneous CGM since frequent sensor insertions through the skin are not needed and the transmitter can be removed easily without the need for sensor replacement, for example during personal care. Furthermore, weekly sensor replacement with warm-up time and the risk of damage to the inserted sensor is no longer applicable. However, the need for implantation and removal through a minor surgical procedure imposes some discomfort on the patient. Currently, no long-term data on implanted sensor accuracy or longevity are available.

In this multinational, multicenter European trial, we aimed to investigate the safety and accuracy of a new type of CGM system using an implantable glucose sensor. In addition, we assessed sensor lifetime, system wear time, participant-reported outcome measures, and measures of glycemic control.

RESEARCH DESIGN AND METHODS

Study Design and Participants

This was a 180-day, prospective, multicenter, pivotal trial. The study was executed between November 2014 and November 2015 and performed at seven clinical sites in Europe. Participants were 18 years or older and had a clinically confirmed diagnosis of type 1 or type 2 diabetes for >1 year and used insulin therapy. People were excluded from study participation if they had any of the following: a history of severe hypoglycemia, diabetic ketoacidosis, symptomatic coronary artery disease, unstable angina, myocardial infarction, or stroke in the past 6 months prior to study; known severe microvascular complications including proliferative diabetic retinopathy, macular edema, active nonproliferative retinopathy, and renal failure; a hematocrit >50% or <30%; lactation, pregnancy, or intending to become pregnant during the course of the study; or a condition likely to require MRI.

A study design diagram is given in Supplementary Fig. 1. The study consisted of 11 clinic visits: a screening visit, a sensor insertion visit, five 24-h and three 8-h device performance assessment visits, and a sensor removal visit. Finally, a follow-up visit was planned 2 weeks after sensor removal. The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional ethics review board at each site. Written and verbal informed consent was given by all participants.

Procedures

During the screening visit, laboratory measurements, a physical examination, and an electrocardiogram were performed. Participants received training in the use of study devices, and written instruction materials were provided. At the sensor insertion visit, a glucose sensor for continuous glucose measurement was implanted in both upper arms of the participant. Participants were free to choose the exact location of sensor implantation within the upper-arm region. Participants decided which of the two implanted sensors was to be designated as the primary sensor. Further information on the insertion and removal procedure is given in Supplementary Section 2. Participants were asked to wear the transmitter over the primary sensor and to perform calibration twice daily using the study self-monitoring of blood glucose device (SMBG, Accu-Chek Aviva; Roche Diagnostics, Mannheim, Germany). The secondary sensor was used and calibrated during the eight device performance assessment visits only. Participants and study personnel were display blinded to CGM glucose values during the device performance assessment visits. For the remainder of the study, continuous glucose data were available to the participants. Participants were asked to confirm the CGM glucose reading using the study SMBG device before making treatment decisions. The maximum study participation was 180 days depending on end of sensor life, which was indicated on the CGM display. The sensor was replaced if sensor functionality was found to be lost due to electronics or mechanical failure prior to visit 7 (study day 90).

Study visits started with a glucose measurement ensuring that current blood glucose was <16.7 mmol/L or 300 mg/dL, and ketone blood content ≤0.6 mmol/L. Safety laboratory tests were performed according to local clinic standard operating procedures. Body temperature (99.5°F or <37.5°C) was registered. If needed, visits were rescheduled. During each study visit, venous plasma samples were taken for determination of dexamethasone concentration to investigate possible systemic absorption of dexamethasone used in the sensor system. This was done in a highly sensitive liquid chromatography–tandem mass spectrometry method, with a lower limit of detection of 2 ng/mL (9). Venous blood samples were taken every 15 min or more frequently during episodes of hypoglycemia (≤4.4 mmol/L or 80 mg/dL reference glucose) using an intravenous line inserted in the dorsal or cubital vein of the participant's arm. During night time (2300–0700 h), samples were collected every 2 h. After bedside centrifuge and visual check for dilution and hemolysis, venous plasma glucose samples were analyzed using a YSI 2300 STAT PLUS glucose and lactate analyzer (YSI, Yellow Springs, OH). Samples were kept on ice and stored in tubes containing dipotassium EDTA to allow for re-analyses. Induction of hypoglycemia and hyperglycemia was performed in a part of the participants per decision of the site investigator (39 completed in 23 subjects). Finally, visits for sensor removal and follow-up were performed. Insertion and sensor removal sites were inspected. Adverse events were registered throughout the study. Participants were asked to complete questionnaires at the start, after 90 days, and at the end of the study.

The CGM system (Senseonics Inc.) used in this study consisted of three components: an implantable fluorescence-based cylindrical glucose sensor sized 3 × 16 mm, a smart transmitter sized 40 × 40 × 14 mm, and a handheld device (iPod Touch; Apple, Inc., Cupertino, CA) running a mobile medical application. The transmitter had to be worn over the implanted sensor for continuous readout of glucose data but could be removed and replaced without the

need for sensor replacement. The transmitter stored the glucose data and provided the participants with on-body vibrations for notification of hypoglycemia and hyperglycemia. Data were continuously transferred to the iPod per secured low-energy Bluetooth transmission, which allowed participants and study staff to review current and historical glucose data in real time. Further product information can be found in Supplementary Section 2.

Outcomes

Primary, secondary, and exploratory outcomes were predefined in a statistical analysis plan; additional analyses were added as indicated. The primary efficacy end point was the mean absolute relative difference (MARD) for reference glucose values >4.2 mmol/L (75 mg/dL), defined as the average of the absolute difference of paired CGM system and YSI readings (reference) divided by the YSI reading multiplied by 100 (10). The secondary efficacy end points included Clarke Error Grid Analyses and alarm performance. Alarm performance was defined as confirmed and missed event detection rates and true and false alarm rates given for low and high glucose alarm (<3.9 and >10 mmol/L or <70 and >180 mg/dL). Confirmed event detection rate was defined as a CGM measurement beyond the alarm threshold within 30 min from the start of the event, expressed as the percentage of total number of events. The true alarm rate was defined as a CGM measurement beyond the alarm threshold confirmed by a YSI measurement within 30 min expressed as percentage of the total number of alarms. The missed event detection rate and false alarm rate were defined as the inverse of the confirmed event detection rate and true alarm rate, respectively. Primary safety end point was incidence of device-related or procedure-related serious adverse events, and secondary safety end points included all device-related or procedure-related adverse events. Quality of life was assessed using the Short Form Health Survey (SF-36) and a device-specific questionnaire developed for the study. Exploratory outcomes included sensor lifetime analyzed using Kaplan-Meier analysis, calibration stability, sensor stability, accuracy (MARD) over sensor life, system lag time, within-subject precision, and person-to-person variability. Additional analyses included MARD over the full glycemic range (2.2–22.0 mmol/L or 40–400 mg/dL) and over the hypoglycemic, normoglycemic, and hyperglycemic ranges (≤4.2, 4.2–10, and >10 mmol/L or ≤75, 76–180, and >180 mg/dL), system wear time, and glycemic control assessed per HbA_{1c} measurement at the first and last study visit. Also, real-time re-analyses of the raw study data using a new data algorithm and analysis of change in HbA_{1c} over the study duration based on HbA_{1c} strata <7.5 and ≥7.5% (58 mmol/mol) were performed.

Statistical Analysis and Power Calculation

An intent-to-treat analysis for the primary efficacy analysis and additional outcome measures was performed based on all evaluable data from all participants with at least one paired glucose reading. We reported variables as mean with SD or median with interquartile range (IQR) where appropriate. CIs for the paired difference (Δ) between outcomes were computed. All reported *P* values are two tailed, and values <0.05 were considered statistically significant. Sensor failures due to mechanical or electronical failure, for which processes of improvements have been implemented, were excluded from sensor life analyses. The impact of a new data algorithm on the system performance was assessed through re-analyses of the raw study data.

Power calculation was based on a test of superiority over a prespecified performance goal of 20% MARD (reference glucose values >4.2 mmol/L or >75 mg/dL), with a conservative estimate of the investigational device performance of MARD <18%, an SD of ≤14%, a power of 80%, and a one-sided significance level of 0.0125. Considering within-subject correlation, data distribution, expected dropout percentage of 20%, and inclusion of up to seven training subjects, the total required number of participants was estimated at 82. SAS 9.1, IBM/SPSS version 21, and Cytel version 10 were used for statistical analyses. This trial is registered with ClinicalTrials.gov, identification number NCT02154126.

RESULTS

Eighty-one participants were included, of which five were used for platform and procedure evaluation and five were designated for site training (further information can be found in Supplementary Fig. 4). The intent-to-treat analyses of the primary efficacy outcome included 71 patients. Participant baseline characteristics are given in Table 1.

The primary efficacy outcome over the study duration showed a MARD for

Table 1—Baseline patient characteristics

Variable	Intent-to-treat population (*n* = 71)
Age (years)	41.7 [12.6]
Sex	
Male	42 (59.2)
Female	29 (40.8)
Type 1 diabetes	66 (93.0)
Type 2 diabetes	5 (7.0)
Diabetes duration (years)	22.2 [12.5]
Insulin delivery mode, CSII	42 (59.2)
BMI (kg/m^2)	27.0 [4.2]
HbA_{1c} (%)	7.6 [1.1]
HbA_{1c} (mmol/mol)	60 [12]
Any history of	
Ketoacidosis	15 (21.1)
Severe hypoglycemia	17 (23.9)
Long-term diabetes complications	
Retinopathy	16 (22.5)
Nephropathy	0 (0)
Neuropathy	7 (9.9)
Cardiovascular disease	21 (29.6)
Foot problems	4 (5.6)

For categorical variables, *n* (%) is presented. For continuous variables, mean [SD] is presented. CSII, continuous subcutaneous insulin infusion.

reference samples >4.2 mmol/L of 11.1% (95% CI 10.5, 11.7). Performance of the CGM system in the hypoglycemic range (≤4.2 mmol/L or ≤75 mg/dL) was less than the overall performance (2.2–22.0 mmol/L or 40–400 mg/dL), 21.7 vs. 11.6% MARD ($P < 0.001$). A statistically significant reduction of CGM accuracy occurred in the last month of use (Table 2). Table 3 provides further data on the accuracy of the CGM system per glycemic range. Real-time re-analyses of the raw study data using a new data algorithm indicated improved performance over the currently used algorithm (MARD 2.2–22.0 mmol/L [40–400 mg/dL]; 10.5 vs. 11.6% [95% CI of Δ −1.1, −0.9], $P < 0.001$; MARD ≤4.2 mmol/L; 18.6 vs. 21.7% [95% CI of Δ −3.8, −2.3], $P < 0.001$). Further information can be found in Supplementary Table 6. A Kaplan-Meier analysis for sensors survival estimated that 100, 82, and 40% of sensors were functional through day 45, day 90, and day 180 in-clinic evaluation sessions, respectively (median sensor life 149 days [IQR 97, 180]) (Fig. 1). Twelve sensors were considered censored in the survival analysis due to either subject withdrawing consent (n = 6) or electronic or mechanical failure (n = 6), and five sensors were replaced due to electronic or mechanical failure within 3 months after study start.

HbA_{1c} improved in the study group from 7.54% (59 mmol/mol) at baseline to 7.19% (55 mmol/mol) at end of study (Δ 0.35% [4 mmol/mol] [95% CI Δ −0.55% (6 mmol/mol), −0.21% (2 mmol/mol)]; $P < 0.001$). A post hoc analysis of participants with a baseline HbA_{1c} <7.5% (58 mmol/mol) showed unchanged HbA_{1c} at the last study visit (−0.04% [95% CI Δ −0.21, 0.14]; P = 0.669) (−0 mmol/mol [95% CI Δ −2, 2]), whereas participants with a baseline HbA_{1c} ≥7.5% (58 mmol/mol) showed a reduction of −0.66% (95% CI Δ −0.91, −0.42; $P < 0.001$) (−7 mmol/mol [95% CI Δ −10, −5]). The clinical performance of the CGM system estimated per Clarke Error Grid Analysis showed 99.2% of samples in the clinically acceptable error zones A (84.3%) and B (14.9%) (Supplementary Fig. 5). The in-clinic alarm performance for the hypoglycemia (<3.9 mmol/L or <70 mg/dL) and hyperglycemia (>10 mmol/L or >180 mg/dL) threshold indicated a confirmed detection rate of 81 and 88%, and an event true rate of 67 and 90%, respectively (Supplementary Table 1). No indication for change in glucose variability over time was found (data not shown). Transmitter wear compliance was a median 23.5 h per day (IQR 23.2, 23.7).

Quality of life measured per SF-36 questionnaire demonstrated unchanged quality of life scores from baseline to end of study. Results from a study-specific questionnaire indicated high device acceptance, with 84% rating "I would want to be inserted with a sensor again" and 90% rating "Using the system helped minimize the burden of diabetes in my life," a score of 5 or higher (scoring range 1–7 points).

The primary safety outcome showed no severe procedure- or device-related serious adverse events. Fourteen device- or procedure-related nonsevere adverse events occurred in 11 out of 71 patients, with a total number of 147 sensors implanted, used, and removed. Five cases of skin reaction were recorded. In all cases, therapy could be continued after a temporary stop of 1–3 weeks. Two cases of incision site infection occurred, one patient received antibiotic treatment and the other infection resolved without need for further medical intervention. Four participants withdrew consent because of study burden (n = 2) and inability to obtain venous access (n = 2), and two subjects withdrew consent due to an adverse event thought to be unrelated to the device. Implantation and removal of sensors was performed by nonsurgically trained doctors (endocrinologist/MDs) in most sites (five out of seven), and the remaining sites (two out of seven) used nonsurgically trained doctors or surgeons depending on daily availability. No level of dexamethasone was measured in any of the venous samples. Further information on safety and adverse events and nonprimary outcomes can be found in Supplementary Table 5.

Table 2—Accuracy of the CGM system versus YSI over time

	Sensor accuracy, MARD (%), over the range of 2.2–22 mmol/L or 40–400 mg/dL			
Day	MARD, % (n)	SD	95% CI	15 mg/dL or 20%,* transitioning at 75 mg/dL
0−180	11.6 (21,527)	11.2	11.5, 11.8	84.0%
1−30	11.6 (10,761)	11.4	11.4, 11.8	83.9%
31−60	11.2 (4,382)	9.8	10.9, 11.5	85.5%
61−90	11.4 (1,429)	10.5	10.9, 11.9	84.3%
91−120	11.9 (2,672)	11.6	11.5, 12.3	82.6%
121−150	12.0 (975)	12.6	11.2, 12.8	84.3%
151−180	12.9 (1,308)	12.6	12.2, 13.6	81.9%

In-clinic accuracy is assessed per venous YSI reference measurement. *Performance of the sensor stability was assessed by calculating the percentage of system readings within 15 mg/dL (for YSI ≤4.2 mmol/L or 75 mg/dL) or 20% (for YSI >4.2 mmol/L or 75 mg/dL) of the paired YSI values.

CONCLUSIONS

The current study, investigating the accuracy, longevity, and impact on the patient experience of a novel implantable CGM system, showed safety and accurate performance of the investigational device over the full sensor life. Participant acceptance of the device was high. The current system was accurate, with an overall MARD of 11.1% for samples >4.2 mmol/L (75 mg/dL). CGM performance was less in the hypoglycemic range, as is also seen with other CGM products (7,8,11,12). A limited but statistically significant reduction of CGM measurement accuracy occurred in the last month of use, possibly due to long-term degradation of the glucose-indicating gel before end of sensor life was reached.

Device use coincided with a significant reduction in HbA_{1c}, consistent with the results of a meta-analysis showing that HbA_{1c} lowering with CGM use depends on baseline HbA_{1c} and device wear time (3). The Clarke Error Grid Analysis estimated high clinical performance, with 99.2% of samples in the clinically acceptable error zones A and B.

Results from questionnaire data indicated high participant acceptance of the system but did not register improved perceived generic quality of life, as assessed per SF-36 questionnaire. Nonetheless study participants did describe the ease of use, ability to remove the

Table 3—Accuracy of the CGM system per glycemic range and rate of change

	Sensor accuracy, MARD						
	Glycemic range			Rate of change			
Venous mmol/L (mg/dL)	MARD, % (*n*) MAD, % (*n*)	SD	95% CI	Venous mmol/L/min (mg/dL/min)	Mean mmol/L (*n*) [mean mg/dL]	SD	95% CI
≤4.2 (75)	21.7 (1,057) 14.2 (1,057)	21.5 13.5	20.4, 23.0 13.4, 15.0	Decreasing glucose <−0.055 (−1)	15.6 (1,964) [280]	16.5	14.9, 16.3
4.2–10.0 (75–180)	11.9 (14,274) –	10.9 –	11.8, 12.1 –	Stable glucose −0.055, 0.055 (−1, 1)	10.7 (14,909) [193]	10.0	10.5, 10.8
>10.0 (180)	9.2 (6,196) –	7.8 –	9.0, 9.4 –	Increasing glucose >0.055 (1)	13.6 (2,443) [245]	10.7	13.2, 14.1

Accuracy is assessed per venous YSI reference measurements.

transmitter without removing the sensor, and availability of on-body vibration alerts as beneficial features of the system. Participants used the CGM for >23 h per day over the full study duration, indicating high acceptance of the system. The implantation, use, and removal of 147 glucose sensors in 71 participants resulted in a limited number of mild to moderate skin reactions and skin infections, and no device- or procedure-related serious adverse events were reported.

A previous implantable glucose sensor was described by Garg et al. (13). Although the authors described acceptable accuracy and longevity of this approach, this CGM system was never commercialized perhaps due to acceptability issues with the surgical implantation procedure related to the sensor size (similar to an AA battery) (13). Other investigators have shown proof of concept of an implantable self-powered CGM in animals, but no human data are available (14). Currently, no implantable glucose sensors are on the market. On the basis of the results of this study, the Eversense implantable sensor received a CE mark on 10 May 2016.

The multicenter approach with real-life use of the system at home and the long duration of the study allowed for assessment of glycemic outcomes, device acceptance, and impact on quality of life on top of system performance. It should be noted that these are uncontrolled observational data. As in most studies testing novel diabetes technology, it can be expected that a more technology-enthusiastic population was included in the study. Also, participants with type 2 diabetes and participants of non-Caucasian descent were underrepresented in this study; as such, one should be careful to directly translate the outcomes of the current study to the wider population.

On the basis of mathematical models, it was recently proposed that an inaccuracy of <10% MARD is not expected to lead to further improvements in clinical outcomes of CGM use (2), although this might be negated by future trials with clinically relevant outcomes. This and competing products are approaching the 10% mark, except for the hypoglycemic range, for which improvements are needed. Results from a real-time re-analysis of the raw study data using a new data algorithm indicated improved performance over the currently used algorithm. The CGM system including the new algorithm is currently investigated in a 90-day U.S. pivotal trial (ClinicalTrials.gov identifier NCT02647905).

The results from this study indicate that the use of a long-term implantable continuous glucose sensor is both effective and safe and provides specific usability benefits. The results support implantable CGM as a worthy alternative to current transcutaneous CGM.

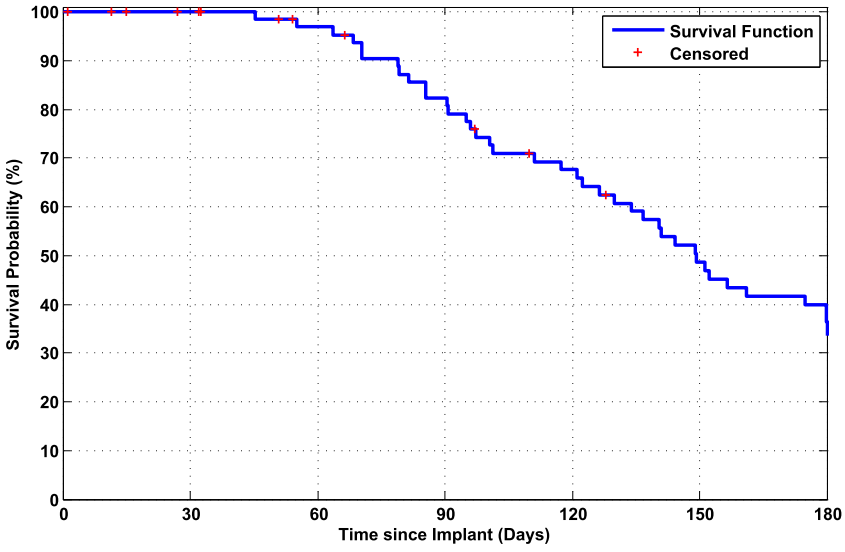

Figure 1—Sensor survival per Kaplan-Meier analyses. Sensor survival is given per individual sensor per Kaplan-Meier analyses. The 71 primary sensors were included in the survival analyses. End of sensor lifetime is indicated by the CGM system. Median sensor lifetime is 149 days.

Acknowledgments. The authors thank the patients and their family members for their continued dedication during the study. The authors acknowledge Dr. R.G. Holcomb (Quintiles Consulting, Rockville, MD), external statistical

consultant, for his work on the statistical analyses and data reporting of the study. The authors acknowledge and thank the study personnel for their help in the successful execution of the study.

Duality of Interest. This study was funded by Senseonics Inc. J.K. received research support from Senseonics Inc. and Dexcom. T.F. received research support and is a consultant/advisor/speaker for AstraZeneca, Eli Lilly and Company, Bristol-Myers Squibb, Sanofi, Boehringer Ingelheim, Novartis, Novo Nordisk, and Berlin-Chemie. A.D. is an employee of Senseonics Inc. J.H.D. received research support and is a consultant/advisor/speaker for Senseonics Inc., Dexcom, Johnson & Johnson (Animas, LifeScan), and Roche Diagnostics. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.K. designed the protocol, collected data, reviewed data reports, drafted the manuscript, and was the main study physician responsible for the trial in Amsterdam. P.C. was the principal investigator of the King's College London trial site. S.N. was the principal investigator of the University of Cambridge trial site. K.B. drafted and executed the system-specific questionnaire. S.C.B. was the principal investigator of the Swansea trial site. C.K. was the principal investigator of the Profil, Neuss, trial site. T.F. was the principal investigator of the Profil, Mainz, trial site. M.L. was the principal investigator of the Ulm trial site. A.D. designed the study protocol, performed data analyses, reviewed data reports, and reviewed the study manuscript. J.H.D. designed the protocol, performed data analyses, drafted the manuscript, and was the principal investigator of the Amsterdam trial site and lead principal investigator for the study. All authors reviewed and provided edits and comments on manuscript drafts. J.K. 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.

Prior Presentation. The abstract was presented as a poster at the 76th Scientific Sessions of the American Diabetes Association, New Orleans, LA, 10–14 June 2016, and as an oral presentation at the 52nd Annual Meeting of the European Association for the Study of Diabetes, Munich, Germany, 12–16 September 2016.

References

1. Miller KM, Beck RW, Bergenstal RM, et al.; T1D Exchange Clinic Network. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. Diabetes Care 2013;36:2009–2014

2. Kovatchev BP, Patek SD, Ortiz EA, Breton MD. Assessing sensor accuracy for non-adjunct use of continuous glucose monitoring. Diabetes Technol Ther 2015;17:177–186

3. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. BMJ 2011;343:d3805

4. Rodbard D. Continuous glucose monitoring: a review of successes, challenges, and opportunities. Diabetes Technol Ther 2016;18(Suppl. 2): S23–S213

5. Englert K, Ruedy K, Coffey J, Caswell K, Steffen A, Levandoski L; Diabetes Research in Children (DirecNet) Study Group. Skin and adhesive issues with continuous glucose monitors: a sticky situation. J Diabetes Sci Technol 2014;8: 745–751

6. Damiano ER, McKeon K, El-Khatib FH, Zheng H, Nathan DM, Russell SJ. A comparative effectiveness analysis of three continuous glucose monitors: the Navigator, G4 Platinum, and Enlite. J Diabetes Sci Technol 2014;8:699–708

7. Bailey TS, Chang A, Christiansen M. Clinical accuracy of a continuous glucose monitoring system with an advanced algorithm. J Diabetes Sci Technol 2015;9:209–214

8. Kropff J, Bruttomesso D, Doll W, et al. Accuracy of two continuous glucose monitoring systems: a head-to-head comparison under clinical research centre and daily life conditions. Diabetes Obes Metab 2015;17:343–349

9. Taylor RL, Grebe SK, Singh RJ. Quantitative, highly sensitive liquid chromatography-tandem mass spectrometry method for detection of synthetic corticosteroids. Clin Chem 2004;50: 2345–2352

10. International Organization for Standardization. In vitro diagnostic test systems–requirements for blood glucose monitoring systems for self-testing in managing diabetes mellitus. Geneva, International Organization for Standardization, 2003, 15197:2013

11. Thabit H, Leelarathna L, Wilinska ME, et al. Accuracy of continuous glucose monitoring during three closed-loop home studies under free-living conditions. Diabetes Technol Ther 2015;17:801–807

12. Luijf YM, Mader JK, Doll W, et al.; AP@home consortium. Accuracy and reliability of continuous glucose monitoring systems: a head-to-head comparison. Diabetes Technol Ther 2013;15: 722–727

13. 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;27:734–738

14. Gough DA, Kumosa LS, Routh TL, Lin JT, Lucisano JY. Function of an implanted tissue glucose sensor for more than 1 year in animals. Sci Transl Med 2010;2:42ra53