Official Title: Benefits of a Long Term Implantable Continuous Glucose Monitoring System for Adults with Diabetes France Adoption Randomized Clinical Trial

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Study Protocol RD003329

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Benefits of a Long term Implantable Continuous Glucose Monitoring System for Adults with Diabetes – France Randomized Clinical Trial

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Confidentiality Statement

SUMMARY OF REVISION HISTORY

Version	Date of issue (dd mmm yyyy)	Reason for change
1.0	12 09 2017	New version
2.0	02 11 2017	New Study Design following HAS advice
3.0	18 12 2017	Modification following Ethics committee review
3.1	23 01 2018	Minor modification on the mobile app for blinded period
4.0	01 06 2018	Suppression of visit 7 : replacement by a phone call Verification of inclusion criteria at visit 3 based of FGM record instead of CGM data
4.1	09 11 2018	Opening of 5 new inclusion centers to improve recruitment New co-investigators for the same purpose Additional information about the patient's newsletter to comply with the GDPR
5.0	10 12 2018	Review of exclusion criteria Lend of mobile device (iPod) Possibility to have a sensor after the study end for the control group Add of questionnaires

STEERING COMMITTEE

In this clinical study, Roche Diabetes Care, the Sponsor, has chosen to appoint a steering committee. This committee may include Investigators, other experts, and representatives of the Sponsor. Roche Diabetes Care may delegate to a steering committee the support of designing the study, providing input in the protocol, protocol amendments, maintaining and supporting the quality of study conduct such as training events, supporting focus groups and writing study publications.
The Steering Committee will convene regularly during the trial (teleconferences or face-to-face meetings) to discuss and report on the study progress.

Roche Diabetes Care representatives include:

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RESPONSIBILITIES OF THE COORDINATING INVESTIGATOR(s)

The Coordinating Investigators from each participating country are appointed by the Sponsor to coordinate work in a multicenter clinical study. During the conduct of the clinical study the Coordinating Investigators will provide scientific advice and support the Sponsor in writing study publications.
In addition, the Sponsor may request that the Coordinating Investigator coordinates the work for this study and supports the submission process to the Ethics Committee/ Institutional Review Board and/or Regulatory Authorities.

PRINCIPAL INVESTIGATORS

The Sponsor shall maintain an updated list of Principal Investigators, study sites, and institutions. This list can be kept separately from the protocol and provided to Principal Investigators. The definitive list shall be provided with the clinical study report. The Principal Investigator is the qualified person for conducting the clinical study at a site.

SIGNATURE SHEET FOR INVESTIGATORS

Principal Investigator	City	Country

Study Protocol RD003329

Benefits of a Long Term implantable Continuous Glucose Monitoring System for Adults with Diabetes France Adoption Randomized Clinical Trial

I have thoroughly read and reviewed the above study protocol, and I agree that it contains all necessary details for carrying out this study.

I agree to conduct the study as specified in this study protocol and in accordance with the principles of the Guidelines of the International Conference on Harmonisation (ICH) on Good Clinical Practice (GCP) where it can be applied to medical devices, with the Declaration of Helsinki, harmonized European standards (ISO 14155:2011(E), the European Medical Device Directive [e.g. 93/42/EEC]) and FDA 21 CFR Parts 11, 50, 54, 56,, 803, 812, 814 and 820.30; as applicable, with all local laws and regulations and with all regulatory requirements for data protection.

I fully understand that any changes instituted by the Investigator(s) without previous discussion with the appropriate sponsor personnel and without approval according to national regulations would constitute a deviation of the protocol, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the well–being of the subjects).

I will discuss this material with subjects to ensure they are fully informed regarding the investigational device and the conduct of the study. I will use only the Informed Consent Form approved by the Sponsor and will fulfil all responsibilities for submitting pertinent information to the EC/IRB responsible for this study.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical study without the prior written consent of Roche Diabetes Care.

I agree that the Study Monitor/Clinical Research Associate (CRA), and/or other Sponsor representatives shall have access to any source data from which case report form information may have been generated.

To be signed by the Principal Investigator and Sub- or Co-Investigator (as appropriate).

Please sign and date next to your printed name:

PRINTED NAME	Signature	Date (dd-mmm-yyyy)

If more space is needed, please use a second copy of this page.

Protocol Outline

For comprehensive details, please refer to the respective sections.

Study Title:	**Benefits of a Long Term implantable Continuous Glucose Monitoring System for Adults with Diabetes France Adoption Randomized Clinical Trial**
Short Name	Clinical benefits of Eversense XL – French clinical trial
Investigational Device:	Eversense Continuous Glucose Monitoring (CGM) System – XL sensor, transmitter, mobile medical application (MMA).
Other Study Devices:	NA
Research Question/ Working Hypothesis:	The purpose of this clinical investigation is to evaluate the ability of a long term implantable CGM system to improve glycemic control in patients with insulin-treated Type 1 or Type 2 diabetes compared to current standard care of self-monitoring blood glucose (capillary blood glucose monitoring or flash glucose monitoring) meter among two cohorts: patients with elevated HbA1c (> 8%) and patients with a high rate of hypoglycemic episodes (more than 1.5 hour with sensor glucose <70 mg/dl per day as a mean for at least 28 days)
Primary Objective:	▪ Cohort 1: To evaluate the efficacy of using the Eversense CGM system on HbA1c level (%) ▪ Cohort 2: To evaluate the efficacy of using the Eversense CGM system on daily time spent with glucose <54 mg/dl
Secondary Objectives:	1. Safety of the insertion and removal procedures and the device defined by adverse events reported 2. Time in range [70mg/dL-180mg/dL] of glucose values 3. Time in hypoglycemia (<70mg/dL and <54mg/dL) and hyperglycemia (>180mg/dL and >250mg/dL) 4. Glucose variability calculated with coefficient of variation as ratio of standard deviation to mean daily glucose 5. Sensor life – number of subjects/Sensors operating at 150 and 180 days post insertion and mean/median Sensor life using Sensor output and long-term performance. 6. Amount and variability of Transmitter wear time (by day/week/months) 7. Frequency of access of app pages (event logs, statistics, etc) 8. Frequency and type of alarms/alerts received 9. HbA1C at D120 for both groups and at D180 for cohort 2 only 10. Patient Reported Outcome Measures (PROMs) to measure treatment satisfaction and quality of life to be completed during Visits 1, 4 and 6 for both groups 11. CGM questionnaire to be completed during Visits 4 and 6 for enabled patient only. 12. Partner reported Outcome Measures to measure the partner-related distress to be completed during visits 1,4 and 6.

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	13. Free text questionnaire for 'enabled' patients only to record the opinion of the patient about the 'enabled' system at the end of the study at D180. 14. Free text questionnaire for study investigators to record the opinion of the principal investigator or co-investigators about the system to be completed at the end of the study. 15. For cohort 2 only : a. Maintain of the Eversense effect on hypoglycemia between D150 and D180 for enabled group b. Comparison of data from D90-D120 period to D150-D180 period for control group
Indication	Continuous glucose monitoring (CGM) in the subcutaneous interstitial fluid for insulin-treated adult patients with Type 1 or Type 2 diabetes.
Target Population	The subject population consists of adult subjects with Type 1 or Type 2 diabetes mellitus under insulin therapy (pump or multiple-daily injections)
Number of Subjects	324 subjects : 159 in cohort 1 165 in cohort 2
Number of Sites	20 sites
Study Design:	This is a two cohort randomized (2:1), prospective, national multi-center study, enrolling approximately 324 adult subjects with diabetes mellitus at up to 20 sites (between 48 and 100 subjects in each arm). The subjects will have one sensor inserted in the upper arm by a trained clinician (investigator). The system will provide real-time glucose information, as well as alarms and alerts during the study period. After 180 days of wear or when the sensor has reached end of life, the sensor will be removed.
Study Duration:	6 months follow-up
Study Visits	- **Visit 1** Screening Visit. Following informed consent process, screening evaluation will determine subject eligibility for enrollment. Visit includes screening of medical and diabetes history, examination and HbA1c assessment. For DT1, the mean time in hypoglycemia in the last 28 days will be recorded from the patient glucose meter (Continuous or Flash meter). Once eligible for one of the two cohorts subjects will complete patient reported outcome measures questionnaires - **Visit 2** Sensor Insertion Visit – (Day 0). The Sensor is inserted by the Investigator in the upper arm of the subject's choice. All subjects will use the blinded system where they are required to wear the transmitter over the sensor and interstitial glucose levels are recorded. During this period the subjects do not have

Study Title:	**Benefits of a Long Term implantable Continuous Glucose Monitoring System for Adults with Diabetes France Adoption Randomized Clinical Trial**
	visibility of the glucose levels. However, patients will enter glucose values for calibration on a special application. Patient will have to install the application on a compatible device with iOS or Android that is wireless and Bluetooth enabled. If there is any kind of problem with the patient mobile device (which was supposed to be compatible) that might interfere with the use of the app, a new mobile device will be lent to the patient. A mobile device (iPod) will be lent to the patient if his mobile device is not compatible with the mobile application . In both case the patient will have to give it back at the end of the study Between visit 2 and 3 a phone call will be scheduled to ensure a good healing after the insertion. - **Visit 3** 30-Day Visit (Day 30 -2/+7 Days). Transmitter and CGM data if any data are downloaded. Sensor insertion site is assessed. Subjects are randomized to either the 'enabled' or the control arm of the study. Subjects in the enabled arm will change from blind to enabled Eversense CGM system and install a new unblinded application. A specific training on how to use the system, will be made to the 'enabled' group. Control subjects will continue to use the blinded CGM system and receive instructions on proper use of a blood glucose meter. - **Visit 4** 60-Day Visit (Day 60 -3/+7 Days) Transmitter and/or meter data is downloaded. Incision sites are inspected. Patients will complete a survey on treatment and CGM satisfaction. Patients in the control group will be informed in case of unexpected and unacceptable glycemic deterioration (recorded sensor data indicates periods of the day with recurrent time in hypoglycemia (<54 mg/dL) and/or in hyperglycemia (>250 mg/dL)). - **Visit 5** 120-Day Visit (Day 120 -3/+7 Days) Transmitter and/or meter data is downloaded. HbA1c will be assessed. Subjects in the control arm of cohort 2 will change from blinded to enabled Eversense CGM system. Those patients will be instructed on use of the features including the mobile medical application. Patients in the control group of cohort 1 will be informed in case of unexpected and unacceptable glycemic deterioration (recorded sensor data indicates periods of the day with recurrent time in hypoglycemia (<54 mg/dL) and/or in hyperglycemia (>250 mg/dL)).

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	- **Visit 6** Sensor Removal Visit– (Day 180 to 187) Patients will complete a survey on treatment and CGM satisfaction. HbA1c will be assessed. Transmitter and/or meter data are downloaded. The Sensor is removed. Patients in the control group of cohort 1 will be informed in case of unexpected and unacceptable glycemic deterioration (recorded sensor data indicates periods of the day with recurrent time in hypoglycemia (<54 mg/dL) and/or in hyperglycemia (>250 mg/dL)). After Visit 6, a phone call will be scheduled to ensure a good healing after the removal of the sensor. NB : patients included in cohort 1,control arm, will have the choice between receiving a compensation in gift vouchers or benefit from the unblinded system for a duration of about 6 months. - **Home Use**: Subjects will wear the Transmitter over the Sensor for data collection and glucose display (including glucose alarms and alerts), except during transmitter charging, bathing or extended water activity. Subjects will follow their usual diabetes care routine as per their medical team recommendations. All diabetes decisions by the subject and health care team will be made based on standard of care with blood glucose monitoring, and not based on System CGM values.
Main Inclusion Criteria:	Male and Female Subjects meeting all of the following inclusion criteria will be included in this study: 1. Written informed consent 2. Male and female patients at least 18 years of age 3. Clinically confirmed diagnosis of Type 1 or Type 2 diabetes mellitus for ≥1 year and using insulin by multiple-daily subcutaneous injections or insulin pump and an HbA1c > 8% (cohort 1) 4. Clinically confirmed diagnosis of Type 1 diabetes mellitus for ≥1 year and using insulin by multiple-daily subcutaneous injections or insulin pump and spending more than more than 1.5 hour with sensor glucose <70 mg/dl per day including excursions below 54 mg/dl as a mean for at least 28 days (cohort 2) 5. Subject is willing to comply with protocol
Main Exclusion Criteria:	Subjects meeting any of the following exclusion criteria at the time of screening will be excluded from this study: 1. Female subjects of childbearing capacity (defined as not surgically sterile or not menopausal for ≥ 1 year) who are lactating or pregnant, intending to become pregnant, or

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	not practicing birth control during the course of the study 2. A condition preventing or complicating the placement, operation or removal of the Sensor or wearing of transmitter, including upper extremity deformities or skin condition 3. History of hepatitis B, hepatitis C, or HIV 4. Currently receiving (or likely to need during the study period): immunosuppressant therapy; chemotherapy; anticoagulant/antithrombotic therapy (excluding aspirin< 2 000 mg per day); antibiotics for chronic infection (e.g. osteomyelitis, endocarditis) 5. A condition requiring or likely to require magnetic resonance imaging (MRI) 6. Known topical or local anaesthetic allergy 7. Known allergy to glucocorticoids ; or using systemic glucocorticoids (excluding topical, optical, or nasal but including inhaled) 8. Any condition that in the investigator's opinion would make the subject unable to complete the study or would make it not in the subject's best interest to participate in the study. Conditions include, but are not limited to, psychiatric conditions, known current or recent alcohol abuse or drug abuse by subject history, a condition that may increase the risk of induced hypoglycaemia or risk related to repeated blood testing. Investigator will supply rationale for exclusion 9. Participation in another clinical investigation (drug or device) within 2 weeks prior to screening or intent to participate during the study period, except observational studies 10. Legal incompetence or limited legal competence 11. Dependency on sponsor or Investigator (e.g. co-worker or family member) 12. The presence of any other active implanted device
Sample Size Calculation:	For the Cohort 1: The primary criterion is HbA1c (%) at D180 visit. The minimum expected absolute effect is 0.5%. With these assumptions, 144 subjects are needed for the analysis of this cohort (96 patients in the enabled arm and 48 patients in the control arm).

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	For the cohort 2: The primary criterion is the percentage of time spent in hypoglycaemia < 54 mg/dl between D90 visit and D120 visit (using CGM system data) compared to baseline (D0-D30 days). The minimum expected relative effect is 42.5%. With these assumptions, 150 subjects are needed for the analysis of this cohort (100 patients in the 'enabled' arm and 50 patients in the control arm). The randomization ratio is 2:1 (2 patients 'enabled': 1 patient control). By considering 10% of non-evaluable patients, the total number of participants is 324 (159 in cohort 1 and 165 in cohort 2).
Statistical Methods:	A Statistical Analysis Plan will be established, validated by the Scientific Committee of the study, detailing the statistical analysis. The statistical analysis will be performed on SAS/WINDOWS XP version 9.4 or later. The analysis will be carried separately for each cohort. The type I error (alpha) is set at 0.05 for each analysis. No adjustment of the alpha risk is planned because these two analyses have a distinct primary objective and criteria.

Schedule of Assessments

	Visit 1 Baseline	Visit 2 Insertion	Visit 3 Randomization	Visit 4	Visit 5	Visit 6
Study day	From -15 to 0 Days	Day 0	Day 30	Day 60	Day 120	Day 180 to 187
Time window (in days)	N/A	±0	-2/+7	-3/+7	-3/+7	NA
Consent	X					
Urine Pregnancy	X	X				
HbA1c Measurement	X				X	X
Medical History	X					
Diabetic History	X					
Physical Exam	X					
Insert Sensor		X				
Examine sensor insertion site		X	X	X	X	X
Confirm Sensor function		X	X	X	X	X
Download Transmitter/meter			X	X	X	X
Adverse Events		X	X	X	X	X
Remove Sensor						X
Patient reported outcome measures questionnaire	X			X		X
CGM satisfaction survey (enabled only)				X		X
Free text questionnaire for patients						X
Partners reported outcome measures questionnaire	X			X		X
Concomitant medication	X	X	X	X	X	X
Randomization			X			

Abbreviations

ADE	Adverse device effect
AE	Adverse events
ANSM	Agence nationale de sécurité du médicament et des produits de santé
BG	Blood Glucose
BG Meter	Blood Glucose Meter (also known as SMBG Meter)
BMI	Body Mass Index
CD	Compact disc
CE	Conformité Européene
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CI	Confidence interval
CIP	Clinical investigation plan; synonym for protocol
CPP	Comité de protection des personnes
CRA	Clinical research associate
CRF	Case Report Form
CRO	Contract Research Organization
CSII	Continuous subcutaneous insulin infusion
CSP	Code de la santé publique
CSR	Clinical Study Report
DCCT	Diabetes Control and Complications Trial
DCF	Data Clarification Form
DKA	Diabetic Ketoacidosis
EC	Ethics Committee
eCRF	electronic case report form
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FDA	Food and Drug Administration
GCP	Good clinical practice
HbA1c	Hemoglobin A1c or A1C
HHD	Hand Held Device
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IDE	Investigational device exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization

MDI	Multiple daily injections
MEDDEV	Medical Devices (Guidance document)
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Mobile Medical Application
MRI	Magnetic Resonance Imaging
PARD	Percent absolute relative difference
PP	Per protocol
Protocol	Synonym for CIP
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDV	Source Data Verification
SMBG	Self-Monitoring Blood Glucose
UADE	Unanticipated Adverse Device Effect
USB	Universal Serial Bus

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1 Introduction

1.1 Introduction and Background

In spite of recent improvement in therapies, diabetes mellitus continues to be a difficult medical condition to treat. The challenge remains to achieve desired glycemic control and to prevent both the short-term consequences (severe hypoglycaemia and DKA) and long-term complications (retinopathy, neuropathy, nephropathy and cardiovascular problems). The monitoring of blood glucose by the patient with diabetes is one of the key tools of diabetes self-care. The current standard glucose monitoring regimen for patients with insulin-treated diabetes includes using a small portable meter to obtain a capillary fingertip glucose measurement multiple times a day. According to the International Society of Pediatric and Adolescent Diabetes (ISPAD), "successful application of intensified diabetes management with multiple-daily injection therapy or insulin infusion therapy requires frequent self-monitoring of blood glucose (four to six times a day) and regular, frequent review of the results to identify patterns requiring adjustment to the diabetes treatment plan.[1] Despite this monitoring and therapeutic interventions, glucose values may fluctuate widely throughout the day due to the nature of diabetes. In addition, as the BG meter value shows only a point in time glucose level, even patients who monitor frequently may miss significant hypoglycaemic and hyperglycaemic excursions. Continuous glucose monitoring (CGM), measuring interstitial glucose levels has been developed recently and has been shown to be associated with improved glycemic control in adults with insulin-treated Type 1 or Type 2 diabetes. Current commercially available CGM devices require the repeated, frequent insertion of a sensor by the patient.

Senseonics, Inc. a medical device manufacturer headquartered in Germantown, Maryland, USA, is developing a new CGM System intended for measuring interstitial fluid glucose levels in adults with diabetes mellitus. The Senseonics CGM System measures interstitial fluid glucose levels continuously and is implanted under the skin by a trained clinician. Unlike commercially available transcutaneous continuous glucose monitoring devices with short operating lives (up to 7 days), the Senseonics Sensor is intended to be inserted subcutaneously with no sensor part protruding from the skin, and the operating life is intended to be up to 150 days or until the end of life indicator is reached (180 days).

Roche Diabetes Care France SAS is the EU distributor of this product and sponsor of this study.

1.2 Intended Use of Study Device

The study investigational Device is the Senseonics Eversense CGM System XL ("System").

The Senseonics Eversense Continuous Glucose Monitoring System is a glucose monitoring device intended to continually measure interstitial fluid glucose levels in individuals with diabetes for the operating life of the sensor. The Senseonics Continuous Glucose Monitoring System is intended to be used:

- To aid in the management of diabetes
- To provide real-time glucose readings directly to the user
- To provide glucose trend information
- To provide alarms for the detection and prediction of episodes of low blood glucose (hypoglycemia) and high blood glucose (hyperglycemia).

1.3 Study Rationale

Several studies have been conducted in Europe and in USA to support the evaluation of the safety and the accuracy of the Eversense system.

The purpose of this new clinical investigation is to evaluate the usefulness of using a long term implantable continuous glucose monitoring (CGM) sensor to improve glycemic control in patients with either Type 1 or Type 2 diabetes mellitus under insulin therapy.

This study will be conducted in France. Data from this clinical trial will be used to support reimbursement dossier that will be submitted to French Health authorities.

This will be the first study to provide evidences of the potential clinical benefits of the Eversense XL system. Those potential clinical benefits can be translated by a reduction of HbA1c and a decrease of time spend in hypoglycaemia.

Regarding HbA1c, any reduction in HbA1c is likely to reduce the risk of complications either in type1 or type 2 diabetics patient as reported by Stratton in 2000 and Bebu in 2017.

Regarding hypoglycaemia, Hypoglycaemia often causes recurrent physical morbidity, recurrent or persistent psychosocial morbidity, or both and sometimes causes death (Cryer, 2003). Even patient under intensive therapy with a low HbA1c are facing severe hypoglycaemia events. Data coming from the DCCT study are supporting this, they have been published by Gubitosi-Klug et al in 2017. With the implantable glucose sensor, hypoglycaemia events, especially during night could be limited.

Threshold for hypoglycaemia have been based on last ADA recommendations published in Standards of Medical Care in Diabetes-2017 :

Level	Glycemic criteria	Description
Glucose alert value (level 1)	≤70 mg/dL	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (level 2)	≤54 mg/dL	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (level 3)	No specific glucose threshold	Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery

Table 1 Classification of Hypoglycemia

2 Study Design and Duration

2.1 Study Design Overview

This is a prospective, two-cohort randomized versus a control arm, multi-center interventional study enrolling approximately 324 adult subjects with diabetes mellitus
Subjects will be allocated to one of the following cohorts:

- Cohort 1 – HbA1c
- Cohort 2 – Time in hypoglycemia

In each cohort subjects will be randomized to one of the following groups:

- Intervention : 'Enabled' arm
- Control : Control arm

Each subject will have a 6-month follow-up. The enrollment period is planned to be around 3 months but could be extended if necessary. The total duration is between 9 to 12 months.

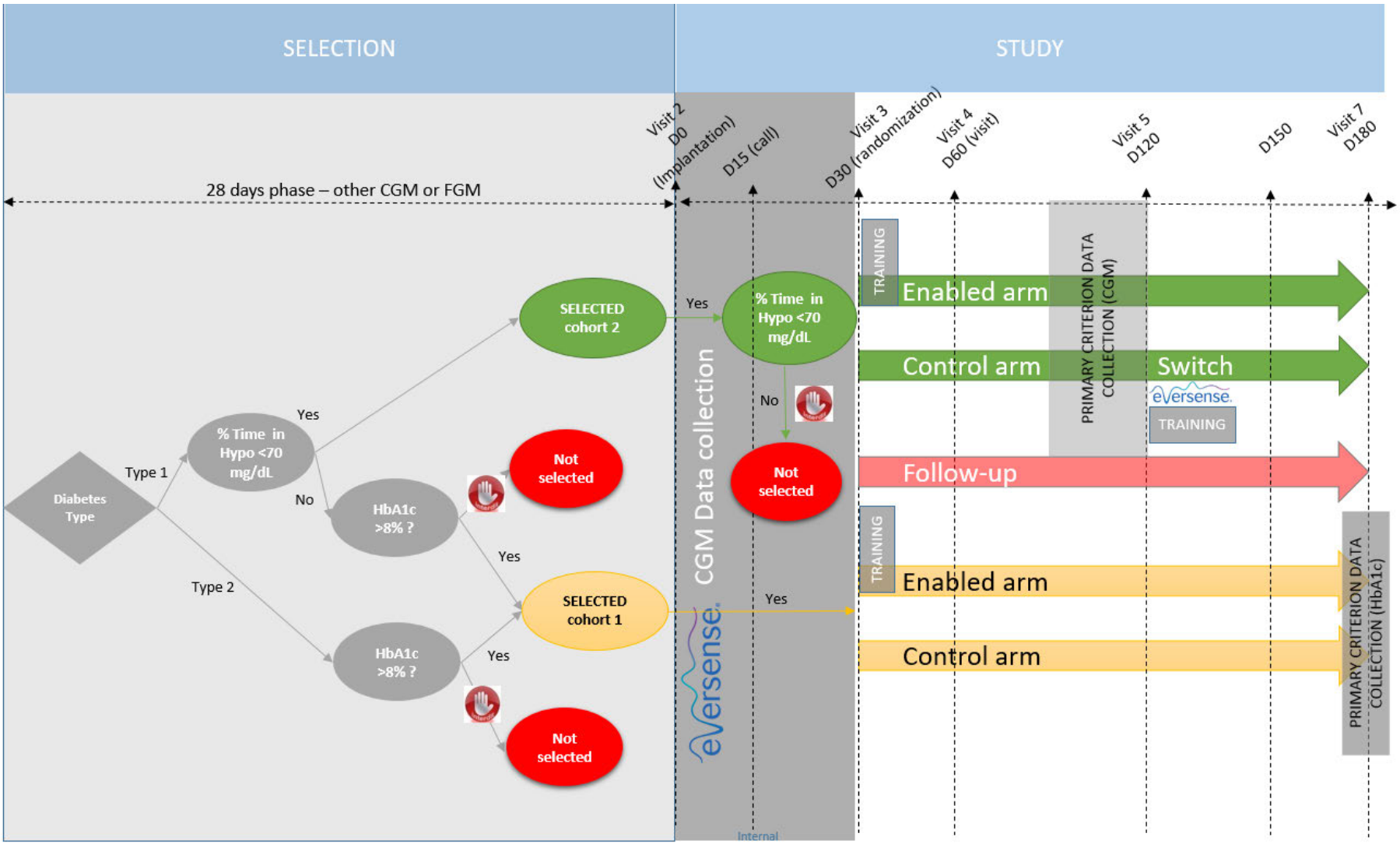


Figure 1 : Study design

Patients with insulin treated diabetes are invited to participate in the study either because they have an HbA1c level > 8.0% (cohort 1) or because they have T1D and spend more than 1.5 hour with FGM <70 mg/dl per day as a mean for at least 28 days (cohort 2). The investigator will inform the patient about the study and review the list of inclusion and exclusion criteria. If they agree to participate, patients will sign a consent form and they will come for a second visit (no more than 15 days later) during which the sensor will be inserted subcutaneously.

After the insertion, all study subjects will wear the blinded transmitter over the sensor continuously except for charging and will be blinded to any glucose values. However, patients will enter glucose values for calibration on a special application. Participants will continue their usual glucose monitoring. After 30 days, they will come for a third visit.

In cohort 1, they will be randomized in the 'enabled' or control group. In the 'enabled' group they will be trained to use the system. They will not be allowed to use another CGM or FGM.
In the control group they will continue with their usual glucose monitoring system (SBMG or FGM) with the CGM in blinded mode.

In cohort 2, if they still comply with the inclusion criteria "time in hypo" based on FGM results, they will be randomized in the 'enabled' or control group. In the 'enabled' group they will be trained to use the system. They will not be allowed to use another CGM or FGM.
In the control group they will continue with their usual glucose monitoring system (SBMG or FGM) with the CGM in blinded mode.
If they no longer comply with the inclusion criteria, they will have the opportunity to start using the system, but in an open phase, the investigator will determine the planning of visits as per their usual follow-up, no data will be collected except the report of any adverse event. They will come at the centre to remove the sensor at the end of the sensor life (180).

A follow-up visit will be performed at day 60 and day 120 for control and enabled patients.

At Day 120, participants in the control group of the cohort 2 will have the opportunity to have the system enabled until it reach the end of the sensor life or have the sensor removed and exit the study.

Patients in the control group of the cohort 1 will be informed in case of unexpected and unacceptable glycemic deterioration (recorded sensor data indicates periods of the day with recurrent time in hypoglycemia (<54 mg/dL) and/or in hyperglycemia (>250 mg/dL)).

After 180, these participants will have the opportunity to have the system enabled for 6 months after study end or have the sensor removed, exit the study and receive gift vouchers

In case of incidents with the enabled system, the report will be made through the regular materiovigilance.

A last follow-up visit by phone call will be performed to evaluate the incision site for healing.

2.2 Rationale for the Study Design

Two separate cohorts have been created in this study to be able to support different potential clinical benefits:

1. HbA1c reduction will be the primary objective for patient having an HbA1c level > 8% that can translate a non-well controlled disease.
2. The time spent per day below 54mg/dL will be the primary objective for patient spending more than 1.5 hour per day with sensor glucose < 70 mg/dL).

To address the risk of foreseeable factors that may compromise the outcome of the clinical study or the interpretation of results, a randomized stratification has been added into the study design. (see §6.5 Randomization)

3 Study Device(s)

3.1 Identification and Description of the Investigational Device: Eversense XL

The Senseonics CGM System consists of:

1. XL Glucose Sensor, (approximately 3.3 mm [0.130"] diameter x 15.7 mm [0.620"] length) which has a ring that elutes the steroid dexamethasone
2. Battery-powered external Transmitter ("Smart Transmitter")
3. Mobile Medical Application (MMA) for display of glucose information that runs on a Handheld Device (HHD).

Sensor Transmitter Mobile Medical Application

Figure 2 : Eversense System

Accessories to the system include:

1. Eversense DMS Application
2. Eversense Insertion tools kit (Blunt dissector for creating a pocket under the skin and Insertion tool used to place the Sensor into the pocket.)
3. Transmitter accessories (power supply, adhesive patches)

The manufacturer of the product is :

Senseonics, Incorporated

20451 Seneca Meadows Parkway

Germantown, MD 20876-7005

USA

Description

The Senseonics CGM Sensor uses a selective, fully reversible binding between glucose and a unique fluorescent indicator macromolecule that is grafted on the surface of the Sensor. The fundamental recognition reaction is a reversible condensation of the cis-diol groups of glucose with the bis-boronate moiety of an indicator. Glucose binding by the indicator macromolecule results in an increase in fluorescence intensity. Glucose signal transduction is accomplished by measuring the fluorescence intensity modulation using the Sensor's optical system.

The Senseonics System Transmitter powers the Sensor and receives signals from the Sensor across the skin. The Sensor does not contain a battery or other stored power source; instead it is powered discretely, as needed, by a simple inductive magnetic link between the Transmitter and Sensor. Signals carrying glucose concentration data are superimposed upon the magnetic power link between the two components. This results in "passive" telemetry, rather than an "active" radio frequency (RF) transmission, between the Sensor and Transmitter. Between readings, the Sensor remains electrically dormant and fully powered down. At each query (automatically set for approximately every five minutes, with a duration of approximately 100 milliseconds), the Transmitter sends power (via magnetic link) to activate the sensor, and then uses this same magnetic link to capture the reading. Finally, the Transmitter calculates and stores the measured glucose value for transmission to the Mobile Medical Application.

Components of the Senseonics CGM System are traced by serial number and/or lot number. The Sensor, Sensor holder, insertion tool, and blunt dissector are provided sterile. Sterilized components also have an expiration date. The device is labeled in compliance with regulatory language requirements identifying it as investigational. The Instructions for Use are provided with each shipment.

Insertion of the Sensor is a minimally invasive procedure and clinical investigators representing the intended use population (Endocrinologists, Internists) will be appropriately trained in the procedure prior to insertion or removal of the Sensor. The procedure is described below (Figure 2):

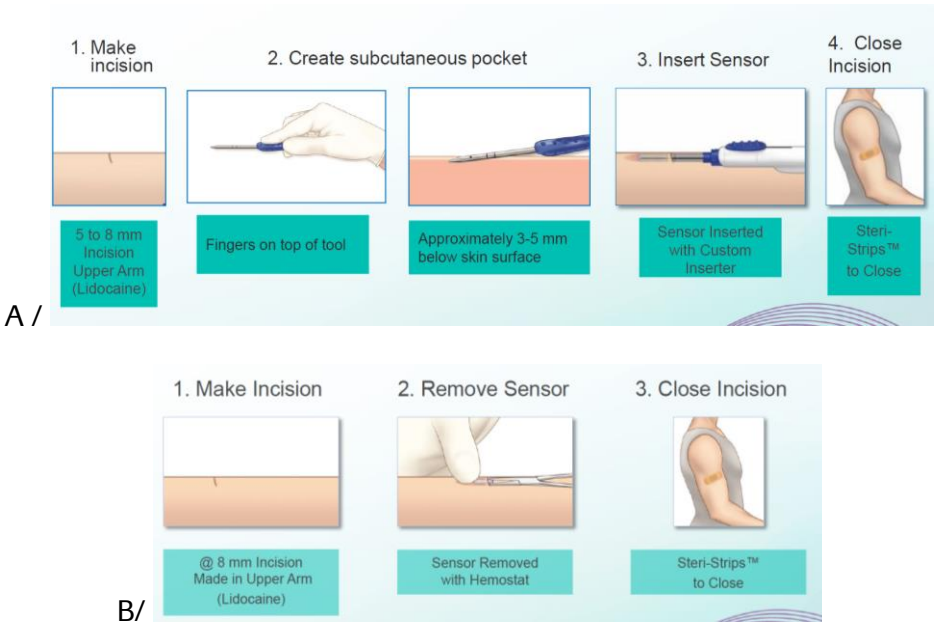


Figure 3: Procedure to insert (A/) and remove (B/) the sensor

Transmitters will be provided for single-subject use in this clinical trial.

Calibration

For the first phase of the study the subjects will be inserted with the sensor in their arm of choice and the transmitter will be blinded. Calibration is required for both transmitters. After study visit 3 the control arm subjects will continue with the blinded function. The study subjects will have the system enabled, they will go into initialization mode with 4 calibrations within the first 24 hours and then be in daily calibration mode. The System will then prompt the subjects to calibrate using SMBG twice per day for the remainder of the study. The System will be calibrated by the Subjects according to the Instructions for Use (IFU), using a study-supplied SMBG Meter, according to the meter manufacturer instructions. The calibration process automatically moves through three phases: Warm Up, Initialization, and Daily Calibration:

- Warm Up is the first 24 hours after Sensor insertion. Glucose information is not displayed. No calibration is performed.
- Initialization can be performed a minimum of 24 hours after Sensor insertion. Following the Warm Up phase, the entering of four successful calibration BG readings within 24 hours is required for successful completion of Initialization. Glucose information will be displayed after the second calibration is entered successfully.
- Daily Calibration requires 2 successful calibrations per day, a minimum of 10 and maximum of 14 hours apart.

Figure 4: Procedure for calibration

If the Subject fails to wear the Transmitter for more than 24 hours, or is unable to enter a successful calibration, then glucose information will not be displayed and the Subject will re-enter the Initialization phase.

Use of Study Devices for Diabetes Treatment

Although the Senseonics Continuous Glucose Monitoring System will display sensor glucose values and will alert subjects for those subjects who have been enabled when sensor values reach or are predicted to reach present glucose thresholds, all diabetes care decisions will be based on SMBG blood glucose values, rather than Senseonics CGM System results as per labelling as an adjunctive device.

Sensor replacement

If a Sensor loses functionality during study and before Day 150, the sensor will be replaced. The subject will stay with the current visit schedule. If the sensor fails after day 150 their data will be

recorded up to the date of failure and the subject will be exited from the study with removal and post removal visits required.

At study end (D180 maximum), all sensors still in function will be removed.

3.2 Consumables of Eversense XL

A new adhesive patch to maintain the transmitter on the skin is needed each time the transmitter is placed on the skin (at minimum after each recharge of the battery).

3.3 Comparator Device

Glucose monitoring is a fundamental requisite for insulin therapy in patients with diabetes. In addition to the routine self-monitoring of blood glucose (SMBG), several products from different brands are available on the French market.

The continuous glucose monitoring (CGM) in the subcutaneous interstitial fluid is also possible. CGM systems can overcome limitations of the SMBG, which provides incomplete glucose profiles and often underestimate nocturnal hypoglycaemia and post-prandial hyperglycaemia. As of today in France no CGM is available for diabetics patient, only one flash glucose monitoring (FGM) system FreeStyle® Libre™ (FSL) is reimbursed. Differently from CGM systems, the FGM system provides actual interstitial glucose concentration on demand, i.e., when patients perform a sensor scan, and has no direct alarms.

In our study either SBMG from different brands or FGM (FSL) are considered as comparators.

3.4 Status of Documentation of Study Device(s)

Eversense system is composed of several devices, the Transmitter and the sensor is an active implantable medical device.

Devices used in this study are listed in table 1.

Device	CE-Mark	FDA cleared/approved
Battery-powered external Transmitter ("Transmitter") And XL Glucose Sensor, (approximately 3.3 mm [0.130"] diameter x 15.7 mm [0.620"] length) which has a ring that elutes the steroid dexamethasone	Yes	No
Mobile Medical Application (MMA) for display of glucose information that runs on a Handheld Device (HHD).	Yes	No

Table 2 List of Study Devices with Status of Documentation

4 Study Objectives

4.1 Primary Objective

Cohort 1: To evaluate the efficacy of using the Eversense CGM system on the HbgA1c level (%)

Cohort 2: To evaluate the efficacy of using the Eversense CGM system on daily severe hypoglycemia (time spent with glucose <54 mg/dl)

Primary Outcome Measures:

Cohort 1: HbA1c (%) at D180 visit

Cohort 2: % of time spent in hypoglycemia between D90 visit and D120 visit (CGM Eversense sensor values uploaded from transmitter)

4.2 Secondary Objectives

The secondary objective(s) of this study are

1. Safety of the insertion and removal procedures and the device defined by adverse events reported
2. Time in range defined as percentage change from blinded period to enabled period of glucose values 70mg/dL-180mg/dL.
3. Time in hypoglycemia (<70mg/dL and <54mg/dL) and hyperglycemia (>180mg/dL and >250mg/dL)
4. Glucose variability calculated with coefficient of variation as ratio of standard deviation to mean daily glucose
5. Sensor life – number of subjects/Sensors operating at 150 and 180 days post insertion and mean/median Sensor life using Sensor output and long-term performance.
6. Amount and variability of Transmitter wear time (by day/week/months)
7. Frequency of access of app pages (event logs, statistics, etc)
8. Frequency and type of alarms/alerts received
9. HbA1C at D120 for both cohorts and at D180 for cohort 2 only
10. Patient Reported Outcome Measures (PROMs) to measure treatment satisfaction and quality of life to be completed during Visits 1, 4 and 6 for both groups.
11. CGM questionnaire to be completed during visits 4 and 6 for enabled patient only
12. Partner Diabetes Distress Scale (Partner-DDS) the questions ask about how the partner have been feeling of someone with diabetes to be completed for both cohorts during visits 1, 4 and 6.

13. **Free text questionnaire for 'enabled' patients only** to record the opinion of the patient about the 'enabled' system at the end of the study at D180.

14. **Free text questionnaire for study investigators** to record the opinion of the principal investigator or co-investigators about the system to be completed at the end the study.

15. For cohort 2 only :

    - Maintain of the Eversense system effect on hypoglycemia between D150 and D180 for enabled group

    - Comparison of data from D90-D120 period to D150-D180 period for control group

5 Subject Selection

Subjects will be identified and recruited from the Investigator's established subject population or from respective group practices using the inclusion/exclusion criteria; see Section 6.

If a subject agrees to consider participation in the study, he/she shall be informed (verbally and in writing by means of the Subject Information Leaflet) and given the possibility to ask questions to authorized study staff. If a subject decides to participate, he/she shall sign the current Ethics Committee (EC) approved Subject Informed Consent Form before any study-related procedures; see Section 15.2.

A subject is considered enrolled in the clinical trial after he or she has provided informed consent, has met all the inclusion criteria and none of the exclusion criteria, and has been enrolled using the appropriate Case Report Form (CRF). Subjects who fail one or more of the eligibility criteria are considered screen failures and are not enrolled in the study. Subjects who withdraw consent or are withdrawn by the investigator after enrollment and prior to the first Sensor insertion attempt are "withdrawn prior to Sensor insertion" and are withdrawn from the study without data acquisition. A listing of screen failures and "withdrawals prior to Sensor insertion" subjects including the reason for study exit will be reported.

Subjects who begin a first Sensor insertion procedure (defined as injection of local anesthetic) remain enrolled in the study and will be analyzed as per the description of study populations in Section 11 Statistical Methods

During the Screening and Baseline Visits, the subject will be interviewed to obtain demographic information and diabetes and other medical history to determine if he/she meets all of the inclusion, but none of the exclusion criteria.

6 Study Population

The study population (cohort 1 and cohort 2) includes 324 adults with Type 1 or Type 2 diabetes mellitus on insulin therapy (multiple-daily injections or pump).

During a visit at hospital, Patients with insulin treated diabetes are invited to participate in the study either because they have an HbA1c > 8.0% (cohort 1) or because they are Type 1 spending more than more than 1.5 hour with FGM <70 mg/dl per day as a mean for at least 28 days (cohort 2). The investigator will inform the patient about the study and review the list of inclusion and exclusion criteria listed below. If they agree to participate, patients will sign a consent form.

6.1 Inclusion Criteria

To be eligible to participate in this clinical study, subjects must meet **ALL** of the following criteria:

1. Written informed consent
2. Male and female patients at least 18 years of age
3. Clinically confirmed diagnosis of Type 1 or Type 2 diabetes mellitus for ≥1 year and using insulin by multiple-daily subcutaneous injections or insulin pump and an HbA1c > 8% (cohort 1)
4. Clinically confirmed diagnosis of Type 1 diabetes mellitus for ≥1 year and using insulin by multiple-daily subcutaneous injections or insulin pump and spending more than more than 1.5 hour with sensor glucose <70 mg/dl per day including excursions below 54 mg/dl as a mean for at least 28 days (cohort 2)
5. Subject is willing to comply with protocol

6.2 Exclusion Criteria

Subjects may not participate in this clinical study if they meet **ANY** of the following criteria:

1. Female subjects of childbearing capacity (defined as not surgically sterile or not menopausal for ≥ 1 year) who are lactating or pregnant, intending to become pregnant, or not practicing birth control during the course of the study
2. A condition preventing or complicating the placement, operation or removal of the Sensor or wearing of transmitter, including upper extremity deformities or skin condition
3. .
4. History of hepatitis B, hepatitis C, or HIV
5. Currently receiving (or likely to need during the study period): immunosuppressant therapy; chemotherapy; anticoagulant/antithrombotic therapy (excluding aspirin< 2 000 mg per day); antibiotics for chronic infection (e.g. osteomyelitis, endocarditis)
6. A condition requiring or likely to require magnetic resonance imaging (MRI)
7. Known topical or local anesthetic allergy
8. Known allergy to glucocorticoids ; or using systemic glucocorticoids (excluding topical, optical, or nasal but including inhaled)
9. Any condition that in the investigator's opinion would make the subject unable to complete the study or would make it not in the subject's best interest to participate in the study. Conditions include, but are not limited to, psychiatric conditions, known current or

recent alcohol abuse or drug abuse by subject history, a condition that may increase the risk of induced hypoglycemia or risk related to repeated blood testing. Investigator will supply rationale for exclusion

10. Participation in another clinical investigation (drug or device) within 2 weeks prior to screening or intent to participate during the study period, except observational studies
11. Legal incompetence or limited legal competence
12. Dependency on sponsor or Investigator (e.g. co-worker or family member)
13. The presence of any other active implanted device*

* An example of an active implanted device includes, but is not limited to an implantable defibrillator. Passive implantable devices are allowed. An example of a passive implantable device includes, but is not limited to a cardiac stent.

6.3 Point of Enrolment and Withdrawal

A subject is considered enrolled in the study:

- As soon as he/she has signed the Subject Informed Consent Form
- And has been deemed eligible according to above inclusion/exclusion criteria.

A subject is considered withdrawn if he/she was first enrolled, and thereafter excluded from further participation.

Reasons therefore may be:

- Screening failure (any reason).
- Not randomized (any reason)
- Withdrawal of consent to participate in the study.
- By decision of the Investigator due to following reasons: Non-compliance with the protocol procedures e.g., subject missed two consecutive study visit and/or do not calibrate the device, do not have any more an appropriate phone…
- Subject becomes pregnant or has discontinued birth control or wishes to start breastfeeding (Sensor will be removed and Subject exits the study.)
- Infection at the sensor insertion site that has not resolved within 3 days
- Subject needs an MRI and Sensor is removed and not replaced.
- Investigator determines it is in Subject's best interest to withdraw.
- Subject is lost to follow-up
- Subject dies

If any of the above occurs, the Investigator will:

- Ensure subject presents at site in order to ensure complete documentation (eCRF, questionnaire), and to return all study materials.
- Complete the Study Completion Form in the eCRF including the date of and reason for early discontinuation.

6.4 Replacements

Subjects who drop-out will not be replaced. Subjects, for whom no informed consent has been obtained, or who have not meet eligibility criteria will not be considered as enrolled, and are therefore also not counted as drop outs and will be replaced. For the sample size calculation a drop-out rate of 10% was considered. Hence, if drop-outs occur the main target may still be achieved.

6.5 Randomization

A centralized randomization via IWRS will be set-up as follows:

- For cohort 1:
  - Randomization 2:1 (2 patients enabled: 1patient control)
  - Stratification variables: center and diabetes type
- For cohort 2:
  - Randomization 2:1 (2 patients enabled: 1patient control)
  - Stratification variables: center

In case of a patient complies the inclusion / exclusion criteria for both cohorts, he/she will be included and randomized in the cohort 2.

7 Visit Schedule, Study Procedures and Laboratories

7.1 Visit Schedule

Subjects will be invited to the clinic for the following visits:

- Visit 1 – Screening/Enrollment
  - Follow-up call
- Visit 2 – Sensor insertion
- Visit 3– Randomization / training for enabled group
- Visit 4 – Follow-up
- Visit 5 – Follow-up and training for control group
- Visit 6 – Sensor removal
  - Follow-up call

Please refer to the overall Schedule of Assessments and the below details for each study visit.

7.2 Visit 1 – Screening (within 15 days of Insertion)

No study-specific procedures must be performed before informed consent has been obtained.

Study procedures include the following assessments:

- Provide information to subject - orally as well as presented in the written Subject Information Leaflet - and ensure possibility to ask questions, See Section 15.2
- Obtain written Informed Consent
- Allocate subject ID number (via the eCRF-system) to each subject who has signed the informed consent form; See Section 16.1.1 for details.
- Assess all applicable inclusion and exclusion criteria and confirm patients' eligibility
- Obtain and record demographics, including age, gender
- Obtain and record weight, height,
- Obtain and record Diabetes Background and History including insulin therapy and diabetes complications
- Obtain and record ongoing Diabetes Medication including but not limited to brand name(s) of insulin used, total daily dose, total basal and bolus doses, sensitivity factors, etc.
- Perform urine pregnancy test (women of child bearing potential, only)
- Blood samples will be drawn for HbA1c dosage and sent to the local lab for processing
- For DT1 in cohort 2, the mean time in hypoglycemia (less than 54mg/dL) in the last 28 days will be recorded from the patient glucose meter (Continuous or Flash meter).
- Make appointment for Visit 2
- Have patient complete Questionnaire
- Record all relevant data in the eCRF

7.3 Visit 2 – Insertion (Day 0)

The Insertion Visit must take place within no more than 15 days after the Screening Visit, and can be combined with the Screening Visit.

Subject Admission

The subject will arrive at the clinic during the day and the following tests will be performed to confirm eligibility:

- Female subjects will perform a urine pregnancy test. If positive, the subject will discontinue study participation. Subject withdrawal will be documented.
- The study team will confirm the absence of a febrile or vomiting illness within 24 hours of the admission.
- If all admission readiness criteria are not met, the subject will be rescheduled. If all of the admission readiness conditions are met, the subject will be admitted to the Clinical Research Unit.

Procedures

- The subject will be asked about any adverse events since the last study visit.
- Fingerstick capillary glucose will be performed shortly after admission. Recommendation regarding glucose level at insertion : If glucose is ≥300 mg/dL the subject will be monitored until glucose is below these levels. Insulin will not be delayed. If glucose is <80 mg/dL the subject will be monitored until glucose is above these levels. Carbohydrates will be given to raise the glucose.

Sensor Insertions

Each subject will have the Sensors inserted at Visit 2 (Day 0); above the elbow of the arm of their choosing. The study team will prepare the Sensor insertion site appropriately. The hair at the insertion area may be clipped order to ensure appropriate visualization of the insertion site. The Sensor will be prepared by qualified personnel (Sponsor personnel or trained investigative staff).

A study physician will insert the Sensor into the subcutaneous tissue using appropriate technique described in the Physicians Guide Instructions for Use. The location of the Sensor will be documented.

Subjects will be advised that they may take over the counter pain medication if needed for any discomfort after the insertion process. No medication, including medication-containing creams and patches is to be applied over the sensor insertion site.

Subjects will be advised to keep the area dry for 48 hours. They should leave the dressing in place until the following day and check whether the healing process is going as expected (minor redness, no swellings, no increased temperature, no increased pain and no sign of infection). Subjects will be advised to change the dressing daily until the wound is closed.

Identification of the Sensor, Transmitter and accessories will be recorded (model number, serial number, lot number and expiration date as applicable).

After sensor insertion, the transmitter will be worn briefly (approximately 20 minutes) to ensure proper operation of the system (confirmation of system operation). Readings will be taken approximately every 5 minutes.

The blinded transmitter will then be placed over the sterile dressing at 24 hours after insertion and secured with the provided adhesive patches.

Calibration

All subjects will use the blind system where they are required to wear the transmitter over the sensor and interstitial glucose levels are recorded. During this period the subjects do not have visibility of the glucose levels. However, patients will enter glucose values for calibration on a special application .

All subjects will be required to provide a compatible mobile device (smartphone iOS or Android or an tablet that is wireless and Bluetooth enabled.) for the use of the application.

If there is any kind of problem with the patient mobile device (which was supposed to be compatible) that might interfere with the use of the app, a new mobile device will be lent to the patient. A mobile device (iPod) will be lent to the patient if his mobile device is not compatible with the mobile application . In both case the patient will have to give it back at the end of the study

Estimated Visit Duration

The total duration of the device training clinic visit is approximately 2 hours.

Follow-up Phone Call

Clinical site staff will follow-up with subject via telephone approximately 2 weeks after sensor insertion to assess for adverse events or device use issues.

7.4 Visit 3 – Randomization (Day 30 [-2/+7 days])

After wearing the Sensor and blinded Transmitter for 30 days at home, Subjects will be randomized to either the enabled or the control arms.

Study procedures include the following assessments:

- Assess all applicable randomization criteria
- Randomization (through the eCRF-system) to one of the two study groups for each cohort,
  - Group Enabled
  - Group Control
- Record any changes to insulin therapy
- Record any changes to Concomitant Medications
- Assess and record any new AE/SAEs and/or changes to ongoing AE/SAEs since the previous visit.
- Make appointment for the following Visit, Visit 4
- Record all relevant data in the eCRF
- Upload BG meter data, FGM data or CGM data and review together with Subject

Enabled arm:

Subjects in the enabled arm will change from blind to enabled transmitter so they gain the full functionality of the Eversense CGM system and have their glucose values visible on their smartphones. They will be instructed on the functions of the system including the mobile medical application.

Subjects will be provided the following devices:

- A Senseonics Continuous Glucose Monitoring System consisting of-
- Transmitter and accessories (charger, adhesive patches)

- Mobile Medical Application (MMA)
- Instructions for Use

Subject training: see §7.11. Training of Subject

Control arm:

Subject will be advice to continue using their usual glucose monitoring system (FGM or SBGM).

For cohort 2 only, they will have the opportunity to use the Eversense system at Day 120. (after Visit 5)

7.5 Visit 4 – Follow-up (Day 60 -3/+7 days])

Study procedures include the following assessments:

- Upload BG meter data or CGM data and review together with Subject
- Record any changes to insulin therapy
- Record any changes to Concomitant Medications
- Record any malfunctions /incidents, Assess and record any new AE/SAEs and/or changes to ongoing AE/SAEs since the previous visit.
- Examine Insertion site, if abnormal take a picture avoiding patient identification
- Make appointment for the following Visit, Visit 5
- Have patient complete Questionnaire (enabled group)
- Record all relevant data in the eCRF

Patients in the control group will be informed in case of unexpected and unacceptable glycemic deterioration (recorded sensor data indicates periods of the day with recurrent time in hypoglycemia (<54 mg/dL) and/or in hyperglycemia (>250 mg/dL)).

7.6 Visit 5 – Follow-up (Day 120 -3/+7 days])

Study procedures include the following assessments:

- Upload BG meter data or CGM data and review together with Subject
- Record any changes to insulin therapy
- Record any changes to Concomitant Medications
- Record any malfunctions /incidents, Assess and record any new AE/SAEs and/or changes to ongoing AE/SAEs since the previous visit.
- Examine Insertion site, if abnormal take a picture avoiding patient identification
- Laboratory testing : blood sample will be drawn for HbA1c dosing
- Make appointment for the following Visit, Visit 6
- Record all relevant data in the eCRF
- Patients in the control group will be informed in case of unexpected and unacceptable glycemic deterioration (recorded sensor data indicates periods of the day with recurrent time in hypoglycemia (<54 mg/dL) and/or in hyperglycemia (>250 mg/dL).Blood samples will be drawn for Hemoglobin A1c dosage and sent to the local lab for processing

For cohort 2 only : Subjects in the control group will be proposed to start use the system at this point of the study. If they are willing to, they will be trained on how to use the system as per the same procedure described in §7.11. Training of Subject. Subjects will change from blind to enabled Eversense CGM system and install a new unblind application compatible with iOS or Android mobile device that is wireless and Bluetooth enabled.

7.7 Visit 6 – Sensor removal (Day 180-187)

The Sensors will be removed at Day 180 or before when the designated time for Sensor removal is reached but no later than Day 187. The removed Sensors will be handled in compliance to institution/regulatory requirements for biomedical waste and returned following specific Instructions and by Biohazard Return Kit.

Study procedures include the following assessments:

- Upload BG meter data or CGM data and review together with Subject
- Record any changes to insulin therapy
- Record any changes to Concomitant Medications
- Examine Insertion site, if abnormal take a picture avoiding patient identification
- Record any malfunctions /incidents
- Assess and record any new AE/SAEs and/or changes to ongoing AE/SAEs since the previous visit.
- Have patient complete Questionnaire
- Record all relevant data in the eCRF
- Blood samples will be drawn for Hemoglobin A1c dosage and sent to the local lab for processing

Patients in the control group of cohort 1 will be informed in case of unexpected and unacceptable glycemic deterioration (recorded sensor data indicates periods of the day with recurrent time in hypoglycemia (<54 mg/dL) and/or in hyperglycemia (>250 mg/dL).

At the end of the 6 months study, all participants exit the study, but these patients will have the . opportunity to have the enabled system for 6 months, In case of incidents with the enabled system, the report will be made through the regular materiovigilance.

Follow-up Phone Call

Clinical site staff will follow-up with subject via telephone approximately 2 weeks after sensor removal to assess for adverse events and healing of the incision.

7.8 Unscheduled Study Visits or Phone Calls

During the course of the study, subjects may require additional (unscheduled) visits with their physicians (Investigators) for any number of reasons including, but not limited to the following:

- Medication adjustment for diabetes and/or other diseases

- Adverse Events such as, but not limited to:
  - Common respiratory infections including colds and flu.
  - Urinary tract infections.
  - Gastrointestinal disturbances.
  - Depression.
  - Minor injuries.

For tracking purposes and future analysis of the potential cost effectiveness, any additional study visits will be documented as **Unscheduled Visits** in the electronic case report form (eCRF).

Any conditions like above should be documented under Adverse Events.

Any changes to medication should be documented, as follow:

- Insulin (any changes in doses or parameters) under Diabetes Medication
- Other relevant medication under Concomitant Medications.

Full documentation of the visit including any assessments or examinations performed should be maintained in the source documents.

7.9 Laboratories

7.9.1 Local Laboratories

Blood samples must be drawn for the determination of the following parameters at the site's local laboratory at :

- HbA1c

Please note that a previous result may be used if less than 1 month prior to the Baseline Visit.

The following urine tests will be performed at the site:

- Pregnancy test, if applicable

7.9.2 Central Laboratory

Not applicable

7.10 Training of Subjects

All subjects in the study will be given instructions on how and when to contact study staff to report any study- related problems. The subject will be instructed to contact the study staff for prolonged hyperglycemia, or if he/she experiences nausea, vomiting, or abdominal pain within 48 hours after discharge. The subject will be instructed to contact the study staff for any problems related to the sensor sites, including fever, pain, redness, itching, discharge, warmth or swelling at the sensor insertion sites. Subjects will be further instructed to advise the investigator if new medications have been prescribed or started, or if any hospitalizations or significant medical changes have occurred.

The same level of information on their pathology and disease management will be provide to patients in both groups.

Subject in the enabled arms as well as control subjects who elect to have their system enabled at the 120 day mark will be instructed on the proper use of the Transmitter and Mobile Medical Application (refer to the Instructions for Use). The transmitter will be worn over the sensor at all times (except while charging, bathing) starting approximately 24 hours post insertion. Subjects will be prompted to calibrate the sensor using fingerstick measurements (a minimum of 2 each day, approximately 12 hours apart) using the study SMBG meter.

Throughout the study, the subject in the enabled arm will be allowed to observe the glucose values displayed from the Transmitter. Glucose alert and alarm features of the Transmitter will be functional.

The Subject will be instructed not to use the CGM data for diabetes care decisions, but rather to use their BG meter. Subject will maintain his or her usual diabetes care routine while at home, according to his or her health care provider's recommendations.

8 Questionnaires

8.1 Subjects Questionnaires

Subjects will be asked to complete a Subject Questionnaire (SQ) at the following visits listed below. Subjects should complete in a quiet undisturbed place using a computer or tablet PC (e.g. iPad). The questionnaire will be part of the eCRF.

	Visit 1	Visit 4	Visit 6
CGM SAT		X (enabled)	X (enabled)
DTSQs	X	X	X
DTSQc			X
ADDQoL	X		X
DDS	X	X	X
HFS	X	X	X
Partner-DDS	X	X	X

- **Satisfaction with CGM (CGM-Sat)**
  44 item scale assessing experiences with CGM over previous 6 months. The scale is designed to measure the impact of CGM on Diabetes management and family relationships, plus on satisfaction with emotional, behavioral and cognitive effects of CGM use. Responses are rated on a 5-point scale from 'strongly disagree' to 'strongly agree'.

  The validation of this questionnaire used in this study are reported by Tubiana-Rufi (2010).

- **The Diabetes Treatment Satisfaction Questionnaire**
  Like the DTSQs (original status), the DTSQc (change version) contains eight items scored on 7-point scales. Six items (Qs.1 and 4–8) measure Treatment Satisfaction (dealing with: satisfaction with current treatment; convenience of the treatment; flexibility; satisfaction with own understanding of their diabetes; how likely to recommend their present treatment; and how satisfied to continue with their present treatment). These are summed to produce a total Treatment Satisfaction score. Questions 2/3, concerning Perceived Frequency of Hyperglycaemia ('Perceived Hyperglycaemia')/Perceived Frequency of Hypoglycaemia ('Perceived Hypoglycaemia') respectively, are treated separately from the satisfaction items and from each other. DTSQs is completed at baseline, visit 4 and at final visit whereas DTSQc is completed only at final visit. The reliability and factor structure of the eight language versions used in this study are reported by Plowright (2000).

- **The Audit of Diabetes-Dependent Quality of Life**
  The ADDQoL measures the impact of diabetes and its treatment on 19 specific aspects of life. The ADDQoL has been designed to permit users to indicate whether potentially affected domains of life apply to them and to rate the impact of their diabetes on all applicable aspects of life, together with the perceived importance of each domain for their QoL.

  The scales range from −3 to +1 for 19 life domains (impact rating) and from 0 to +3 in attributed importance (importance rating). A weighted score for each domain is calculated as a multiplier of impact rating and importance rating (ranging from −9 to +3).

The validity and reliability of the 19-item ADDQoL are reported by Wee (2006).

- **Diabetes Distress Scale (DDS) Screening scale**

  The DDS2 is a 2-item diabetes distress screening instrument asking respondents to rate on a 6-point scale the degree to which the following items caused distress: (1) feeling overwhelmed by the demands of living with diabetes, and (2) feeling that I am often failing with my diabetes regimen. Its validation has been published by Fischer (2008).

- **Hypoglycemia Fear Survey part (HFS) II – worry subscale**

  HFS II - worry items describe specific concerns that patients may have about their hypoglycemic episodes (e.g., being alone, episodes occurring during sleep, or having an accident). The scale range from 0 (never) to 4 (almost always).

  The validity and reliability of the scale are reported by Gonder-Frederick (2011)

8.2 Additional Questionnaires

- **Partner Diabetes Distress Scale (Partner-DDS)**

  The Partner-DDS is a 21-item self-report scale that highlights four critical dimensions of partner-related distress: “my partner’s diabetes management”, “how best to help”, “diabetes and me”, and hypoglycemia. The scales range from 0 (not at all) to 4 (a great deal).

  The validity and reliability of the scale are reported by Polonsky (2016)

- **Free text questionnaire for ‘enabled’ patients**

  This questionnaire contains six questions that have the aim to record the opinion of the patient about the ‘enabled’ system at the end of the study.. These questionnaire will add the depth of data and context to the quantitative PRO data that is being collected.

- **Free text questionnaire for study investigators**

  This questionnaire contains seven questions which have the aim to record the opinion of the principal investigator or co-investigators about the system.

9 Data Collection

A **Subject Screening and Enrolment Log** will be completed for all subjects who have provided their informed consent i.e., signed the Subject Informed Consent Form - with the reasons for non-eligibility, if applicable.

eCRF

An eCRF will be provided by the CRO.

For each subject who has signed the Subject Informed Consent Form, the Investigator must allocate a **subject ID number** via the eCRF-system of two digits for the site and three digits for the subject: **SS-XXX**.

For each enrolled subject, an eCRF must be completed (throughout the study) and electronically signed by the Principal Investigator or Sub-/ Co-Investigator (at the end of the subject's participation in the study).

Upon training, Investigators and authorized study staff will enter subject data during or shortly after the respective visits.

Data Discrepancy Management

Subsequently, the entered data will be systematically checked:

- by means of pre-defined computerized validation checks (as outlined in the Data Management Plan)
- by data review by the Sponsor including but not limited to the Data Manager, Monitor and Study Manager.

All data discrepancies will result in data queries within the eCRF-system, which must be addressed (data confirmed or changed) by the study site staff and closed by the originator.

In addition, protocol deviations must be recorded in the eCRF throughout the study, and documented further via the query-system, as applicable (see Section 13).

If a subject withdraws from the study, the reason must be recorded on the eCRF.

Questionnaire

Subjects, their partners and Investigators will be asked to complete a questionnaire at several visits, see Section 8.

9.1 Data Download & access to CGM / SMBG data

During the study data will be downloaded, as follows:

- Download CGM data from the CGM-systems to the site´s computer/laptop (by means of SmartPix or other). Subjects will not have access to blinded CGM-data during these 4 weeks. Investigators / site staff will review CGM data once it is transferred via Smart Pix.

- Thereafter, CGM data must be uploaded to a secure server.

- Download **SMBG-data** to the site´s computer/laptop (by means of SmartPix or other). Thereafter, the data are uploaded to a secure server.

9.2 Data from not selected patients

Data from not selected patients will not be included in the database.

There is one exception, for patients who no longer comply with the inclusion criteria at visit 3, it has been mentioned that they will have the opportunity to start using the system, but in an open phase, the investigator will determine the planning of visits as per their usual follow-up, no data will be collected except the report of any adverse event.

9.3 Database Closure

Quality control of the database will be made throughout the study conduct in order to prepare the database closure. After the database has been declared clean (i.e. complete and accurate), the database will be locked.

Any changes to the database after that time can only be made by joint written agreement between the Study Manager and the Statistician.

10 Risk/Benefit Analysis of the Investigational Device and Clinical Investigation

Components of the Senseonics CGM System are manufactured under the Quality System provisions of ISO 13485.

Risk analysis and control has been performed as prescribed in relevant provisions of IEC 62304, ISO 14971, and IEC 60601-1, in accordance with the requirements of ISO 13485. Residual risks associated with the device included selected risks in the categories of electromagnetic and thermal energy, biocompatibility, biologic, chemical and mechanical factors and user error. All identified risks have been mitigated to an "As far as Possible" (ALARP) level of risk by various methods including software revision and re-validation, hardware design modification, packaging and sterilization process validation and labeling revision. The residual risks were determined to be acceptable for conduct of this clinical investigation.

10.1 Potential Risks

The Senseonics CGM System is approved for CE mark for adjunctive use in managing glucose values in patients with diabetes. Subjects will be instructed not to use the occurrence of glucose alarms/alerts or displayed sensor glucose values to make treatment decisions, but to use values obtained from the SMBG meter. The following are potential risks related to use of the device.

During participation in this clinical study, subjects may encounter the following known potential risks of the Eversense system:

Likely:

- Excessive bleeding during insertion or removal
- Bruising or swelling
- Hematoma formation
- Puritis (itching of the incision while healing)

Less Likely:

- Skin irritation and/or redness
- Discoloration of skin
- Device migration
- Device malfunctions of the sensor and/or transmitter with possible need to remove and/or replace the Sensor and/or transmitter
- Burning sensation or pain.
- Elevated blood pressure
- Water retention in the tissue, swelling or edema
- Confusion
- Disorientation
- Increased or decreased sensitivity to touch or pain
- Metallic taste
- Sleepiness
- Visual disturbances and/or blurred vision

- Tinnitus
- Impaired wound healing
- Headache
- Weight gain
- Nausea and/or vomiting
- Malaise
- Irritability
- Insomnia
- Heartburn
- Hyperglycemia
- Ketosis
- Headaches
- Dizziness, lightheadedness, and/or fainting
- Fluid/electrolyte disturbances such as fluid retention
- Muscle weakness
- Osteoporosis
- Peptic ulcer
- Pancreatitis
- Glaucoma

Rarely but Serious:

- Infection, local or systemic
- Poor wound healing after insertion or removal
- Keloid and/or scar formation
- Excessive or prolonged pain or discomfort at the Sensor site
- Nerve damage causing tingling, numbness, pain or weakness
- Electrostatic shock
- Skin erosion
- Allergic reaction to the device components, local anesthetic, or other medication or materials used in the procedure
- Anxiety and/or nervousness and/or lack of sleep
- Device fragments or particulate matter remaining in the body
- Failure to retrieve device or device left behind
- Difficulty in removing device that may require second attempt or surgery
- It is possible that the use of the Senseonics CGM system could cause a reaction other than listed or previously seen
- It has not been determined whether the risks usually associated with injectable dexamethasone apply to the use of dexamethasone elution ring, a highly localized, controlled-release device
- The dexamethasone ring could cause other adverse events not listed or previously seen
- Other adverse events typically related to diabetes treatment and diabetes are unknown

This clinical investigation involves subjects with diabetes mellitus. These subjects may experience hyperglycemia and hypoglycemia as a consequence of their existing condition and medical management (e.g. insulin administration). For this study, hyperglycemia and hypoglycemia will not be reported as adverse events unless meeting criteria of a Serious Adverse Event. Should a known side effect(s) occur to administered medication(s) used in the intervention, such effects will be reported as part of the adverse event description and will not be considered a separate adverse event.

Subject may have an X-ray or ultrasound of the sensor site. X-rays may cause damage to cells in the body, which in turn may increase the risk of developing cancer. This increase in risk associated with each X-ray procedure is extremely low but does slowly increase with the increasing number of X- rays tests you have.

Subjects must not undergo MRI while the Sensor is inserted or the Transmitter is in place. Both are incompatible with MRI procedures. Serious injury such as internal tissue burn (from the Sensor overheating) or topical skin burn (from the Transmitter overheating) may occur during an MRI and subsequent localized infection may develop as a result of the Sensor overheating.

If an MRI is required for subject care, the Sensor should be removed and the Subject will be withdrawn from the study, according to study stopping rules.

In the event of a situation where MRI is required and it is not possible to remove the Sensor, the medical staff must contact the Sponsor.

10.2 Minimization of Risks

The Sponsor has minimized the potential of the above risks to occur by:

- Selection of qualified Investigators consulting study subjects during the scheduled visits including an inspection of insertion site during each in-clinic visit and document any suspected adverse event. Subjects will be instructed to contact the investigator immediately upon any sign of significant irritation or discomfort or evidence of infection as described previously.
- Subjects are advised not to change their current diabetes therapy without consulting their physician (Investigator).
- Investigators will be trained in the technique for Sensor insertion and removal.

10.3 Potential Benefits

The study subjects may experience the following potential benefits while participating in this study:

- Study devices (acc. to randomization) will be provided at no charge to subjects.
- Subjects may be motivated to learn more about diabetes and to have better discussions of potential issues with their health care providers.
- Subjects may gain personal satisfaction from participating in this study but also improve their quality of life by having a better and easier glucose monitoring system (less frequent SBMG), system can be removed from the skin, they can be reassured by knowing they will be alerted by alarms in case of hypo or hyperglycemia …)Subjects may reduce

- HbA1c
- time spent out of range:
  1. below range < 54 mg/dL
  2. in hyperglycemic range > 250 mg/dL

10.4 Medical Care after Study Participation

Upon the subject´s termination (premature or planned) in the clinical study, it is up to the subject him/herself, preferably in agreement with the treating physician, for the future treatment

- to return to the device used prior to the study or
- to use any other suitable device available on the market.

11 Adverse Events Recording and Reporting

11.1 Definitions of Adverse Events

The definitions are based on ISO 14155:2011(E), French law and respective ordinances and respective sections CFR Title 21 for Medical Device Studies.

11.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

In addition, this definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

11.1.2 Serious Adverse Event

A Serious Adverse Event (SAE) is any AE that fulfils at least one of the following criteria:

- Led to death.
- Led to a serious deterioration in the health of a subject resulting in:
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, or
  - An in-patient or prolonged hospitalization, or
  - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Foetal distress, foetal death or a congenital abnormality or birth defect.

A planned hospitalization for a pre-existing condition, or a procedure required by the study procedure, without serious deterioration in health, is not considered an SAE.

11.2 Definition of Hypoglycemia, Hyperglycemia Episodes and Diabetic Ketoacidosis

Hypoglycemia and hyperglycemia can be symptomatic or asymptomatic and are subset of AEs occurring within Diabetes studies.

Any hypoglycemia or hyperglycemia episode which occurs during the course of the study will be documented by the subject him-/herself in his/her individual Subject Diary, if applicable, or will be defined specifically by the study procedure e.g. in the visit description of this study protocol.

11.2.1 Hypoglycemia Episode

An asymptomatic or symptomatic hypoglycemic episode is defined as a low blood glucose reading below 70 mg/dL (3.9 mmol/L) without external intervention is considered as a non-captured expected AE described in Section 11.3.1.2.

Symptoms might include but are not limited to: sweating, dizziness, light-headedness, tremors, nervousness, hunger, headaches, weakness or tiredness.

11.2.2 Severe Hypoglycemia Episode

A severe hypoglycemia episode is defined as symptoms in loss of consciousness and/or seizures resolving upon administration of glucose or glucagon by another person (only third party assistance). It usually requires needing assistance that can require in addition medical attention (emergency room, hospitalization).

Such episodes are defined as SAEs and, thus, they must follow the SAE reporting pathway via the eCRF (or mailed / faxed).

11.2.3 Hyperglycemia Episode

Hyperglycemia is defined as high blood glucose readings, a recommended threshold to intervene could be defined as values above 250 mg/dL (13.9 mmol/L). However, investigators should consider the condition of the individual subject.

Only hyperglycemia episodes in combination with medical intervention or additional diagnostic procedures have to be documented as AEs or SAEs in the eCRF, as described in Section 11.3.1.1.

11.2.4 Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is a rare yet potentially fatal potentially life-threatening complication that can occur in patients with both type1 and 2 Diabetes mellitus. DKA results from a shortage of insulin; in response the body switches to burning fatty acids and producing acidic ketone bodies that cause most of the symptoms and complications.

It is a medical emergency requiring hospitalization to the emergency room for the majority of patients.

Symptoms are polydipsia, polyphagia, polyuria, nausea, vomiting, dehydration, but also deep gasping breathing, confusion and occasionally coma are typical symptoms.

Diabetic ketoacidosis is diagnosed when the combination of hyperglycemia (high blood sugars (>250 mg/dL, typically 350–800 mg/dL), profuse glycosuria (2–4 mg/min/kg), large amounts of ketones in the blood (β-hydroxybutyrate) or on urinanalysis (acetoacetate) and acidosis demonstrated by arterial blood gas measurement.

It is categorized in adults into one of three stages of severity:

- Mild: blood pH decreased to between 7.25 and 7.30 (normal 7.35–7.45); serum bicarbonate decreased to 15–18 mmol/l (normal above 20); the person is alert
- Moderate: pH 7.00–7.25, bicarbonate 10–15, mild drowsiness may be present
- Severe: pH below 7.00, bicarbonate below 10, stupor or coma may occur

Elements of management include making the appropriate diagnosis using current laboratory tools and clinical criteria and coordinating fluid resuscitation, insulin therapy, and electrolyte

replacement through feedback obtained from timely patient monitoring and knowledge of resolution criteria.

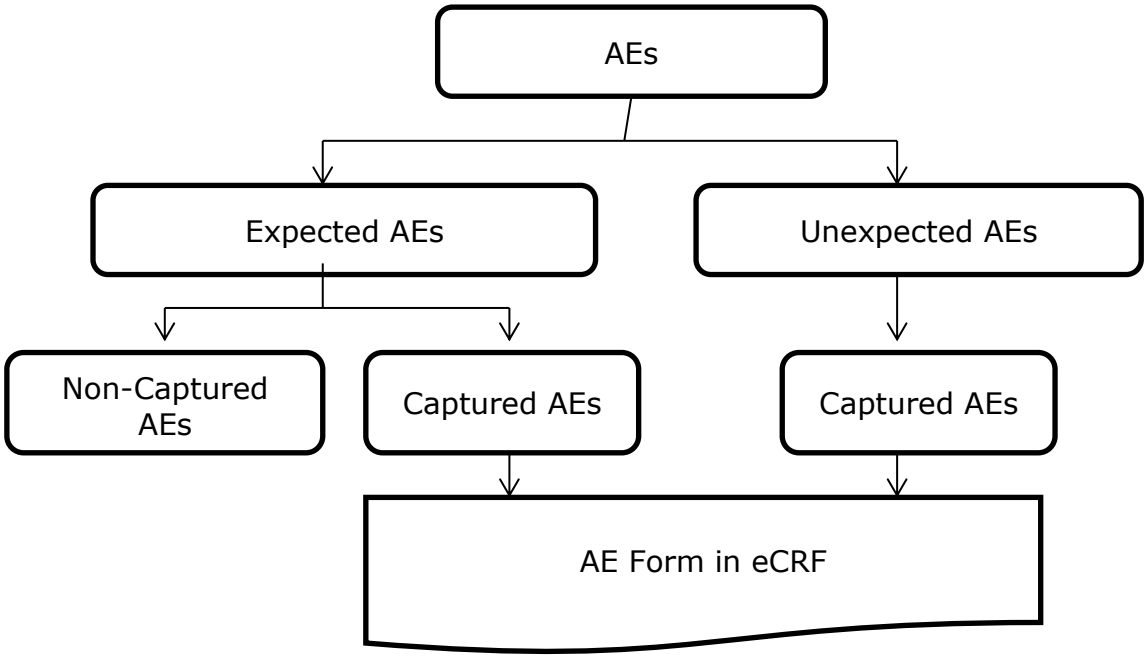
Such episodes are defined as AE but can also be defined as SAEs and, thus, they must follow the SAE reporting pathway via the eCRF (or mailed or faxed).

11.3 Expectedness Classification of Adverse Events

An AE will be classified as either expected or unexpected (see Figure 5).

For the purpose of this study, expected AEs will be divided into non-captured and captured AEs. These distinctions were made based on the frequency of occurrence, severity of event, and risk to subject. All captured AEs will be documented in the eCRF.

Figure 5 : Expectedness Classification of Adverse Events



Abbreviations: AE = adverse event; eCRF = electronic Case Report Form.

11.3.1 Expected Adverse Events

11.3.1.1 Captured Expected Adverse Events

The following expected AEs may occur at any time in the course of managing diabetes. Immediate or short term risks to subjects from some of these expected AEs are higher than those identified under Non-Captured Expected AEs.

Therefore, for the purposes of this study, the following expected AEs will be considered captured expected AEs and the AE Form in the eCRF needs to be completed:

- Hypoglycemia episodes with external intervention (see Section 11.2.1).
- Hyperglycemia in combination with medical intervention.

- Hyperglycemia in combination with medical intervention or suspected by the site staff to be caused by insulin leakage or infusion set occlusion.
- Generalized hypersensitivity reactions.
- Ketosis and ketoacidosis.

These captured expected AEs will be handled as follows:

Subjects will be instructed to follow their personal physicians' instructions for management of low and high blood glucose values or otherwise as instructed by the Investigator.

11.3.1.2 Non-Captured Expected Adverse Events

Non-Captured expected AEs may occur at any time in the normal course of managing diabetes. For the purpose of this study, they will be considered as non-captured expected AEs and will not be documented in the eCRF, these include:

- Asymptomatic or symptomatic hypoglycemia episode without external intervention (see Section 11.2.1).
- Hyperglycemia without medical intervention.
- In the event of a sore finger, subjects will be advised to avoid taking self-monitoring blood glucose samples from that finger.
- In the event of a mild infection at a lancing site, the study subject will be reminded to wash hands before all blood tests and encouraged to consult their nurse or physician on the management of an infection.

Since these non-captured expected Adverse Events identified above are common as well as expected and pose minimal immediate risk to the subjects, they will not be tracked and logged as AEs during the course of the study. Investigators may log reports of these non-captured expected AEs as is customary within their practice.

These non-captured expected AEs will be handled as follows:

Subjects will be instructed to follow their personal physicians' instructions for management of low and high blood glucose values as well as for minor skin damage, minor bleeding and mild discomfort.

11.3.2 Unexpected Adverse Events

All AEs which do not meet the criteria mentioned under expected AEs (Section 11.3.1) are considered as unexpected AEs and will be documented in an AE Form in the eCRF.

11.3.3 Anticipated adverse device effects

The following events have been identified as possible device-related adverse events of sensor insertion and wear:

- Excessive pain or discomfort from system deployment
- Excessive bleeding

- Hematoma (slight ecchymosis is a known consequence of needle skin puncture and will not be captured as an AE)
- Excessive edema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- Excessive erythema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- Local infection
- Sensor or introducer needle fracture during insertion/wear/removal
- Degrees of edema, erythema, or infection that may occur at the sensor insertion or adhesive tape site will be assessed by the subject and documented for review by study staff. An AE will be recorded as severe in intensity if skin appearance indicates significant edema or erythema (per definition above) and/or if infection, defined as the presence of pus, at the sensor insertion or adhesive tape site occurs.

Information regarding device-related AEs that occur during the study will be entered into appropriate CRFs. Such information will include, at a minimum:

- Date of event
- Severity
- Outcome
- Resolution of event

11.4 Assessment of Causality in Relationship to Device

11.4.1 Related

An AE is deemed related with a device if **ALL** of the following criteria apply:

- There is a reasonable temporal sequence between AE and use of the device.
- It follows a known or expected response pattern of the device.
- It cannot be reasonably explained by the known characteristics of subject's clinical state.

Adverse events resulting from insufficiencies and/or inadequacies in the instructions for use or the deployment of the device will be classified as related.

Adverse events resulting from a user error will be classified as related.

11.4.2 Possibly Related

An AE is deemed possibly related if:

- There is a reasonable temporal relationship between the AE and use of the device; and
- It follows a known or expected response pattern of the device but could have been easily produced by a number of other aetiologies.

11.4.3 Unrelated

When there is no reasonable temporal association between the device and the AE or the event was related to the subject's clinical state or concomitant treatment(s).

11.4.4 Not Assessable

When there is not sufficient information to assess a relationship.

11.5 Period of Observation

All AEs ongoing at the time of study termination - irrespective their severity - should be followed up – via telephone - for a maximum of 5 days after the subject's last visit to the site. A medical statement should be included in the AE Form in the eCRF for all ongoing AEs after the Period of Observation.

11.6 Investigators' Responsibility to Report Serious Adverse Events/Serious Adverse Device Effects

Investigators must immediately or within 24 hours report all SAEs/SADEs on the SAE Report Form which has been integrated in the eCRF - irrespective of expectedness or relationship to study procedures or study devices.

For reported deaths, the Investigator should provide any additional information, as requested and required, such as autopsy reports or terminal medical reports.

The Investigator should complete and sign the form (can be electronically)

- **The Study Safety Officer:** ([redacted]) will be informed automatically in case of SAE.

In case, the eCRF system is not functioning, a paper version of the form should be completed by hand, signed and sent as described above (faxed or e-mailed).

If SAE/SADE information is unsatisfactory and essential data is missing, the Investigator is requested to conduct the necessary follow-up actions and/or to provide additional information as soon as possible.

11.7 Sponsor's Responsibility to Report Serious Adverse Events/Serious Adverse Device Effects

The below Study Safety Officer is responsible for all safety related topics of the study:

Name [redacted]
Email: [redacted]
Phone [redacted]
Fax [redacted]

Upon receipt of an SAE Report Form, the Study Safety Officer will:

- Review the SAE Report Form for completeness and make a medical assessment.

- Ensure that additional (i, follow-up and final) information is obtained and communicated, as applicable.

After Safety Assessment the SAE/SADE is reported, as applicable, via the following internal lines.
Roche Diabetes Care Vigilance Group responsible for Vigilance Reporting to:

– Regulatory Authorities in EEA countries

The sponsor Study Manager or designee is responsible for reporting to:

- Ethics Committees
- Other Investigators, if applicable.

12 Incident Reporting

The CE-marked medical devices observed in this study are used within the Intended Use.

The documentation and reporting of the incidents and indirect harms will follow the guidance provided in Medical Devices (MEDDEV) 2.12.-1 rev. 8 (January 2013).

Incidents and malfunctions determined by the investigator must be reported on an "Incident Report" and sent to the Sponsor immediately or within 24 hours. Respective contact details can be found in the investigator file and the eCRF.

In addition, all incidents and indirect harms are also to be documented in the source data. The following details should be provided:

- Description of event/incident
- Start date.
- Resolution date.
- Action taken.
- Outcome.

Even if the requested information is not yet complete, it is required to submit the report immediately.

Respective contact details can be found in the Investigator site file and in the Incident Report in the eCRF.

In case of doubt on the duty to report an incident, there should be a pre-disposition to report rather than not to report - as a general principle.

Incidents with devices from other manufacturers should be reported directly to the respective manufacturer.

Identified defect devices will be submitted to the Sponsor and documentation provided via the eCRF.

12.1 Definitions

Complaint
Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. (21 CFR 820)

Incidents
Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health. (MEDDEV 2.12-1 rev. 8, Jan. 2013)

Indirect Harm
In the majority of cases, diagnostic devices […] will, due to their intended use, not directly lead to physical injury or damage to health of people […]. These devices are more likely to lead to indirect harm rather than to direct harm. Harm may occur as a consequence of the medical decision, action taken/not taken on the basis of information or result(s) provided by the device […].
Examples of indirect harm include

- misdiagnosis,

- delayed diagnosis,
- delayed treatment,
- inappropriate treatment,
- absence of treatment
- transfusion of inappropriate materials.

(MEDDEV 2.12-1 rev. 8, Jan. 2013)

Malfunction or deterioration in the characteristics of performance of a device:
A malfunction or deterioration should be understood as a failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions. (MEDDEV 2.12-1 rev. 8, Jan. 2013)

Device deficiency
Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. (MEDDEV 2.7/3, Dec. 2010).

12.2 Sponsor's Responsibility to Report

Please note that of easier handling the form – "Incident Report Form" covers all information in order to comply with EU and US reporting requirements. The Study Safety Officer is also responsible for all safety related topics of the study:

Upon receipt of an Incident Report Form, the Study Safety Officer will:

- Review the Incident Report Form for completeness and make a medical assessment.
- Ensure that additional (follow-up and final) information is obtained and communicated, as applicable.

After Safety Assessment, the incident is reported, as applicable, via the following internal lines:

- Roche Diabetes Care Vigilance Group responsible for Vigilance Reporting to:

– Regulatory Authorities in EEA countries
– The sponsor Study Manager or designee is responsible for reporting to:
– Ethics Committees

13 Reporting of Protocol Deviations

Deviation is any instance of failure to follow, intentionally or unintentionally, the requirements of the study protocol.

In order to match all of possible regulations and fulfill all of the responsibilities regarding recording and reporting as well as to allow correct handling of different deviations there are three categories of deviations defined:

Non Relevant Deviation - Deviation which does not affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation.

Relevant Deviation – Deviation which may affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation.

Serious Deviation - Deviation affects subject's rights, safety and wellbeing, or the scientific integrity of the clinical investigation. Deviation must be reported to the Sponsor, who is responsible to report according to national regulations.

Protocol Deviations may be recorded in the eCRF throughout the study, and documented further via a specific form or the query-system, as applicable.

The Investigator must notify the Sponsor of any **serious deviation** to protect the life or physical well-being of a subject in an emergency as soon as possible/promptly after the emergency occurred.

In this study, visit time windows deviations are not considered as protocol deviations, but will not be documented separately. There will be review of these during each data analysis

14 Statistical Considerations and Data Analysis

A Statistical Analysis Plan will be established, validated by the Scientific Committee of the study, detailing the statistical analysis. The statistical analysis will be performed on SAS/WINDOWS XP version 9.4 or later.

The analysis will be carried separately for each cohort.

The type I error (alpha) is set at 0.05 two-sided for each analysis. No adjustment of the alpha risk is planned because these two analyses have a distinct primary objective and criteria.

14.1 Null Hypothesis and Sample Size Calculation

Cohort 1

The primary criterion is the HbA1c (%) at D180 visit.

The calculation is based on a comparison between enabled and control groups.

The randomization ratio is 2:1 (2 patients enabled: 1 patient control).

Given the inclusion and exclusion criteria for this study, the following assumptions were made:

- Standard deviation: 1%
- Minimum expected absolute effect: 0.5%
- Power : 80%
- Type I error : 5%

With these assumptions, 144 subjects are needed for the analysis of this cohort (96 patients in the enabled arm and 48 patients in the control arm).

Since a maximum of 10% of non-evaluable patients is expected, the number of subjects to be randomized is 159.

Cohort 2

The primary criterion is the percentage of time spent in hypoglycemia < 54 mg/dl between D90 visit and D120 visit (using CGM system data).

The calculation is based on a comparison between enabled and control groups.

The randomization ratio is 2:1 (2 patients enabled: 1 patient control).

Given the inclusion and exclusion criteria for this study and the results of the IMPACT study, the following assumptions were made for the sample size calculation:

- % of time spent in hypoglycemia < 54 mg/dl: 6.625%
- Pooled standard deviation at the end of the study of 5.75% (using Cohen method : Cohen, J. (1988), Statistical Power Analysis for the Behavioral Sciences, 2nd Edition. Hillsdale: Lawrence Erlbaum. Hedges L. V., Olkin I. (1985). Statistical methods for meta-analysis. San Diego, CA: Academic Press)
- Minimum expected relative effect : 42.5%
- Power : 80%

- Type I error : 5% two-sided

With these assumptions, 150 subjects are needed for the analysis of this cohort (100 patients in the enabled arm and 50 patients in the control arm).

Since a maximum of 10% of non-evaluable patients is expected, the number of subjects to be randomized is 165 (110 patients enabled and 55 patients control).

14.2 Populations for Analysis

o Full Analysis Set (FAS) Population: The FAS population will consist of all randomized patients with the sensors inserted at Visit 2 and with at least one CGM data available from randomization visit to D180 visit. This is the primary population for the analysis of efficacy.

o Per-Protocol (PP) population: The Per-Protocol population consists of all FAS patients without major protocol deviation, defined blindly by the scientific committee during the data review before the data base lock. This is the secondary population for the analysis of efficacy.

o Safety Population: The Safety population will consist of all patients with the sensors inserted at Visit 2. This is the primary population for the analysis of safety.

14.3 Subject Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by study group:

- Gender, age.
- Height, weight, body mass index.
- Diabetes Background and History
- Diabetes Family History
- Diabetes Medication.
- Baseline HbA1c.
- Medical history - diseases other than Diabetes
- Previous Medications for diseases other than Diabetes

All subject characteristic variables will be summarized descriptively. For continuous data: number of missing data, number of data analyzed, mean, standard deviation, Q1, Q3, minimum, maximum and median and 95% confidence interval.

For categorical data: number of missing data, frequencies and percentages of each modality, and 95% confidence intervals using binomial law. The percentage of subjects will be calculated once missing data are excluded from the denominator.

14.4 Primary Objective Analysis

Cohort 1

The primary criterion is the HbA1c (%) at D180 visit.

The comparison between both groups will be carried out using a covariance analysis model adjusted on the site factor and the level of HbA1c at baseline and including stratification

variables. In case of non-normal distribution, a study will be done in order to use non-parametric tests. A non-parametric approach will be performed.

Cohort 2

The primary criterion is the percentage of time in hypoglycemia <54 mg/dl between D90 visit and D120 visit.

The comparison between both groups will be carried out using a covariance analysis model adjusted on the level of hypoglycemia at baseline (time in hypoglycemia <54 mg/dl between D0 visit and D30 visit) and including stratification variables. In case of non-normal distribution, a study will be done in order to use either a model based on Poisson distribution or a non-parametric test approach.

14.5 Secondary Objective(s) Analysis

14.5.1 Definition of secondary criteria

1. Safety of the insertion and removal procedures and the device defined by adverse events reported
    - Frequency of AEs from D0 to D187
2. Time in range [70mg/dL-180mg/dL] (%) of glucose values:
    - From D150 to D180
    - From D90 to D120
3. Time (%) in hypoglycemia (<70mg/dL and <54mg/dL) and hyperglycemia (>180mg/dL and >250mg/dL)
    - Hypoglycemia (<70mg/dL) from D150 to D180 and from D90 to D120
    - Hypoglycemia (<54mg/dL) from D150 to D180 and from D90 to D120
    - Hyperglycemia (>180mg/dL) from D150 to D180 and from D90 to D120
    - Hyperglycemia (>250mg/dL) from D150 to D180 and from D90 to D120
4. Glucose variability calculated with coefficient of variation as ratio of standard deviation to mean daily glucose
    - Measured from D150 to 180 and D90 and D120
5. Sensor life – number of subjects/Sensors operating at 150 and 180 days post insertion and mean/median Sensor life using Sensor output and long-term performance.
6. Amount and variability of Transmitter wear time (by day/week/months)
    - Measured from D0 to D187
7. Frequency of access of app pages (event logs, statistics, etc)
    - Measured from D0 to D187
8. Frequency and type of alarms/alerts received
    - Measured from D0 to D187
9. HbA1C
    - HbA1c (%) at D120 visit
    - HbA1C (%) at D180 visit for cohort 2 only
10. For cohort 2 only :

- Maintain of the Eversense effect on hypoglycemia between D150 and D180 for enabled group
- Comparison of data from D90-D120 period to D150-D180 period for control group

11. Patient Reported Outcome Measures (PROMs) to measure treatment satisfaction and quality of life to be completed during Visits 1, 4 and 6 for both groups.
12. CGM questionnaire to be completed during Visits 4 and 6 for enabled patient only.

Continuous criteria will be compared between both groups using the same analysis model as planned for the primary criterion (analysis of covariance model).

Categorical criteria will be compared between both groups using a logistic regression model including baseline value if available and stratification variables.

14.6 Safety Analysis

A descriptive analysis of the safety criteria will be performed for each cohort.

Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Only AEs occurring after the start of the sensor insertion after Visit 2 will be included in the AEs tables.

Summaries of incidence rates (frequencies and percentages) of individual AEs by MedDRA System Organ Class and Preferred Term will be prepared. Such summaries will be displayed for all AEs, AEs by maximum severity, AEs by strongest causality to study device and AEs leading to withdrawal of study device.

Deaths, other SAEs and AEs leading to withdrawal will be listed separately.

In addition, the sub-group of ADEs and SADEs will also be summarized by MedDRA System Organ Class and Preferred Term including summaries by study device.

Moreover, incidence rates of specific types of error messages (as defined in the SAP) per 100 patient years will be calculated together with exact two-sided 95% CI.

Episodes (numbers) of the following AEs will be summarized:

- Symptomatic hypoglycemia
- Severe hypoglycemia (SAEs)
- Diabetic Ketoacidosis (SAEs)

The following ADEs are of particular interest:

- ADEs and unanticipated ADEs leading to replacement of device.

Incidence rates of all ADEs and of these ADEs and AEs of special interest (as captured on the AE Form in the eCRF) per 100 patient years will be calculated together with exact two-sided 95% CIs assuming that the number of special AEs observed in the study is Poisson distributed.

14.7 Concomitant Medication

Previous and concomitant medications (separated for Diabetes and for other indications) will be listed by subject.

14.8 Interim Analysis

No interim analysis is planned for this study.

15 Ethical and Legal Considerations

15.1 Statement of Compliance

The study will be performed in accordance with the principles stated in the World Medical Association's Declaration of Helsinki "Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects" (most recent version), that are consistent with the principles outlined in the ICH Guideline on GCP E6 (R2) where it applies to medical devices and the applicable national regulations for medical device law and applicable ordinances, for the provisions of ISO 14155:2011(E), the European Medical Device Directive (e.g. 93/42/EEC), FDA 21 CFR Parts 11, 50, 54, 56, 803, 812, 814 and 820.30, as applicable in each participating country.

15.2 Subject Informed Consent

It is the responsibility of the Investigator to obtain informed consent in compliance with French requirements from each subject prior to entering the study.

The informed consent document used by the Investigator for obtaining subject's informed consent will be written in French, and will be reviewed and approved by the Sponsor before the Ethics Review Committee submission.

The informed consent form and procedure comply with art. L 1122-1 to L. 1122-2 French Code Santé Publique (CSP).

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written Subject informed consent – before any study procedures - from each subject considering participation in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study – orally as well as presented in the written Subject Information Letter.

The Investigator or designee (if applicable) must also explain that the subject is completely free to refuse to enter the study or to withdraw from the study at any time, for any reason and could return to standard care.

The Investigator or authorized staff must document the date of each subject´s informed consent in the respective eCRF.

Furthermore, in case that Visit 1 and Visit 2 are combined, the time point of the Subject inform consent must be documented.

If any new safety information results in significant changes in the risk/benefit assessment, the Subject Information Leaflet and/or the Informed Consent Form should be reviewed, updated and re-submitted to the EC for approval by sponsor.

Subjects already participating in the study should be informed of the new information, and asked to give their written inform consent to continue in the study.

New subjects shall only receive the updated documents.

All subjects will be given a copy of the signed Subject Informed Consent Form(s).

15.3 Confidentiality of Study Documents and Subject Records

The Investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On the eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by a unique study identification code, i.e. Subject ID (Number).

The Investigator will keep a **Subject Screening and Enrolment Log** linking study identification codes, and subject contact information. The Investigator will maintain these study documents e.g. subjects' written inform consent forms, in strict confidence and as part of the Investigator's Site File.

Any data obtained from subjects participating in the study may be used to build case studies for educational purposes and all identifying data will be completely removed or blacked-out for these purposes.

15.4 Data Protection

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical study. All data shall be secured against unauthorized access.

The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

The Principal Investigator or institution shall provide direct access to source data during and after the clinical study for monitoring, audits, ethics review and Regulatory Authority inspections.

Roche Diabetes care France ensures that the personal data will be treated in compliance with the law 2016/679 of April 27th 2016, the RGPD (Réglement Général sur la Protection des Données) as textual reference, in addition to data protection of January 6th 1978 in its latest version.

The sponsor is registered to the CNIL (Commission Nationale d'Informatiques et des Libertés) and follows the guideline MR-001 for biomedical studies.

The subject will be informed of his/her right of access, objection and correction of the data recorded during this study, and that this right may be exercised at any time through his/her physician.

For partners that will answer to the partners questionnaire, no personal data will be recorded.

Information relating to participating physicians will be declared and the physicians will be informed – within the framework of their agreement – of their right to access, object to and correct this information.

15.5 Ethics Committee

This protocol, informed consent document, any supporting supplemental materials to the and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent) as well as any advertising used or compensation given to the subject, will be submitted by the Sponsor to an EC. Approval from the committee must be obtained before starting the study, and should be documented in a letter to the Sponsor specifying the date on which the committee met and granted the approval. Any modifications made to the protocol after receipt of the EC approval must be re-submitted by the Sponsor to the Committee in accordance with local procedures and regulatory requirements.

15.6 Regulatory Authorities

Submissions and/or notification to Regulatory Authorities will be performed as required by local legislation in each participating country for this type of study.

15.7 Amendments to the Clinical Study Protocol

Study protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the Sponsor and the Investigator. These modifications must be prepared by a representative of the Sponsor and initially reviewed and approved by the appropriate representatives of the Sponsor and Statistician.

The Investigator is obliged, to conduct the clinical investigation in compliance with the study protocol, encouraged to propose to the sponsor any appropriate modification(s) of the study or investigational device or of the use refrain from implementing any modifications to the CIP without agreement from the sponsor, EC and regulatory authorities, if required, document and explain any deviation from the approved study protocol that occurred during the course of the clinical investigation, of the investigational device.

All study protocol modifications must be submitted to the appropriate EC for approval in accordance with local procedures, and Competent/Regulatory Authorities as required. Approval must be granted in writing before any changes can be implemented, except for those changes necessary to eliminate an immediate hazard to the subjects, or when the change(s) involve only logistical or administrative aspects of the study (e.g. change in Monitor, change of telephone number). Note: these changes will be re-submitted for EC/IRB review and approval as soon as possible.

15.8 Suspension or Premature Termination of the Clinical Study

Both the Sponsor and the Investigator reserve the right to terminate the clinical study at any time. Should this be necessary, the parties will arrange the procedures on an individual basis after review and consultation. The only reason for early termination of the study by the Sponsor would be the occurrence of unexpected safety or ethical consideration for the protection of the subject's interests. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subject's interests. Early termination of the study shall be reported to the IRB/EC and to regulatory authorities, as applicable

15.9 Record Retention

In order to comply with Roche Diabetes Care's requirements, Investigators must maintain all required essential documents – in the Investigator Site File - at the site for at least 15 years after the study ends.

Essential study documents are those documents which individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced – stored before during and after the study conduct in the Investigator´s Site File. They include but are not limited to, those pertaining to subject files and other source data (e.g. hospital files, consultation records, laboratory reports, etc). The Investigator should ensure that the Investigator Site File is stored in a secure location and should take measures to prevent accidental or premature destruction of any documents.

The Investigator must contact the Sponsor for approval prior to discarding any study-related documents, even if retention requirements have been met.

If the Investigator leaves the clinical site at which the study has been conducted, he/she or current representative must contact the Sponsor to make suitable arrangements to ensure that the study records, including a copy of the **Screening and Enrolment Log** are retained as specified above and to provide for the continuing access to the records by Sponsor representatives and Regulatory Authorities.

15.10 Reimbursement, Indemnity and Insurance

Reimbursement, indemnity and insurance shall be addressed in a separate agreement agreed upon by the parties.

15.11 Publication of Data and Protection of Trade Secrets

The results of this study may be published or presented at scientific meetings.

Publication by Roche and/or Senseonics

Roche France and/or Senseonics may at any time publish the results of and information pertaining to the investigation Subject only to ensure compliance with regulatory requirements pertaining to subject protected health information.

Publication by the Investigational Sites

If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to Roche Diabetes Care prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.
Any formal publication of the study in which input of Roche Diabetes Care personnel exceeds that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Roche Diabetes Care personnel. Authorship will be determined by mutual agreement.

16 Clinical Conduct, Study Material and Accountability

Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical study and according to the study protocol.

The Sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the study sites until return or disposal.

The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include:

- The date of receipt.
- Identification of each investigational device (batch number/serial number or unique code).
- The expiry date, if applicable.
- The date or dates of use.
- Subject identification.
- Date on which the investigational device was returned/explanted from subject, if applicable.
- The date or return of unused, expired or malfunctioning investigational devices, if applicable.

A summary of the necessary training and experience needed to use the investigational device shall also be provided.

16.1 Material and Procedures

16.1.1 Numbering of Subjects

As soon as a subject has signed the Informed Consent Form, the Investigator or authorized study staff will allocate a subject ID number via the eCRF-system.

The subject ID number consists of 2 digits for the site and 3 digits for the subject: **SS-XXX**.

16.1.2 Supply of Study Material to Study Sites

The Investigator will receive all of the materials needed to initiate and conduct the clinical study. The materials include, but are not limited to:

- Study protocol, final approved version.
- Information letter and consent form.
- Electronic CRF, available on-line.
- Investigator Site File including all relevant documents.
- Study devices:
  - Insertion tool kit.
  - Sensors.
  - Transmitter
  - Adhesives
  - Subjects Questionnaires.
- Packaging material for return of study devices

16.1.3 Dispensing of Study Devices

The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include:

- The date of receipt.
- Identification of each investigational device (batch number/serial number or unique code).
- The expiry date, if applicable.
- The date or dates of use.
- Subject identification.

The site will be responsible for maintaining a supply inventory log recording receipt and disposition of all the devices with serial or batch numbers and supply materials, if applicable.

For this purpose, a study-specific **Supplies Dispense & Return Form** shall be completed for each subject.

16.1.4 Return of Study Devices

The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include:

- Subject identification.
- Date on which the investigational device was returned/explanted from subject, if applicable.
- The date or return of unused, expired or malfunctioning investigational devices, if applicable.

Subjects are asked to return all study devices (used, unused, expired or malfunctioning) at the following visit.

For this purpose, a study-specific **Supplies Dispense & Return Form** shall be completed for each subject.

16.1.5 Destruction of Study Devices

It will be decided if the study devices will be returned to the Sponsor for after-use-inspection.

If devices are not to be returned to the Sponsor, destruction (of used and used devices including comparative devices) is only allowed upon written permission from the Sponsor.

16.2 Site Selection

Sites will be selected for participation in this clinical study by the Sponsor. These sites must have qualified personnel and must be equipped with the appropriate medical facilities to fulfil the study requirements. These sites must also have an adequate subject population to meet the study requirements.

Sites will be approved for participation by the Study Manager.

16.3 Responsibilities of the Principal Investigator(s)

The site Principal Investigator(s) shall be responsible for the day-to-day conduct of the clinical study as well as for the safety and well-being of the study subjects.

The site Principal Investigator(s) must satisfy the following requirements:

- Have adequate knowledge and experience in diabetes care management as documented in the Investigator's Curriculum Vitae.
- Have the resources and time to comply with the requirements of this clinical study.
- Have access to an appropriate medical facility and equipment necessary for the conduct of this clinical study.
- Have primary responsibility for the accuracy, legibility and security of all study data.
- Have an adequate subject population to meet the requirements of the study.
- Observe confidentiality at all times throughout the study.
- Are responsible for protecting the rights, safety, and welfare of subjects under their care and to ensure only eligible subjects, per the approved study protocol, are enrolled into the study and that written informed consent is obtained from each subject.
- Follow protocol procedures and provide accurate data in a timely manner.
- Agrees to conduct this study in accordance with applicable federal and local regulations.
- Agrees to sign this protocol prior to commencement of any study-related activities
- Are responsible for ensuring completion of the eCRFs per the study timelines discussed in the site initiation visit and subsequent monitoring visits

16.4 Study Monitoring and Auditing

16.4.1 Study Monitoring and Source Data Verification

It is understood that the responsible Roche Diabetes Care Monitor (or designee) will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various source documents and other records of the study (eCRFs and other pertinent data) provided that subject confidentiality is maintained in accord with local requirements. It will be the Monitor's responsibility to review the eCRFs at regular intervals throughout the study, to verify protocol compliance and the completeness, consistency and accuracy of the data being entered. The Monitor should have access to the laboratory test reports and other subject records to verify the entries on the eCRFs. The Investigator (or designee) agrees to cooperate with the Monitor to ensure that any problems detected in the course of these Monitoring Visits are reviewed and resolved.

The Investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

Details about requirements for Source Data Verification (SDV) and other aspects of Monitoring will be described in the Study Monitoring Plan.

16.4.2 Clinical Site Visit Schedule

A **Site Initiation Visit** will be conducted prior to the start of the study to ensure:

- Investigator understands and accepts his/her obligations in conducting the clinical study according to the protocol.
- Investigator and study staff have reviewed and understood the study protocol.

- Training regarding study devices and study procedures.

Regular Monitoring Visits will take place during the course of the study to ensure:

- Continued acceptability of facilities and oversight of the study by the EC.
- Adherence to protocol and applicable regulation.
- Maintenance of adequate subject records.
- All SAEs/AEs are reported to Sponsor and to responsible authority, as required.
- Verification of source data to CRFs/eCRFs.

Detailed outline and guidance of study monitoring is detailed in the study handbook.

At the study termination, study staff will collect all applicable materials and supplies and return them to the Sponsor. After all study data has been collected and verified and the study database has been locked, a **Close-Out Visit** will occur to:

- Ensure all supplies have been accounted for and documented according to the study protocol and the remaining materials either returned to the Sponsor or distributed to the subjects as outlined in the study protocol.
- Complete all monitoring at the study site and close-out any open data discrepancies.
- Ensure all regulatory documents are on file at the clinical site.
- Review the Investigator's responsibilities after the termination activities have been completed.

16.5 Training of Investigators and Study Site Staff

All Investigators and study staff, authorized to perform study procedures, will receive training on the following aspects of the study:

- Clinical study protocol including:
  - Principles of the Declaration of Helsinki, GCP and ISO 14155.
  - relevant national legal requirements
  - Protocol and study procedures.
  - SAE Reporting procedures including completion of SAE Report Form (eCRF) and/or Malfunction /Incident Reporting procedures
  - Monitoring and Audits.
  - As necessary for compliant study conduct.
- Study devices:
  - Eversense XL sensor.
  - Transmitter
  - Mobile Medical Application.
- Completion of eCRF:
  - Passwords, Data Entry, Corrections, Query process, and Sign-off.
  - Completion of SAE Report Form and sending to the Sponsor.
  - Documentation of protocol deviations.
- Completion of Subject Questionnaire.

In this study, visit time windows deviations are not considered as protocol deviations.

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