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EVERSENSE

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

STATISTICAL ANALYSIS PLAN

Version 2.0 – 30/09/2020

Written by RCTs

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1. STATISTICAL ANALYSIS PLAN - APPROVAL FORM

Function	Name	Signature	Date
[redacted]	[redacted]	[redacted] Sep 30, 2020 08:56 GMT+2)	Sep 30, 2020

Scientific committee

Function	Name	Signature	Date
Principal investigator [redacted]	Prof. [redacted]	[redacted]	Oct 1, 2020

Function	Name	Signature	Date
[redacted]	[redacted]	[redacted]	Oct 7, 2020

2. VERSION HISTORY

Version	Date	Author	Comment / changes
0.1	30/04/2019	RCTs	Initial draft version (based on protocol v5.0 dated of 11/12/2018)
0.2	03/07/2019	RCTs	Including comments from Roche Diabetes Care (France)
0.3	09/10/2019	RCTs	Including comments from Roche Diabetes Care (France)
0.4	29/11/2019	RCTs	Including lasts comments from Roche Diabetes Care (France)
0.5	13/12/2019	RCTs	Including comments from Roche Diabetes Care (France)
1.0	28/01/2020	RCTs	Final version
1.1	29/09/2020	RCTs	Revised version following Data Review meeting
2.0	30/09/2020	RCTs	Final version 2.0

3. ABBREVIATIONS

Abbreviation	Description
ADDQoL	Audit of Diabetes Dependent Quality of Life
ADE	Adverse device effect
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BG	Blood Glucose
BGRI	Blood Glucose Risk Index
BOCF	Baseline Observation Carried Forward
CGM-Sat	Continuous Glucose Monitoring – Satisfaction scale
CI	Confidence interval
CV	Coefficient of Variation
eCRF	Electronic case report form
FAS	Full analysis set
FGM	Flash glucose monitoring
GLM	Generalized Linear Model
HbA1c	Glycated hemoglobin
HBGI	High Blood Glucose Index
INN	International nonproprietary name
IRB	Independent review board
ITT	Intent-to-treat
LBGI	Low Blood Glucose Index
LLN	Lower limit of normal
LLT	Lowest level term
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
CGM	Continuous glucose monitoring
MNAR	Missing not at random
MD	Missing data
MDP	Missing data pattern
PP	Per protocol
PT	Preferred term

Abbreviation	**Description**
Q1	First quartile
Q3	Third quartile
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TEAE	Treatment emerged adverse events
UADE	Unanticipated Adverse Device Effect
WHO-DD	World Health Organization drug dictionary

4. PROTOCOL

This Statistical Analysis Plan refers to protocol version 5.0 dated December 11th, 2018.

5. ANALYSIS SETS AND SUBGROUPS

5.1. Analysis sets

The analysis sets are defined below:

- **Screened Set:** The Screened Set population consists of all patients who signed an informed consent.
- **Randomized Set (RS):** The Randomized Set consists of all patients from the Screened Set who have been randomized.
- **Full Analysis Set (FAS)**: The FAS population consists of all randomized patients with the sensor inserted at Visit 2 (D0) and with at least one CGM data available from randomization visit to D180 visit. This is the primary population for the analysis of efficacy.
- **Per-Protocol (PP):** 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 (see Section 8.2 for definition of major protocol deviations).
- **Safety Set (SAF):** The Safety Set consists of all patients with the sensor inserted at Visit 2 (D0). This is the primary population for the analysis of safety.

5.2. Cohort analysed

The following cohorts are defined according to the type of diabetes or HbA1c (%) level during selection phase and will be studied:

- **Cohort 1:** patients with HbA1c level > 8.0% (either type 1 or type 2 diabetes)
- **Cohort 2:** patients having type 1 diabetes and spending more than 1.5 hour with FGM <70 mg/dl per day as a mean for at least 28 days.

5.3. Follow-up group

According to protocol section 2.1, patients selected in cohort 2 at D0 who no longer comply with the inclusion criteria (i.e. spend more than 1.5 hour with FGM <70 mg/dl per day as a mean for at least 28 days) at D30, 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.

The follow-up group will be computed as follows:

- Patients pre-selected in cohort 2 at D0 (i.e. Type 1 Diabetes and spend more than 1.5 hour with FGM <70 mg/dl per day as a mean for at least 28 days), and
- Patients not randomized, and
- Patients with date of end of study (*) > date of D30.

(*) with date of end of study defined as the minimum between date of study withdrawal, consent withdrawal, last contact date, or death.

6. ENDPOINTS

Unless otherwise specified, endpoints will be computed per patient (i.e. the statistical unit is the patient).

6.1. Primary efficacy endpoint

As described in protocol section 14.4, "the primary efficacy objective for **cohort 1** is to evaluate the difference between Enabled and Control arms in HbA1c (%) level at D180". Analysis of the primary endpoint for Cohort 1 is described in Section 8.6.1.1.

For **cohort 2**, the primary efficacy objective is to evaluate the difference between Enabled and Control arms in percentage of time spent in hypoglycemia < 54 mg/dl between D90 visit and D120 visit (using CGM system data). Analysis of the primary endpoint for Cohort 2 is described in Section 8.6.1.2.

This endpoint will be computed as follows:

- Percentage of time spent in hypoglycemia < 54mg/dL =

$$100 * \frac{duration\ (min)\ spent\ with\ glycemia\ <\ 54\ mg/dL\ between\ D90\ and\ D120}{duration\ (min)\ with\ CGM\ data\ available\ (i.e.\ excluding\ temporary\ discontinuations)}$$

The algorithm is defined in section 9.2.

6.2. Secondary efficacy endpoints

Unless otherwise specified, the following secondary efficacy criteria will be computed for both cohorts.

6.2.1. Safety of the insertion and removal procedures and safety of the device

The following pre-specified AE reported in the eCRF from D0 to D187 will be used:

- Infection, local or systemic
- Excessive bleeding
- Bruising or swelling
- Keloid and/or scar formation
- Skin irritation and/or redness
- Nerve damage causing tingling, numbness, pain or weakness
- Puritis (itching of the incision while healing)
- Discoloration of skin
- Hematoma formation
- Burning sensation or pain
- Device migration

Pre-specified AE which occurred after sensor insertion and after sensor removal will be analyzed separately.

6.2.2. Percentage of time spent in the [70mg/dL-180mg/dL] glucose range

- From D90 to D120

- From D150 to D180

These endpoints will be computed using CGM data . The algorithm is defined in section 9.2.

See Section 7.5 for definition of time-windows D90-D120 and D150-D180.

6.2.3. Percentage of time spent in hypoglycemia and hyperglycemia

The following endpoints will be computed using CGM data. The algorithm is defined in section 9.2.

- Hypoglycemia (<70mg/dL) from D90 to D120
- Hypoglycemia (<70mg/dL) from D150 to D180
- Hypoglycemia (<54mg/dL) from D90 to D120
- Hypoglycemia (<54mg/dL) from D150 to D180
- Hyperglycemia (>180mg/dL) from D90 to D120
- Hyperglycemia (>180mg/dL) from D150 to D180
- Hyperglycemia (>250mg/dL) from D90 to D120
- Hyperglycemia (>250mg/dL) from D150 to D180

See Section 7.5 for definition of time-windows D90-D120 and D150-D180.

6.2.4. Glucose variability estimated with coefficient of variation calculated by 24h as ratio of standard deviation to mean daily glucose

Glucose variability will be evaluated using the following indices.

6.2.4.1. Coefficient of variation (CV)

CV measured from D90 to D120:

This endpoint will be computed using CGM data with the following formula.

$$Coefficient\ of\ variation\ (\%) = \frac{\sum_{i=90}^{i=120} \frac{SD_i}{Mean_i}}{n} * 100$$

Where

- SD_i = Standard deviation of CGM glycemia measured values on Day i,
- $Mean_i$ = mean of CGM glycemia measured on Day i,
- Day i starts at 00:00 and stop at 23:59,
- N is the number of days with available CV value.

CV measured from D90 to D120 will also be classified as ≤36% and >36%:

Note: According to Monnier et al. (1), a CV threshold set to 36% allows to distinguish between stable and unstable glycemia.

CV measured from D150 to D180:

Same computation rule.

CV measured from D150 to D180 will also be classified as ≤36% and >36%.

6.2.4.2. Blood Glucose Index

Measured from D90 to D120:

$$LBGI = \frac{1}{N}\sum_{i=1}^{N} rl(BG_i) \qquad HBGI = \frac{1}{N}\sum_{i=1}^{N} rh(BG_i)$$

$$BGRI = LGBI + HGBI$$

Where:

- BG = Blood Glucose (mg/dL) recorded by the CGM
- $BG^{new} = 1.509 \cdot ([\log(BG)]^{1.084} - 5.381)$
- $r(BG) = 10 \cdot BG^{new\,2}$
- $rl(BG) = r(BG)$ if $BG^{new} < 0$ and 0 otherwise
- $rh(BG) = r(BG)$ if $BG^{new} > 0$ and 0 otherwise

Low Blood Glucose Index (LBGI), High Blood Glucose Index (HBGI) and Blood Glucose Risk Index (BGRI) formulas are described by Fabris et Al. (2)

Measured from D150 to D180:

Same computation rule.

Note: See Section 7.5 for definition of time-windows D90-D120 and D150-D180.

6.2.5. Sensor life

Sensor life will be computed as the number of subjects/Sensors operating at 150- and 180-days post insertion and mean/median Sensor life using Sensor output and long-term performance.

The following endpoints will be computed using CGM data.

- For the first sensor:
  - Lifespan (days) for the first sensor = Date of the last glucose measurement by the sensor – date of the first glucose measurement by the sensor + 1
  - Patients having first sensor operating at D150 (= Yes if lifespan of the first sensor ≥ 150 days, = No otherwise)
  - Patients having first sensor operating at D180 (= Yes if lifespan of the first sensor ≥ 180 days, = No otherwise)
- Number of sensors used (0, 1, 2, 3, etc.)
  - Between D0 and D180
  - Between D30 and D120
  - Between D30 and D180

See Section 7.5 for definition of time-windows D0-D180, D30-D120 and D30-D180.

6.2.6. Transmitter wear time

Amount and variability of Transmitter wear time (by day/week/months) will be computed using CGM data.

- For the first transmitter:
  - Lifespan (days) for the first transmitter = Date of the last glucose measurement with the transmitter – date of the first glucose measurement with the transmitter + 1
- Number of transmitters per patients (0, 1, 2, 3, etc.)

- Between D0 and D180 (or last visit)
- Between D30 and D120
- Between D30 and D180 (or last visit)

6.2.7. Availability of sensor data

This endpoint will be computed for the following studied periods:

- Between D0 and D180
- Between D30 and D120
- Between D30 and D180
- Between D0 and D30
- Between D30 and D60
- Between D60 and D90
- Between D90 and D120
- Between D120 and D150
- Between D150 and D180

$$\text{Availability of sensor data (\%)} = 100 * \frac{Duration\ (min)\ of\ available\ CGM\ data}{Duration\ (min)\ of\ studied\ period}$$

If duration of the studied period is missing (i.e. the patient withdrew the study prior to the studied period), the availability of sensor data will be set to missing.

If duration of the studied period is not missing and duration of available CGM data is 0 min (i.e. no CGM data available for the studied period), the availability of sensor data will be set to 0%.

See Section 7.5 for definition of time-windows.

Data downloaded from the CGM file will be used for this purpose.

6.2.8. Frequency of access of app pages

This endpoint is not available in CGM files and cannot be computed.

A descriptive analysis of the following data collected in eCRF will be performed:

- Does the patient use the "report" function?
- Does the patient use the "historic of alerts" function?
- Does the patient use the "log event" function?
- Does the patient use his phone to look at his glucose level?

6.2.9. Frequency and type of alarms/alerts received

As patients in cohort 2 will use the CGM in blinded mode, result of this endpoint will be provided for cohort 1 only.

Measured from D0 to D187: this endpoint is defined as the number of alarms received by the patient (for each type of alarm and overall). This endpoint will be computed using data downloaded from the CGM system. The type of alarms recorded in CGM system are the following:

Group	Alarm type	Message	Received alert
READER ERROR	Sensor related	Ambient Light Warning	High Ambient Light Alert
READER ALARM	Calibration	Calibration Expired Alarm Asserted	Calibration Expired
	Calibration	Calibration Grace Period Alarm Asserted	Calibration Past Due
	Sensor Glucose	Falling Rate Alert Asserted	Rate Falling
	Sensor Glucose	High Glucose Alarm Asserted	Hight Glucose
	Sensor Glucose	Invalid High Glucose Asserted	Out of Range High Glucose
	Sensor Glucose	Invalid Low Glucose Asserted	Out of Range Low Glucose
	Sensor Glucose	Low Glucose Alarm Asserted	Low glucose
	Sensor Glucose	Predictive Falling Rate Alert Asserted	Predicted Low Glucose
	Sensor Glucose	Predictive Rising Rate Alert Asserted	Predicted High Glucose
	Sensor Glucose	Rising Rate Alert Asserted	Rate Rising
READER MISC	Transmitter related	BLE disconnect event	Transmitter Disconnect
	Transmitter related	Critical Fault	Transmitter Error
	Transmitter related	High Transmitter Temperature	High Transmitter Temperature
	System Related	Calibration Phase	Displayed on the Status Bar of the App
	Sensor related	High Sensor Temperature	High Sensor Temperature
	Sensor related	Low Sensor Temperature	Low Sensor Temperature
	Sensor related	MEP Alarm	Sensor Replacement
	Sensor related	Sensor Retired	Sensor Replacement
	Sensor Glucose and Calibration	Sensor Stability Alarm Activated	Sensor Check

Note: only messages displayed to the patient are listed in this table. Internal messages (i.e. for engineering use only and not displayed to the patient) are not listed in this table and will not be analyzed.

6.2.10. HbA1C (%) level

- HbA1c (%) at D120 visit
- HbA1c (%) at D180 visit **for cohort 2 only** (see Section 6.1 Primary endpoint for cohort 1).
- HbA1c at D120 visit classified as follows: ≤7% / >7%
- HbA1c at D120 visit classified as follows: ≤6.5% / >6.5%
- HbA1c at D180 visit classified as follows: ≤7% / >7%
- HbA1c at D180 visit classified as follows: ≤6.5% / >6.5%

These endpoints will be studied using data as collected in the eCRF.

6.2.11. Maintain of the Eversense effect on hypoglycemia between D150 and D180 for enabled group

The percentage of time spent in hypoglycemia < 54 mg/dl between D150 and D180 will be computed as described in section 6.2.3. This endpoint will be analyzed for patients randomized in Enabled arm of cohort 2 only (cf. section 8.6.2.11).

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

The percentage of time spent in hypoglycemia < 54 mg/dl between D90-D120 and between D150-D180 will be computed as described in section 6.2.3. This endpoint will be analyzed for patients randomized in Control arm of cohort 2 only (cf. section 8.6.2.12).

6.2.13. Patient Reported Outcome Measures (PROMs)

6.2.13.1. CGM questionnaire (CGM SAT)

The CGM-SAT is collected on D60 and D180 for enabled patients only.

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'.

Overall score corresponds to the mean of the 44 items. In case of missing items, the overall score will be the mean of available items.

The absolute change in overall CGM-SAT score from D60 to D180 will be computed.

The data will be used as collected in the eCRF.

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

6.2.13.2. Diabetes Treatment Satisfaction Questionnaire original status (DTSQs)

The DTSQs is collected at screening visit, D60 and D180. The DTSQs contains eight items scored on 7-point scale (i.e. each item is scored from 0 to 6).

DTSQs: Treatment Satisfaction score:

The Treatment Satisfaction score is computed by adding the six items 1, 4, 5, 6, 7 and 8. The Treatment Satisfaction score has a minimum of zero and a maximum of 36.

The absolute changes in Treatment Satisfaction score will be computed:

- from D0 to D180
- from D0 to D60.

DTSQs: Items 2 and 3:

Items 2 (Perceived Frequency of Hyperglycemia) and 3 (Perceived Frequency of Hypoglycemia) are treated individually in data analysis. The absolute changes for item 2 and item 3 will be computed:

- from D0 to D180
- from D0 to D60.

DTSQs: Items 1, 4, 5, 6, 7 and 8:

Each items will be be analyzed separately. For each items, the absolute changes 3 will be computed:

- from D0 to D180
- from D0 to D60.

DTSQs: Handling of missing scores on the six Treatment Satisfaction items:

In case of missing items, the Treatment Satisfaction score will be computed as follows:

- Step 1: sum the existing items scores
- Step 2: divide this sum by the number of existing items scores
- Step 3: multiply by 6 (the number of items in the subscale)
- Step 4: use this computation to estimate subscale scores, providing the number of missing values does not exceed the number tolerable without unacceptable loss of reliability for the language version in use.

Note: language version in use is French. The number of tolerable missing items is 3.

DTSQs: Handling of missing data for item-by-item analysis:

According to the DTSQ user guidelines, it is recommended to treat a missing score as missing for any item-by-item analyses and do not include computed scores in such analyses. Therefore, missing data will not be replaced for item-by-item analyses.

Note: the reliability and factor structure of the eight language versions used in this study are reported by Plowright (2000).

6.2.13.3. The Diabetes Treatment Satisfaction Questionnaire change version (DTSQc)

The DTSQc is collected at D180. The DTSQc contains eight items scored on 7-point scale (i.e. each item is scored from -3 to +3).

DTSQc: Treatment Satisfaction score:

The Treatment Satisfaction score is computed by adding the six items 1, 4, 5, 6, 7 and 8. The Treatment Satisfaction score has a minimum of -18 and a maximum of +18.

DTSQc: Items 2 and 3:

Items 2 (Perceived Frequency of Hyperglycemia) and 3 (Perceived Frequency of Hypoglycemia) are treated individually in data analysis.

DTSQc: Items 1, 4, 5, 6, 7 and 8:

Each items will be analyzed separately.

DTSQc: Handling of missing scores on the six Treatment Satisfaction items:

In case of missing items, the Treatment Satisfaction score will be computed as follows:

- Step 1: sum the existing items scores
- Step 2: divide this sum by the number of existing items scores
- Step 3: multiply by 6 (the number of items in the subscale)
- Step 4: use this computation to estimate subscale scores, providing the number of missing values does not exceed the number tolerable without unacceptable loss of reliability for the language version in use.

Note: language version in use is French. The number of tolerable missing items is 3.

DTSQc: Handling of missing data for item-by-item analysis:

According to the DTSQ user guidelines, it is recommended to treat a missing score as missing for any item-by-item analyses and do not include computed scores in such analyses. Therefore, missing data will not be replaced for item-by-item analyses.

Note: the reliability and factor structure of the eight language versions used in this study are reported by Plowright (2000).

6.2.13.4. The Audit of Diabetes-Dependent Quality of Life (ADDQoL)

The ADDQoL is collected at screening visit and D180.

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 scale ranges 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). Finally, a mean weighted impact score (ADDQOL score) is calculated for the entire scale across all applicable domains.

The absolute change in overall ADDQOL score from screening visit to D180 will be computed.

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

6.2.13.5. Diabetes Distress Scale 2 (DDS2)

The DDS2 is collected at screening visit, D60 and D180.

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).

DDS2 score is the mean of the two items. If one item is missing, then no score will be computed.

In addition, the two items will be analyzed separately.

The absolute change in overall DDS2 score will be computed from screening visit to D60 and from screening visit to D180.

6.2.13.6. Hypoglycemia Fear Survey part II (HFS II)

The HFS II – worry scale is collected at screening visit, D60 and D180.

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 ranges from 0 (never) to 4 (almost always).

- HFS score = Sum of all items.

It is not planned to replace missing items. If one item is missing, the HFS score will not be computed.

The absolute change in overall HFS II score will be computed from screening visit to D60 and from screening visit to D180.

This endpoint will be studied using data collected in the eCRF.

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

6.2.13.7. Partner reported Outcome Measures (Partner-DDS) to measure the partner-related distress

This questionnaire is collected at screening visit, D60 and D180.

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 scale ranges from 0 (not at all) to 4 (a great deal).

The PARTNER DDS yields a total diabetes distress score plus 4 subscale scores:

- Total DDS Score = Mean of the 21 items
- My partner’s diabetes management = Mean of item 3, 4, 10, 12, 14, 15 and 20
- How best to help = Mean of item 2, 6, 7, 11 and 13
- Diabetes and me = Mean of items 5, 8, 9, 16 and 21
- Hypoglycemia = Mean of items 1, 17, 18 and 19.

The absolute change will be computed from screening visit to D60 and from screening visit to D180 for each score.

The data will be used as collected in the eCRF.

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

6.2.13.8. Free text questionnaire for 'enabled' patients only to record the opinion of the patient about the 'enabled' system

This questionnaire is collected at D180 and contains six questions that have the aim to record the opinion of the patient about the 'enabled' system at the end of the study. This questionnaire will add the depth of data and context to the quantitative PRO data that is being collected.

The data will be used as collected in the eCRF.

6.2.13.9. Free text questionnaire for study investigators to record the opinion of the principal investigator or co-investigators about the system

This questionnaire is collected at D180 and contains seven questions which have the aim to record the opinion of the principal investigator or co-investigators about the system.

The data will be used as collected in the eCRF.

6.3. Safety endpoints

6.3.1. Adverse events

The following adverse events will be studied:

- All adverse events (AE)
- Treatment emergent adverse events (TEAE) [1]
- Serious TEAE
- Fatal TEAE
- Related TEAE (i.e. with possible or probable relationship) to the investigational device according investigator)
- TEAE leading to discontinuation of the investigational device (i.e. temporary or definitive discontinuation)
- TEAE by maximum severity:
    - mild TEAE
    - moderate TEAE
    - severe TEAE

[1] TEAE = AEs occurring on or after the start of the sensor insertion at D0 (Visit 2).

The following AEs will also be studied. Their definition is provided hereafter.

- Symptomatic hypoglycemia
- Severe hypoglycemia (SAEs)
- Serious Diabetic Ketoacidosis (SAEs)
- Adverse Device Effect (ADE) (i.e. anticipated and unanticipated) as collected in the eCRF
    - Anticipated ADE are defined as all AEs which were pre-specified in the eCRF (i.e. Bleedings, Discoloration of skin, Edema or swelling, Hematoma formation, Infection ,local or systemic, Itching and / or puritis, Nerve damage causing tingling, numbness, pain or weakness, Pain and / or burning sensation, Skin irritation and / or redness, …)

- Unanticipated ADE are defined as all related AEs (i.e. with possible or probable relationship) which were not pre-specified in the eCRF.

- ADE as reported to the hotline
-

Programming definitions:

Hypoglycemia will be identified in AE forms using the following Standardized MedDRA Queries (SMQ)

SMQ: Hypoglycaemia **SMQ code: 20000226** **Narrow definition**	
PT	**PT code**
Blood glucose decreased	10005555
Hyperinsulinaemic hypoglycaemia	10077216
Hypoglycaemia	10020993
Hypoglycaemia neonatal	10020994
Hypoglycaemia unawareness	10020997
Hypoglycaemic coma	10021000
Hypoglycaemic encephalopathy	10021002
Hypoglycaemic seizure	10048803
Hypoglycaemic unconsciousness	10065981
Nesidioblastosis	10080024
Neuroglycopenia	10054998
Postprandial hypoglycaemia	10059035
Shock hypoglycaemic	10040576

Symptomatic hypoglycemia: all hypoglycemia reported in AE forms will be considered as symptomatic.

Severe hypoglycemia: all hypoglycemia reported in AE forms with item Serious = Yes and Intensity = “Severe” or “Life threatening”.

As define in section 11.2.2 of the protocol, 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). Severe hypoglycemia are defined as SAEs.

Serious Diabetic Ketoacidosis will be identified in AE forms using the following MedDRA terms:

System Organ Class (SOC Code)	Preferred Term (PT Code)	Lowest Level Term (LLT Code)
Metabolism and nutrition disorders (10027433)	Euglycaemic diabetic ketoacidosis (10080061)	Euglycaemic diabetic ketoacidosis (10080061) Euglycemic diabetic ketoacidosis (10080062)
	Diabetic ketoacidosis (10012671)	Acidosis diabetic (10000488) Diabetes mellitus with ketoacidosis (10012622) Diabetes with ketoacidosis (10012632) Diabetic acidosis (10012642) Diabetic ketoacidosis (10012671) Ketoacidosis (diabetic) (10023380) Type I diabetes mellitus with ketoacidosis (10045230) Type II diabetes mellitus with ketoacidosis (10045244)
	Diabetic ketoacidotic hyperglycaemic coma (10012672)	Diabetic ketoacidotic hyperglycaemic coma (10012672) Diabetic ketoacidotic hyperglycemic coma (10060579)
	Ketoacidosis (10023379)	Acetone breath (10000413) Breath odor ketones (10006329) Ketoacidosis (10023379) Breath odor ketones (10055425)

Note: as defined in the section 11.2.4 of the protocol, diabetic ketoacidosis can be serious or non-serious AEs. Only serious ketoacidosis episodes will be considered for this analysis.

According to protocol section 11.3.3, Anticipated Adverse Device Effect (ADE) are:

- 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

AEs will be coded using the MedDRA dictionary version 20.1.

6.4. Other endpoints and variables

6.4.1. Demographic data and other baseline characteristics

The following standard characteristics will be used as recorded in the eCRF:

- Baseline characteristics at V1 (i.e. age, sex, weight, height, etc.)

- Diabetes history (i.e. diabetes duration, type of diabetes, usual blood glucose monitoring: capillary blood glucose or flash system, mean daily duration in hypoglycemia < 70 mg/dL, mean daily duration in hypoglycemia < 54 mg/dL, etc.)
- Diabetes complications
- Last HbA1c analysis
- Diabetes Family History
- Diabetes Medication
- Medical history - diseases other than Diabetes
- Previous medications for diseases other than Diabetes
- Training at sensor insertion (D0) (arm chosen for the insertion, trained physician, etc.)
- Training to the device after randomization (at D30) – for Enabled group

In addition, the following variables will be computed:

- Age (years) = (date of signed consent – date of birth) / 365.25
- BMI classified according to the World Health Organization (WHO):
  - <18.5 – Underweight
  - 18.5 – <25 – Normal weight
  - 25 – <30 – Pre-obesity
  - ≥30 – Obesity
- Percentage of time spent in hypoglycemia < 70 mg/dL at screening and inclusion visit= (mean daily duration in hypoglycemia < 70 mg/dL (minutes) * 100) / 1440
- Percentage of time spent in hypoglycemia < 54 mg/dL at screening and inclusion visit= (mean daily duration in hypoglycemia < 54 mg/dL (minutes) * 100) / 1440
- Time since start of diabetes (years) = (date of signed consent – diabetes start date) / 365.25
- Time since last blood test for HbA1c (days) = (date of screening visit – date of blood test +1)
- Duration of insertion procedure (minutes) = (end time of laying strips - opening time of the kit + 1)
- Duration of removal procedure (minutes) = (end time of procedure - start time of procedure +1)

6.4.2. Follow-up data

The following data will be used as recorded in the eCRF:

- Characteristics at follow-up visit: D60, D150 and D180 (including the percentage of sensor use since the last visit, etc.)
- Training to the device at D120 – for patients who switched from control to enabled group

6.4.3. Medical history

Medical and surgical history will be coded with the MedDRA version 20.1.

6.4.4. Prior and concomitant therapies

Prior therapies are therapies which stopped before the sensor introduction. Concomitant therapies are therapies which ended on or after the sensor introduction or are ongoing at the end of the trial.

Prior and concomitant therapies will be coded with the WHO-DD version SEP 2013 format C.

6.4.5. Extent of exposure

Extent of exposure will be computed as follows:

- Extent of exposure (days) to investigational system = removal date of the last sensor – insert date of the first sensor + 1 day.
- Extent of exposure (days), excluding period when the patient has no sensor inserted = [(removal date of the first sensor - insert date of the first sensor) + (removal date of sensor n°X – insert date of sensor n°X)] + 1 day

Note:

Patient [redacted] from Center [redacted] died on [redacted] Removal date of this sensor in place this day will be replaced with the date of the death.

Patient [redacted] from Center [redacted] encountered a natural ejection of the sensor. An adverse event form has been completed accordingly. Removal date of this sensor will be replaced with the resolution date of this AE.

7. DATA ANALYSIS CONSIDERATIONS

7.1. Statistical software

The statistical analysis will be performed using SAS® software v9.4 (or a more recent version).

7.2. Type I error, handling of multiplicity issues and alpha adjustment procedures

The global significance level (type I error rate) is set to $\alpha = 0.05$ (two-sided).

The analysis will be carried separately for each cohort. No adjustment for multiplicity is planned because analyses of both cohorts have distinct primary objective and distinct primary endpoint.

No adjustment for multiplicity with regards to multiple secondary efficacy endpoints is planned.

7.3. Center effect and pooling of Centers

Center effect will be included in the statistical analysis of:

- The primary endpoint of cohort 1
- The primary endpoint of cohort 2
- The secondary efficacy endpoints of cohort 1 (see section 8.6 for further details).
- The secondary efficacy endpoints of cohort 2 (see section 8.6 for further details).

For each analysis, p-value of the Center effect will be displayed. No by-center analysis is planned. Center effect will not be studied for other endpoints.

If needed (e.g. if size of some Centers is small), Centers will be pooled together according to geographic region.

Reminder: the randomization has been stratified by Center (for cohort 2) and by Center and diabetes type (for cohort 1).

7.4. Descriptive analyses of quantitative and qualitative variables

Continuous data will be described by the number of missing data, number of data analyzed, mean, standard deviation, median, Q1, Q3, minimum, maximum and 95% confidence interval of the mean (using the normal law).

Categorical data will be described by the number of missing data, frequencies and percentages of patients in each modality, and 95% confidence intervals (using binomial law). The percentage of patients will be calculated once missing data are excluded from the denominator.

7.5. Definition of baseline, time-windows and analysis periods

Baseline:

As a general rule, baseline is defined as the last available value collected prior to start of trial medication. Note that for some trial procedures this may be the value measured on the same day the trial medication was started.

Time-windows:

For eCRF data, dates of visit will be used as collected in the eCRF.

For endpoints calculated with CGM data, actual dates recorded in CGM files will be used. Days will be computed using date of randomization (D30) as the reference date, for example:

- D0 = date of D30 - 30 days
- D30 = date of D30
- D60 = date of D30 + 30 days
- D90 = date of D30 + 60 days
- D120 = date of D30 + 90 days
- D150 = date of D30 + 120 days
- D180 = date of D30 + 150 days

Time-windows for CGM endpoints are defined as follows:

Time-windows	**Start datetime**	**Stop datetime[1]**
D0-D30	Date of visit 2 and end time of laying strips* as recorded at visit 2 (D0) + 24 hours**	Date and time of randomization recorded at D30 – 1 minute For follow-up group: date of visit D30 at 23:59.
D30-D60	Date and time of randomization recorded at D30 For follow-up group: date of visit D30 at 23:59 + 1 minute.	D59 (date of visit D30 + 29 days) at 23:59
D60-D90	D60 (date of visit D30 + 30 days) at 00:00	D89 (date of visit D30 + 59 days) at 23:59
D90-D120	D90 (date of visit D30 + 60 days) at 00:00	D119 (date of visit D30 + 89 days) at 23:59 For control group of cohort 2: minimum date between (D119 at 23:59) and (date of switch at 23:59)
D120-D150	D120 (date of visit D30 + 90 days) at 00:00 For control group of cohort 2: minimum date between (D120 at 00:00) and (date of switch at 23:59 + 1 minute)	D149 (date of visit D30 + 119 days) at 23:59

Time-windows	**Start datetime**	**Stop datetime[1]**
D150-D180	D150 (date of visit D30 + 120 days) at 00:00	Date of visit 7 and time of sensor removal*** as recorded at visit 7 (D180)

* If end time of laying strips is missing at visit 2, then replaced by 23:59.
** The blinded transmitter is placed 24 hours after insertion.
*** If time of sensor removal is missing at visit 7, then replaced by 00:00.
[1] For each time windows, the stop datetime will be set to the date of premature discontinuation of the patient at 23:59 if it happens during this period, with date of premature discontinuation defined as the minimum between date of study withdrawal, consent withdrawal, last contact date, or death.

7.6. Handling of missing data and intercurrent events

Date of birth:

Date as collected in the CRF	**Imputed date (for the analysis)**
Year is complete, month is complete	Day replaced with 01.
Year is complete, month is missing	Day and month replaced with 01-Jul.
Year is missing, month is missing	Not replaced.

Start date of diabetes:

Date as collected in the CRF	**Imputed date (for the analysis)**
Year is complete, month is complete, day is missing	Day replaced with 01.
Year is complete, month and day are missing	Day and month replaced with 01-Jul.
Year, month and day are missing	Not replaced.

Handling of missing date for AE:

Onset date of AE	**Imputed AE onset date (for the analysis)**
Completely missing	Date of sensor insertion
Day is missing, month and year are filled in	If month and year are different from the first sensor insertion: Day will be replaced with first day of the month. If month and year are identical to the first sensor insertion: AE onset date will be replaced with date of first sensor insertion.
Day and month are missing, year is filled in	If year is different from the first sensor insertion: Day and month will be replaced with 1st January.

Onset date of AE	**Imputed AE onset date (for the analysis)**
	If year is identical to the first sensor insertion AE onset date will be replaced with date of first sensor insertion.

Partially or completely missing end dates of AE will not be imputed.

Handling of missing date for sensor insertion:

Sensor insertion date	**Imputed date of sensor insertion**
Completely missing	Date of first measurement for this sensor using CGM data.
Day is missing, month and year are filled in	If month and year are different from the first measurement for this sensor using CGM file: Day will be replaced with first day of the month. If month and year are identical to the first measurement for this sensor using CGM file: Sensor insertion date will be replaced with date of first measurement for this sensor using CGM data.
Day and month are missing, year is filled in	If year is different from the first measurement for this sensor using CGM file: Day and month will be replaced with 1st January. If year is identical to the first measurement for this sensor using CGM file: Sensor insertion date will be replaced with date of first measurement for this sensor using CGM data.

Handling of missing date for sensor removal:

Sensor removal date	**Imputed date of sensor removal**
Completely missing	Date of last measurement for this sensor using CGM data.
Day is missing, month and year are filled in	If month and year are different from the last measurement for this sensor using CGM file: Day will be replaced with first day of the month. If month and year are identical to the last measurement for this sensor using CGM file: Sensor removal date will be replaced with date of last measurement for this sensor using CGM data.
Day and month are missing, year is filled in	If year is different from the last measurement for this sensor using CGM file: Day and month will be replaced with 1st January. If year is identical to the last measurement for this sensor using CGM file:

Sensor removal date	**Imputed date of sensor removal**
	Sensor removal date will be replaced with date of last measurement for this sensor using CGM data.

Handling of intercurrent events for HbA1c (%) values:

HbA1c (%) values measured more than 30 days after the last measurement of glycemia using CGM will be excluded from the analysis (i.e. set to missing).

Handling of missing HbA1c (%) level:

HbA1c (%) level	**Imputed value of HbA1c (%) level**
D180 is missing, D120 and D0 are available	Last Observation Carried Forward (LOCF) imputation
D120 is missing, D180 and D0 are available	Linear interpolation
D120 and D180 are missing, D0 is available	Baseline Observation Carried Forward (BOCF) imputation
D0 is missing	No replacement, no matter if D120 and/or D180 are available

Note: HbA1c (%) level is collected at D0, D120 and D180.

Handling of missing percentage of time spent in-, below- and above- target ranges:

Note: as a general rule, Method 2 + Method 3 will be used for primary analyses. Method 1 will be used for sensitivity analyses. Method 3 (only) will be used for sensitivity analyses. See Section 8.6 for further details.

Method 1: observed cases (i.e. no replacement)

Percentages of time will be computed using all available CGM data in the specified time-window, according to the algorithm defined in section 9.2. If no CGM data is available in the specified time-window (e.g. no CGM data recorded between D90 and D120), the percentage of time spent in hypoglycemia, euglycemia and hyperglycemia will be considered as missing.

Method 2: shift of the time-window

Assuming a specific time-window with a lower bound (L) and an upper bound (U). D is the date of measurement of the last glycemia value recorded within the time-window, and Δ is the number of days between D and U.

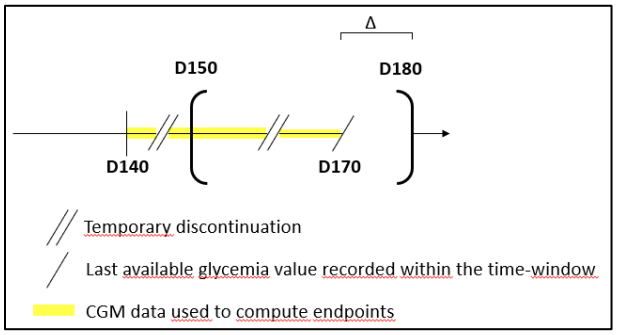
- If D = U (i.e. there was no interruption of the CGM system): the percentages of time spent in-, below- and above the target range and the availability of sensor data will be computed within the (L;U) time-window.
- If D < U (i.e. there was an interruption of the CGM system): the percentages of time spent in-, below- and above the target range and the availability of sensor data will be computed within the (L-Δ ; U-Δ) time-window.

Note:

This method doesn't apply if no glycemia data has been recorded within the time window (L;U).

For example:

Within the time-window D150-D180, the last available glycemia value is recorded at D170. Then, the percentages of time spent in-, below- and above the target range will be computed using all available CGM data within the D140-D170 time-window.



Method 3: linear interpolation, LOCF and BOCF.

Percentages of time will first be computed according to the algorithm defined in section 9.2, using all available CGM data in each of the following time-windows: D0-D30, D30-D60, D60-D90, D90-D120, D120-D150 and D150-D180. If no CGM data is available in one or several time-windows, the endpoint will be imputed as follows.

1. Endpoint missing in time-window N and available in time-windows N-1 and N+1:

D0-D30	D30-D60	D60-D90	D90-D120	D120-D150	D150-D180	Imputed percentage
X	.	X	X	X	X	Linear interpolation
X	X	.	X	X	X	Linear interpolation
X	X	X	.	X	X	Linear interpolation
X	X	X	X	.	X	Linear interpolation
X	.	.	X	X	X	Linear interpolation
X	X	.	.	X	X	Linear interpolation
X	X	X	.	.	X	Linear interpolation
X	.	.	.	X	X	Linear interpolation
X	X	.	.	.	X	Linear interpolation
X	.	.	.	.	X	Linear interpolation

"X": endpoint is available
"." : endpoint is missing (i.e. no CGM data collected during this time-window).

2. Endpoint available in time-window N and missing in all subsequent N+1 time-window(s):

D0-D30	D30-D60	D60-D90	D90-D120	D120-D150	D150-D180	Imputed percentage
X	X	X	X	X	.	LOCF
X	X	X	X	.	.	LOCF
X	X	X	.	.	.	LOCF

D0-D30	D30-D60	D60-D90	D90-D120	D120-D150	D150-D180	Imputed percentage
X	X	.	.	.	.	LOCF
X	.	.	.	.	.	BOCF

"X": endpoint is available
"." : endpoint is missing (i.e. no CGM data collected during this time-window).

Note: this algorithm doesn't apply to availability of CGM data (see Section 6.2.7 for computation rules of availability of CGM data).

8. PLANNED STATISTICAL ANALYSES

Patients will be analyzed as treated for all analyses.

8.1. Disposition of patients

The following will be provided by cohort, by intervention arm for the follow-up set of patients and overall:

- Number of screened patients
- Number of patients with the sensor inserted at V2 (D0)
- Number of randomized patients
- Number of patients not randomized
- Among randomized patients:
  - Number and percentage of patients who completed the trial
  - Number and percentage of patients who prematurely discontinued from trial and reasons for withdrawal
- For cohort 2, patient randomized in control arm:
  - Number and percentage of patients who switched to enabled arm at D120.

The following templates will be used.

	C1	C2	Total
Patients screened	-	-	xxx
Patient with no sensor inserted at V2 (D0)	xxx	xxx	xxx
If no sensor inserted, reasons for withdrawal:			
Withdrawal of consent	xxx	xxx	xxx
Lost view	xxx	xxx	xxx
Death	xxx	xxx	xxx
Investigator's decision	xxx	xxx	xxx
Non randomization	xxx	xxx	xxx
Other	xxx	xxx	xxx
Patients with the sensor inserted at V2 (D0)	xxx	xxx	xxx
If sensor inserted, patients not randomized	xxx	xxx	xxx
Withdrawal of consent	xxx	xxx	xxx
Lost view	xxx	xxx	xxx
Death	xxx	xxx	xxx
Investigator's decision	xxx	xxx	xxx
Non randomization	xxx	xxx	xxx
Other	xxx	xxx	xxx

	Cohort 1		
	Enabled Arm	Control arm	Total
Patients randomized	xxx	xxx	xxx
Among randomized patients			
trial completed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
prematurely discontinued	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reasons for withdrawal:			
Withdrawal of consent	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lost view	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Investigator's decision	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non randomization	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

	Cohort 2		
	Enabled Arm	Control arm	Total
Patients randomized	xxx	xxx	xxx
Patients not randomized	xxx	xxx	xxx
Included in the follow-up set	xxx	xxx	xxx
Not included in the follow-up set	xxx	xxx	xxx
Among randomized patients			
trial completed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
prematurely discontinued	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Patients who switched to enabled arm at D120	-	xx (xx.x%)	xx (xx.x%)
Reasons for withdrawal:			
Withdrawal of consent	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lost view	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Investigator's decision	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non randomization	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

In addition, the following data will be provided:

- Date of first patient screened (i.e. date of signed consent)
- Date of first patient with inserted sensor
- Date of last patient with inserted sensor

- Date of first patient randomized
- Date of last patient randomized
- Date of last patient out (i.e. last visit performed)
- Overall study duration (days) = date of last patient last visit - date of first patient screened +1

8.2. Protocol deviations

Major protocol deviations will be described on all randomized patients, by intervention arm and overall.

Pre-specified major protocol deviations categories are:

- Inclusion criteria not met and/or exclusion criteria met [1]
- Informed consent not available or given too late
- Patient selected in the wrong cohort (e.g. Cohort 1 instead of Cohort 2)
- Patient randomized in the wrong intervention arm (e.g. Enabled instead of Control)
- Use of prohibited (prior and / or concomitant) medication
- Missing primary endpoint (i.e. missing CGM data or insufficient availability of CGM data)

Further categories of major protocol deviations can be defined during the data review meeting. List of major protocol deviations will be finalized in the data review minutes and approved by the Sponsor.

[1] Note: Exclusion criterion 3 is not collected for patients selected before March 29th, 2019. Definition of exclusion criterion 5 and criterion 7 is not the same for patients selected before and after March 29th, 2019.

8.3. Analysis sets and cohorts analyzed

Frequency and percentage of patients included in each analysis sets defined in Section 5 will be provided by treatment group and overall by cohort, by intervention arm and overall.

8.4. Demographic data and baseline characteristics, including medical history and therapies

8.4.1. Analysis of demographic data and other baseline characteristics

Descriptive analyses will be provided by cohort and overall on the Safety Set.

In addition, percentage of time spent in hypoglycemia <54 mg/dL as collected in the eCRF at visit V1 (i.e. screening) for Cohort 1 and at visit V3 (i.e. D30) for Cohort 2 according to the usual glucose monitoring system will be compared to percentage of time spent in hypoglycemia <54 mg/dL as computed with CGM data between D0-D30 using a (non parametric) Wilcoxon test. This analysis will be provided by cohort, on the safety set. The following templates will be used.

	Statistical test	Cohort 1	
		Data collected in eCRF at visit 1 (D0) [1] (N=xxx)	Data computed with CGM data between D0-D30 [2] (N=x)
Percentage of time spent in hypoglycemia <54mg/dL: N Mean (SD) Median Q1 ; Q3 Min; Max	Wilcoxon p = x.xxx	 xxx xx.x (xx.x) xx.x xx.x ; xx.x xx.x ; xx.x	 xxx xx.x (xx.x) xx.x xx.x ; xx.x xx.x ; xx.x

[1] computed as (100 * daily mean time (minutes) spent below 54 mg/dL during the last 28 days according to usual glucose monitoring system and reported in the eCRF by investigators) / 1440.
[2] computed using CGM data from Eversense system, according to algorithm defined in SAP.

	Statistical test	Cohort 2	
		Data collected in eCRF at visit 3 (D30) [1] (N=xxx)	Data computed with CGM data between D0-D30 [2] (N=x)
Percentage of time spent in hypoglycemia <54mg/dL: N Mean (SD) Median Q1 ; Q3 Min; Max	Wilcoxon p = x.xxx	 xxx xx.x (xx.x) xx.x xx.x ; xx.x xx.x ; xx.x	 xxx xx.x (xx.x) xx.x xx.x ; xx.x xx.x ; xx.x

[1] computed as (100 * daily mean time (minutes) spent below 54 mg/dL between visit V2 (i.e. D0,_insertion) and visit V3 (i.e. D30, randomization) according to usual glucose monitoring system and reported in the eCRF by investigators) / 1440.
[2] computed using CGM data from Eversense system, according to algorithm defined in SAP.

8.4.2. Analysis of follow-up data

Descriptive analyses will be provided by cohort and overall on the Safety Set.

8.4.3. Analysis of Medical and surgical history

Descriptive analyses will be provided by cohort and overall on the Safety Set.

Medical and surgical history will be analyzed by MedDRA System Organ Class (SOC) and Preferred Term (PT). The SOC will be sorted by descending frequency and PT will be sorted by descending frequency (within SOC, on «total» column).

8.4.4. Analysis of Prior and concomitant therapies

Descriptive analyses will be provided by cohort and overall on the Safety Set.

Prior and concomitant therapies will be analyzed separately, by WHO-DD preferred name and ATC3. The ATC3 will be sorted by descending frequency and WHO-DD preferred names will be sorted by descending frequency (within ATC3, on « total » column).

8.5. Analysis of extent of exposure and treatment compliance

The criteria defined in section 6.4.5 will be described by cohort, intervention arm and overall on the Safety Set.

8.6. Efficacy analysis

As a general rule, statistical models for cohort 1 will include center and diabetes type as stratification variables and HbA1c (%) at D0 as baseline covariate. Statistical models for cohort 2 will include center as stratification variable and HbA1c (%) as baseline covariate.

8.6.1. Analysis of the primary efficacy endpoint

8.6.1.1. Cohort 1: HbA1c (%) at D180

Descriptive analysis:

A descriptive analysis of HbA1c (%) at D180 will be provided by intervention arm on the FAS (with handling of intercurrent events and missing HbA1c values). The following template will be used.

	Cohort 1	
	Enabled arm N=XXX	Control arm N=XXX
HbA1C (%) at baseline (screening visit)		
Non-missing	xx	xx
Missing	xx	xx
Mean (±SD)	xx.x (±xx.x)	xx.x (±xx.x)
95% CI	[xx.x;xx.x]	[xx.x;xx.x]
Median	xx.x	xx.x
Q1-Q3	[xx.x;xx.x]	[xx.x;xx.x]
Min-Max	[xx.x;xx.x]	[xx.x;xx.x]
HbA1C (%) at D180		
Non-missing	xx	xx
Missing	xx	xx
Mean (±SD)	xx.x (±xx.x)	xx.x (±xx.x)
95% CI	[xx.x;xx.x]	[xx.x;xx.x]
Median	xx.x	xx.x
Q1-Q3	[xx.x;xx.x]	[xx.x;xx.x]
Min-Max	[xx.x;xx.x]	[xx.x;xx.x]
Change in HbA1C (%) between baseline and D180		
Non-missing	xx	xx
Missing	xx	xx
Mean (±SD)	xx.x (±xx.x)	xx.x (±xx.x)
95% CI	[xx.x;xx.x]	[xx.x;xx.x]
Median	xx.x	xx.x
Q1-Q3	[xx.x;xx.x]	[xx.x;xx.x]
Min-Max	[xx.x;xx.x]	[xx.x;xx.x]

Main analysis (parametric model):

The analysis of the primary endpoint for cohort 1 will be an analysis of covariance (ANCOVA) comparing the HbA1c (%) at D180 visit between treatment arms. The statistical model will include randomization arm, center and diabetes type as fixed classification effects and HbA1c (%) at D0 as baseline covariates. Adjusted means with their 95% CI will be provided. P-values of each effects and covariates will be displayed. Intercurrent events and missing HbA1c values will be handled as described in Section 7.6. The primary analysis will be provided on the FAS. The following template will be used.

	Cohort 1		
	Enabled arm N=XXX	Control arm N=XXX	Difference (Enabled – control)
HbA1C (%) at D180 Adjusted mean 95% CI p value	xx.x [xx.x;xx.x]	xx.x [xx.x;xx.x]	xx.x [xx.x;xx.x] p=0.xx
From an ANCOVA model including Center (p=0.xxx) and diabetes type (p=0.xxx) as fixed classification effect, HbA1c (%) level at baseline (p=0.xxx) as baseline covariates.			

Note: the primary endpoint for Cohort 1 is HbA1C (%) at D180.
Note: HbA1C (%) at D180 is a secondary endpoint for Cohort 2.

The same analysis will be provided for the absolute change in HbA1c (%) from baseline to D180. The following template will be used.

	Cohort 1		
	Enabled arm N=XXX	Control arm N=XXX	Difference (Enabled – control)
Change in HbA1C (%) between baseline and D180 Adjusted mean 95% CI p value	xx.x [xx.x;xx.x]	xx.x [xx.x;xx.x]	xx.x [xx.x;xx.x] p=0.xx
From an ANCOVA model including Center (p=0.xxx) and diabetes type (p=0.xxx) as fixed classification effect, HbA1c (%) level at baseline (p=0.xxx) as baseline covariates.			

Note: normality of distribution will be studied using a histogram with the normal probability density curve. Distribution of HbA1c (%) at D180 in Cohort 1 may be skewed, due to inclusion criterion #3 (i.e. HbA1c level at baseline > 8%). The gamma distribution will be studied using a histogram with the gamma probability density curve. If applicable, the ANCOVA models described above will be replaced by a Generalized Linear Models (GLM) using a Gamma distribution and a LOG link function. The statistical model will include randomization arm, center and diabetes type as fixed classification effects and HbA1c (%) at D0 as baseline covariates. Adjusted means with their 95% CI will be provided. P-values of each effects and covariates will be displayed. The same templates will be used.

Sensitivity analysis #1: (non-parametric model)

The primary endpoint will be classified as follows: less than 6%, 6-<7%, 7-<8%, 8-<9% 9-<10%, 10% and more. A Generalized Linear Model (GLM) for ordinal data with multinomial distribution and a cumulative link will be used. The cumulative logit model will include randomization arm, center, diabetes type and HbA1c (%) at D0 as baseline covariates. Log odds ratio will be exponentiated to form odds ratio estimates. This model will be used to compute odds ratio with their 95% CI and corresponding p-value. The primary analysis will be provided on the FAS with method 3 (“linear interpolation, LOCF and BOCF”, cf. Section 7.6) for handling of missing data.

The following template will be used.

	Cohort 2	
	Enabled N=XXX	Control N=XXX
HbA1C (%) at D180 - N(%)		
Less than 6%	xx (xx.x)	xx (xx.x)
6-7%	xx (xx.x)	xx (xx.x)
7-8%	xx (xx.x)	xx (xx.x)
8-9%	xx (xx.x)	xx (xx.x)
9-10%	xx (xx.x)	xx (xx.x)
More than 10%	xx (xx.x)	xx (xx.x)
Adjusted odds ratio (Enabled vs Control) [1] 95% CI p-value	xx.x [xx.x;xx.x] p=0.xxx	-
[1] From a cumulative logit model including center (p=0.xxx) as fixed classification effect and HbA1c (%) level at baseline (p=0.xxx) as covariate.		

Note: an odds ratio "x" statistically greater than 1.0 (i.e. 95% low confidence limit > 1.0) will indicate odds of Enabled group being in lower HbA1c categories is "x" times the odds of Control group being in lower HbA1c categories. Since the lower categories represent the more favorable results, this would indicate that Enabled group is significantly better than Control group.

Sensitivity analysis #2:

The main analysis and descriptive analysis described above will be provided on the FAS on all observed cases (i.e. without handling of intercurrent events and without replacement of missing data).

Sensitivity analysis #3:

The main analysis and descriptive analysis described above will be provided on the Per Protocol Set. Intercurrent events and missing HbA1c values will be handled as described in Section 7.6.

8.6.1.2. Cohort 2: Percentage of time in hypoglycemia <54mg/dL between D90 visit and D120 visit

Descriptive analysis:

A descriptive analysis, both continuous and qualitative (i.e. by classes of 1%), of the percentage of time spent in hypoglycemia <54mg/dL between D90 and D120 and at baseline (i.e. between D0 and D30) will be provided by cohort and by intervention arm, on the FAS with method 3 ("linear interpolation, LOCF and BOCF", cf. Section 7.6) for handling of missing data..

The following template will be used.

	Cohort 2	
	Enabled N=XXX	Control N=XXX
Percentage of time spent in hypoglycemia <54mg/dL between D0 and D30		
Non-missing	xx	xx
Missing	xx	xx
Mean (±SD)	xx.x (±xx.x)	xx.x (±xx.x)
95% CI	[xx.x;xx.x]	[xx.x;xx.x]
Median	xx.x	xx.x
Q1-Q3	[xx.x;xx.x]	[xx.x;xx.x]
Min-Max	[xx.x;xx.x]	[xx.x;xx.x]
Less than 1%	xx (xx.x)	xx (xx.x)
1-<2%	xx (xx.x)	xx (xx.x)
2-<3%	xx (xx.x)	xx (xx.x)
3-<4%	xx (xx.x)	xx (xx.x)
4-<5%	xx (xx.x)	xx (xx.x)
5-<6%	xx (xx.x)	xx (xx.x)
6-<7%	xx (xx.x)	xx (xx.x)
7-<8%	xx (xx.x)	xx (xx.x)
8-<9%	xx (xx.x)	xx (xx.x)
9-<10%	xx (xx.x)	xx (xx.x)
10-<11%	xx (xx.x)	xx (xx.x)
Etc.%	...	...
Percentage of time spent in hypoglycemia <54mg/dL between D90 and D120		
Non-missing	xx	xx
Missing	xx	xx
Mean (±SD)	xx.x (±xx.x)	xx.x (±xx.x)
95% CI	[xx.x;xx.x]	[xx.x;xx.x]
Median	xx.x	xx.x
Q1-Q3	[xx.x;xx.x]	[xx.x;xx.x]
Min-Max	[xx.x;xx.x]	[xx.x;xx.x]
Less than 1%	xx (xx.x)	xx (xx.x)
1-<2%	xx (xx.x)	xx (xx.x)
2-<3%	xx (xx.x)	xx (xx.x)
3-<4%	xx (xx.x)	xx (xx.x)
4-<5%	xx (xx.x)	xx (xx.x)
5-<6%	xx (xx.x)	xx (xx.x)
6-<7%	xx (xx.x)	xx (xx.x)
7-<8%	xx (xx.x)	xx (xx.x)
8-<9%	xx (xx.x)	xx (xx.x)
9-<10%	xx (xx.x)	xx (xx.x)
10-<11%	xx (xx.x)	xx (xx.x)
Etc.%	...	...

Note: the primary endpoint for Cohort 2 is the percentage of time in hypoglycemia.
Note: Percentage of time in hypoglycemia is a secondary endpoint for Cohort 1.
Note: Percentage of time in hypoglycemia between D0 and D30 is the baseline value.

Main analysis (parametric model):

The analysis of the primary endpoint for cohort 2 will be an analysis of covariance (ANCOVA) comparing the percentage of time spent in hypoglycemia <54mg/dL between D90 visit and D120 visit between treatment arms. The statistical model will include randomization arm and center as fixed classification effects and the level of hypoglycemia at baseline (i.e. percentage of time spent in hypoglycemia <54 mg/dl between D0 visit and D30 visit) as baseline covariates. Adjusted means with their 95% CI will be provided. P-values of each effects and covariates will be displayed. Missing values will be handled as described in Section 7.6 using method 3 "linear interpolation, LOCF and BOCF". The primary analysis will be provided on the FAS.

The following template will be used.

	Cohort 2		
	Enabled N=XXX	Control N=XXX	Difference (Enabled – control)
Percentage of time in hypoglycemia <54mg/dL between D90 and D120			
Adjusted mean	xx.x	xx.x	xx.x
95% CI	[xx.x;xx.x]	[xx.x;xx.x]	[xx.x;xx.x]
p value			p=0.xxx
From an ANCOVA model including Center (p=0.xxx) as fixed classification effect, time spent in hypoglycemia <54 mg/dl from D0 visit to D30 visit (p=0.xxx) as baseline covariate.			

Note: Normality of distribution will be studied using a histogram with the normal probability density curve.

Sensitivity analysis #1 (non-parametric model):

The primary endpoint will be classified as follows: less than 1%, 1-<2%, 2-<3%, etc., 9-<10%, 10% and more. A Generalized Linear Model (GLM) for ordinal data with multinomial distribution and a cumulative link will be used. The cumulative logit model will include randomization arm, center and percentage of time spent <54mg/dL from D0 to D30 as covariates. Log odds ratio will be exponentiated to form odds ratio estimates. This model will be used to compute odds ratio with their 95% CI and corresponding p-value. The primary analysis will be provided on the FAS with method 3 ("linear interpolation, LOCF and BOCF", cf. Section 7.6) for handling of missing data.

The following template will be used.

	Cohort 2	
	Enabled N=XXX	Control N=XXX
Percentage of time in hypoglycemia <54mg/dL between D90 and D120 - N(%)		
Less than 1%	xx (xx.x)	xx (xx.x)
1-2%	xx (xx.x)	xx (xx.x)
2-3%	xx (xx.x)	xx (xx.x)
3-4%	xx (xx.x)	xx (xx.x)
4-5%	xx (xx.x)	xx (xx.x)
5-6%	xx (xx.x)	xx (xx.x)
6-7%	xx (xx.x)	xx (xx.x)
7-8%	xx (xx.x)	xx (xx.x)
8-9%	xx (xx.x)	xx (xx.x)
9-10%	xx (xx.x)	xx (xx.x)
More than 10%	xx (xx.x)	xx (xx.x)
Adjusted odds ratio (Enabled vs Control) [1] 95% CI p-value	xx.x [xx.x;xx.x] p=0.xxx	-
[1] From a cumulative logit model including center (p=0.xxx) as fixed classification effect and percentage of time spent <54mg/dL from D0 to D30 (p=0.xxx) as baseline covariate.		

Note: an odds ratio "x" statistically greater than 1.0 (i.e. 95% low confidence limit > 1.0) will indicate odds of Enabled group being in lower percentage of time categories is "x" times the odds of Control group being in lower percentage of time categories. Since the lower categories represent the more favorable percentage of time results, this would indicate that Enabled group is significantly better than Control group.

Sensitivity analysis #2:

The main analysis and descriptive analysis will be provided on the FAS using method 1 (observed cases, no replacement) for handling of missing data.

Sensitivity analysis #3:

The main analysis and descriptive analysis will be provided on the FAS, using method 2 (shift of the time-window) and method 3 (linear interpolation, LOCF and BOCF) for handling of missing data.

Sensitivity analysis #4:

A (non-parametric) rank-ANCOVA will be performed on the FAS with method 3 (linear interpolation, LOCF and BOCF) for handling of missing data. Rank transformation will be applied to the primary endpoint. The same ANCOVA model described above will be run on the rank-transformed primary endpoint. Only p-values will be displayed, as the computed mean values and confidence intervals are not interpretable. The purpose of this sensitivity analysis is to check robustness of the primary analysis, if normality of distribution of the primary endpoint is rejected.

The following template will be used.

Rank-ANCOVA model for percentage of time spent in hypoglycemia <54mg/dL between D90 and D120	
Treatment arm effect:	p=0.xxx
Center effect:	p=0.xxx
Time in hypoglycemia <54 mg/dl from D0 visit to D30 visit effect	p=0.xxx

Sensitivity analysis #5:

A (non-parametric) Wilcoxon-Mann-Whitney test will be performed on the FAS with method 3 (linear interpolation, LOCF and BOCF) for handling of missing data.

The following template will be used:

		Cohort 2	
		Enabled N=XXX	Control N=XXX
Percentage of time spent in hypoglycemia <54mg/dL between D90 and D120 Non-missing Missing Median Q1-Q3 Min-Max	 Wilcoxon p=0.xxx 	 xx xx xx.x [xx.x;xx.x] [xx.x;xx.x]	 xx xx xx.x [xx.x;xx.x] [xx.x;xx.x]

Sensitivity analysis #6:

The main analysis and descriptive analysis described above will be provided on the Per Protocol Set. Missing values will be handled as described in Section 7.6 using method 3 “linear interpolation, LOCF and BOCF”.

8.6.2. Analysis of the secondary efficacy endpoints

8.6.2.1. Safety of the insertion and removal procedures and safety of the device

A descriptive analysis of pre-specified AEs listed in section 6.2.1 will be provided by cohort and by intervention arm, on the FAS.

The following template will be used.

Pre-specified AEs which occurred after sensor insertion	**Cohort 1**		**Total N=xxx**
	Control N=xxx	**Enabled N=xxx**	
Infection, local or systemic	xx (xx.x)	xx (xx.x)	xx (xx.x)
Excessive bleeding	xx (xx.x)	xx (xx.x)	xx (xx.x)
Edema or swelling	xx (xx.x)	xx (xx.x)	xx (xx.x)
Scar formation and/or Keloid	xx (xx.x)	xx (xx.x)	xx (xx.x)
Skin irritation and/or redness	xx (xx.x)	xx (xx.x)	xx (xx.x)
Nerve damage causing tingling, numbness, pain or weakness	xx (xx.x)	xx (xx.x)	xx (xx.x)
Puritis (itching of the incision while healing)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discoloration of skin	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hematoma formation	xx (xx.x)	xx (xx.x)	xx (xx.x)
Burning sensation and/or pain	xx (xx.x)	xx (xx.x)	xx (xx.x)
Device migration	xx (xx.x)	xx (xx.x)	xx (xx.x)

The same template will be used for:

- Cohort 1: pre-specified AEs which occurred after sensor removal

- Cohort 1: pre-specified AEs which didn't occur after sensor insertion or removal
- Cohort 2: pre-specified AEs which occurred after sensor insertion
- Cohort 2: pre-specified AEs which occurred after sensor removal
- Cohort 2: pre-specified AEs which didn't occur after sensor insertion or removal

8.6.2.2. Analysis of percentage of time spent in the [70mg/dL-180mg/dL] glucose range

Time in range [70mg/dL-180mg/dL] of glucose values from D150 to D180.

This endpoint will be analyzed as described for the primary analysis of the cohort 2 primary endpoint, i.e. descriptive analysis and ANCOVA model on the FAS with method 3 (linear interpolation, LOCF and BOCF) for handling of missing data.

The same analysis will be provided for cohort 1.

Time in range [70mg/dL-180mg/dL] of glucose values from D90 to D120.

This endpoint will be analyzed as described for the primary analysis of the cohort 2 primary endpoint, i.e. descriptive analysis and ANCOVA model on the FAS with method 3 (linear interpolation, LOCF and BOCF) for handling of missing data.

The same analysis will be provided for cohort 1.

8.6.2.3. Analysis of percentage of time spent in hypoglycemia and hyperglycemia

- Time in hypoglycemia (<70mg/dL) from D150 to D180
- Time in hypoglycemia (<70mg/dL) from D90 to D120
- Time in hypoglycemia (<54mg/dL) from D150 to D180
- Time in hypoglycemia (<54mg/dL) from D90 to D120
- Time in hyperglycemia (>180mg/dL) from D150 to D180
- Time in hyperglycemia (>180mg/dL) from D90 to D120
- Time in hyperglycemia (>250mg/dL) from D150 to D180
- Time in hyperglycemia (>250mg/dL) from D90 to D120

These endpoints will be analyzed as described for the primary analysis of the cohort 2 primary endpoint, i.e. descriptive analysis and ANCOVA model on the FAS with method 3 (linear interpolation, LOCF and BOCF) for handling of missing data.

The same analysis will be provided for cohort 1.

8.6.2.4. Analysis of glucose variability estimated with coefficient of variation calculated by 24h as ratio of standard deviation to mean daily glucose

8.6.2.4.1. Analysis of Coefficient of Variation

CV (%) measured from D90 to D120 and CV measured from D150 to D180 will be analyzed as described for the primary analysis of the cohort 2 primary endpoint, i.e. descriptive analysis and ANCOVA model on the FAS with method 3 (linear interpolation, LOCF and BOCF) for handling of missing data.

The following template will be used for the ANCOVA.

	Cohort 2		
	Enabled N=XXX	Control N=XXX	Difference (Enabled – control)
CV (%) between D90 and D120 Adjusted mean 95% CI p value	xx.x [xx.x;xx.x]	xx.x [xx.x;xx.x]	xx.x [xx.x;xx.x] p=0.xxx
From an ANCOVA model including Center (p=0.xxx) as fixed classification effect and CV (%) from D0 to D30 visit (p=0.xxx) as baseline covariate.			

The same analysis will be provided for cohort 1.

Analysis of binary CV endpoints (<36, ≥36%):

Binary endpoints (i.e. CV measured from D90 to D120 < 36% and CV measured from D150 to D180 < 36%) will be compared between treatment groups using a logistic regression model including randomization arm, center, diabetes type and HbA1c (%) at D0 as baseline covariates. This model will be used to compute odds ratio with their 95% CI and corresponding p-value. The analysis will be provided on the FAS with method 3 ("linear interpolation, LOCF and BOCF", cf. Section 7.6) for handling of missing data.

The following template will be used.

	Cohort 1	
	Enabled N=XXX	Control N=XXX
CV (%) from D90 to D120- N(%) < 36% >=36%	 xx (xx.x) xx (xx.x)	 xx (xx.x) xx (xx.x)
Adjusted odds ratio (Enabled vs Control) [1] 95% CI p-value	xx.x [xx.x;xx.x] p=0.xxx	-
[1] From a logistic model including center (p=0.xxx) and diabetes type (p=0.xxx) as fixed classification effects and HbA1c (%) level at baseline (p=0.xxx) as covariate.		

8.6.2.4.2. Analysis of Blood Glucose Indexes

LBGI, HBGI and BGRI measured from D90 to D120 and measured from D150 to D180 will be analyzed as described above for the analysis of Coefficient of Variation (see section above).

8.6.2.5. Analysis of sensor life

A descriptive analysis will be provided by cohort and by intervention arm, on the FAS.

The following templates will be used.

	Cohort 1		
	Control N=XXX	Enabled N=XXX	Total N=XXX
Lifespan (days) for the first sensor:			
Non-missing	xx	xx	xx
Missing	xx	xx	xx
Mean (±SD)	xx.x (±xx.x)	xx.x (±xx.x)	xx.x (±xx.x)
95% CI	[xx.x;xx.x]	[xx.x;xx.x]	[xx.x;xx.x]
Median	xx.x	xx.x	xx.x
Q1-Q3	[xx.x;xx.x]	[xx.x;xx.x]	[xx.x;xx.x]
Min-Max	[xx.x;xx.x]	[xx.x;xx.x]	[xx.x;xx.x]
Patients having first sensor operating at D150			
Yes [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
No [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patients having first sensor operating at D180			
Yes [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
No [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Cohort 1		
	Control N=XXX	Enabled N=XXX	Total N=XXX
Number of sensors used between D0 and D180			
Non-missing	xx	xx	xx
Missing	xx	xx	xx
Mean (±SD)	xx.x (±xx.x)	xx.x (±xx.x)	xx.x (±xx.x)
95% CI	[xx.x;xx.x]	[xx.x;xx.x]	[xx.x;xx.x]
Median	xx.x	xx.x	xx.x
Q1-Q3	[xx.x;xx.x]	[xx.x;xx.x]	[xx.x;xx.x]
Min-Max	[xx.x;xx.x]	[xx.x;xx.x]	[xx.x;xx.x]
Number of sensors used Between D0 and D180 – N(%) [95%CI]			
1 sensor	xx (xx.x) [xx.x;xx.x]	xx (xx.x) [xx.x;xx.x]	xx (xx.x) [xx.x;xx.x]
2 sensors	xx (xx.x) [xx.x;xx.x]	xx (xx.x) [xx.x;xx.x]	xx (xx.x) [xx.x;xx.x]
3 sensors	xx (xx.x) [xx.x;xx.x]	xx (xx.x) [xx.x;xx.x]	xx (xx.x) [xx.x;xx.x]
4 sensor s (…)	xx (xx.x) [xx.x;xx.x]	xx (xx.x) [xx.x;xx.x]	xx (xx.x) [xx.x;xx.x]

Same template for number of sensors used between D0-D120, and between D30-D180.

A Kaplan-Meier plot of the lifespan for the first sensor will be provided (overall) on the FAS. The 95% confidence limits of the survival curve will be displayed. Confidence interval will be computed using LOG-LOG transformation.

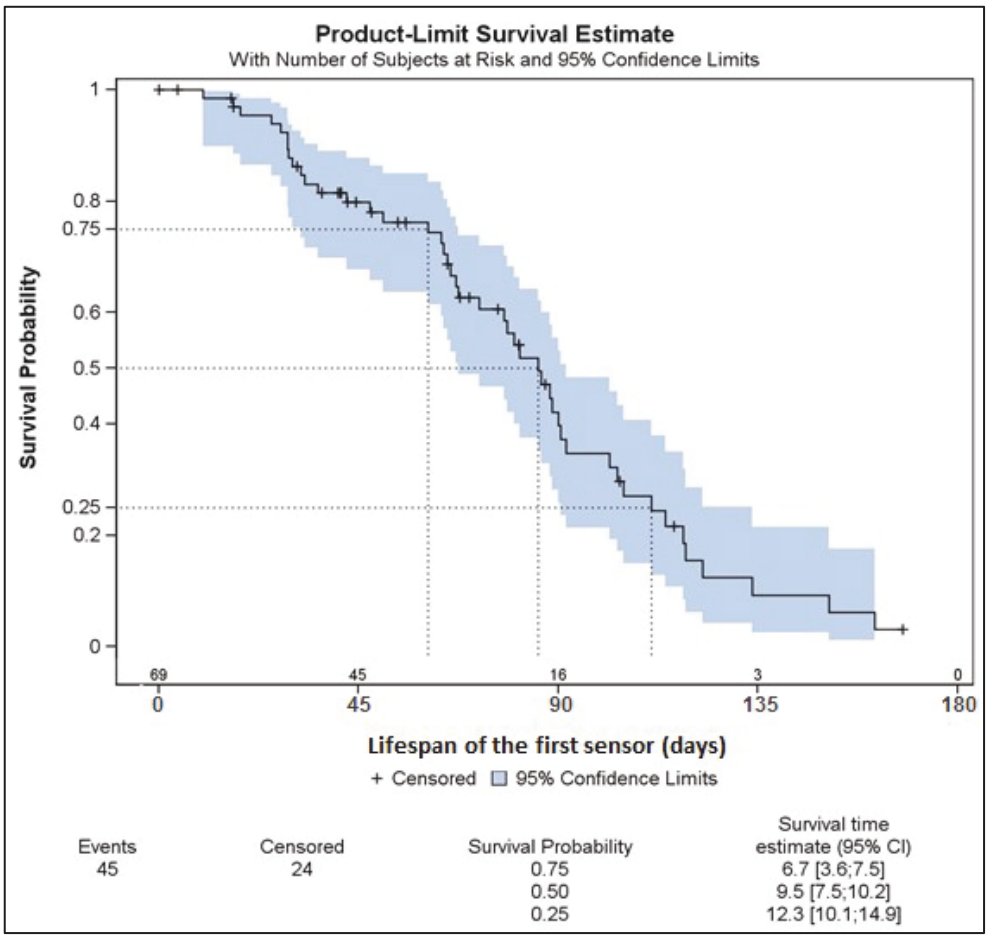
Reminder of endpoint's definition (see section 6.2.5):

- Lifespan (days) for the first sensor = Date of the last glucose measurement by the sensor – date of the first glucose measurement by the sensor + 1

Censoring:

- Patients with first sensor removed at D180 visit will be censored to the date of D180 visit.
- Patients with missing data (i.e. no CGM records) are excluded from the FAS.
- No other censoring rules is defined.

The following template will be used.



8.6.2.6. Analysis of transmitter wear time

A descriptive analysis will be provided by cohort and by intervention arm, on the FAS. This endpoint will be analyzed using the same template as for the previous criterion.

8.6.2.7. Analysis of availability of sensor data

A descriptive analysis will be provided by cohort and by intervention arm, on the FAS.

The following template will be used.

	Cohort 1		
	Control N=XXX	Enabled N=XXX	Total N=XXX
Availability of sensor data between D0 and D30:			
Non-missing	xx	xx	xx
Missing	xx	xx	xx
Mean (±SD)	xx.x (±xx.x)	xx.x (±xx.x)	xx.x (±xx.x)
95% CI	[xx.x;xx.x]	[xx.x;xx.x]	[xx.x;xx.x]
Median	xx.x	xx.x	xx.x
Q1-Q3	[xx.x;xx.x]	[xx.x;xx.x]	[xx.x;xx.x]
Min-Max	[xx.x;xx.x]	[xx.x;xx.x]	[xx.x;xx.x]
[…]	[…]	[…]	[…]
Availability of sensor data between D0 and D180 (or last visit):			
Non-missing	xx	xx	xx
Missing	xx	xx	xx
Mean (±SD)	xx.x (±xx.x)	xx.x (±xx.x)	xx.x (±xx.x)
95% CI	[xx.x;xx.x]	[xx.x;xx.x]	[xx.x;xx.x]
Median	xx.x	xx.x	xx.x
Q1-Q3	[xx.x;xx.x]	[xx.x;xx.x]	[xx.x;xx.x]
Min-Max	[xx.x;xx.x]	[xx.x;xx.x]	[xx.x;xx.x]

8.6.2.8. Analysis of frequency of access of app pages

A descriptive analysis will be provided by cohort and by intervention arm and overall, on the FAS.

The following template will be used for cohorts 1 and 2 at visits D60, D120 and D180.

	Cohort 1
	Enabled N=XXX
The patient use the "report" function	
Yes [n (%)]	xx (xx.x)
No [n (%)]	xx (xx.x)
The patient use the "historic of alerts" function	
Yes [n (%)]	xx (xx.x)
No [n (%)]	xx (xx.x)
The patient use the "log event" function	
Yes [n (%)]	xx (xx.x)
No [n (%)]	xx (xx.x)
The patient use his phone to look at his glucose level	
Yes [n (%)]	xx (xx.x)
No [n (%)]	xx (xx.x)

The following template will be used for cohort 2 at D180 visit.

	Cohort 2		
	Switch N=XXX	**Enabled N=XXX**	**Total N=XXX**
The patient use the "report" function			
Yes [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
No [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
The patient use the "historic of alerts" function			
Yes [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
No [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
The patient use the "log event" function			
Yes [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
No [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
The patient use his phone to look at his glucose level			
Yes [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
No [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)

8.6.2.9. Analysis of frequency and type of alarms/alerts received

A descriptive analysis will be provided by cohort and by intervention arm and overall, on the FAS.

The following template will be used.

Alerts from D0 to D30:

	Cohort 2								
	Future Control N=XXX			Future Enabled N=XXX			Total N=XXX		
	N Evt	N	%	N Evt	N	%	N Evt	N	%
READER ALARM	xxx	xx	xx.x	xxx	xx	xx.x	xxx	xx	xx.x
Calibration	xxx	xx	xx.x	xxx	xx	xx.x	xxx	xx	xx.x
Calibration Expired	xxx	xx	xx.x	xxx	xx	xx.x	xxx	xx	xx.x
Calibration Past Due	xxx	xx	xx.x	xxx	xx	xx.x	xxx	xx	xx.x
Sensor Glucose	xxx	xx	xx.x	xxx	xx	xx.x	xxx	xx	xx.x
Rate Falling	xxx	xx	xx.x	xxx	xx	xx.x	xxx	xx	xx.x
Hight Glucose	xxx	xx	xx.x	xxx	xx	xx.x	xxx	xx	xx.x
Out of Range High Glucose	xxx	xx	xx.x	xxx	xx	xx.x	xxx	xx	xx.x
Out of Range Low Glucose	xxx	xx	xx.x	xxx	xx	xx.x	xxx	xx	xx.x
Etc.	xxx	xx	xx.x	xxx	xx	xx.x	xxx	xx	xx.x
READER MISC	xxx	xx	xx.x	xxx	xx	xx.x	xxx	xx	xx.x
Etc.									

Note: N Evt = nb of events (i.e. alarms), N = nb of patients with at least one alarm, % = percentage of patients with at least one alarm.

The same template will be used for cohort 1.

Alerts from D30 to D180:

	Cohort 2											
	D30-D120 Control N=XXX			D30-D120 Enabled N=XXX			D30-D180 Enabled N=XXX			D120-D180 Switch N=XXX		
	N Evt	N	%	N Evt	N Evt	N Evt	N Evt	N	%	N Evt	N	%
READER ALARM	xxx	xx	xx.x	xxx	xxx	xxx	xxx	xx	xx.x	xxx	xx	xx.x
Calibration	xxx	xx	xx.x	xxx	xxx	xxx	xxx	xx	xx.x	xxx	xx	xx.x
Calibration Expired	xxx	xx	xx.x	xxx	xxx	xxx	xxx	xx	xx.x	xxx	xx	xx.x
Calibration Past Due	xxx	xx	xx.x	xxx	xxx	xxx	xxx	xx	xx.x	xxx	xx	xx.x
Sensor Glucose	xxx	xx	xx.x	xxx	xxx	xxx	xxx	xx	xx.x	xxx	xx	xx.x
Rate Falling	xxx	xx	xx.x	xxx	xxx	xxx	xxx	xx	xx.x	xxx	xx	xx.x
Hight Glucose	xxx	xx	xx.x	xxx	xxx	xxx	xxx	xx	xx.x	xxx	xx	xx.x
Out of Range High Glucose	xxx	xx	xx.x	xxx	xxx	xxx	xxx	xx	xx.x	xxx	xx	xx.x
Out of Range Low Glucose	xxx	xx	xx.x	xxx	xxx	xxx	xxx	xx	xx.x	xxx	xx	xx.x
Etc.	xxx	xx	xx.x	xxx	xxx	xxx	xxx	xx	xx.x	xxx	xx	xx.x
READER MISC	xxx	xx	xx.x	xxx	xxx	xxx	xxx	xx	xx.x	xxx	xx	xx.x
Etc.												

Note: N Evt = nb of events (i.e. alarms), N = nb of patients with at least one alarm, % = percentage of patients with at least one alarm.

The same template will be used for cohort 1 without "D120-D180 Switch" column.

8.6.2.10. Analysis of HbA1C (%) level

HbA1c (%) level at D120 visit:

This endpoint will be analyzed as described for the primary analysis of the cohort 1 primary endpoint, i.e. descriptive analysis and ANCOVA model on the FAS with method 3 (linear interpolation, LOCF and BOCF) for handling of missing data.

The same analysis will be provided for cohort 2.

HbA1c (%) at D180 visit **for cohort 2 only**:

This endpoint will be analyzed as described for the primary analysis of the cohort 1 primary endpoint, i.e. descriptive analysis and ANCOVA model on the FAS with method 3 (linear interpolation, LOCF and BOCF) for handling of missing data.

HbA1c at D120 visit classified as follows: ≤7% / >7%

This endpoint will be analyzed as described for the analysis of % CV < 36% / ≥ 36%, section 8.6.2.4.1.

HbA1c at D120 visit classified as follows: ≤6.5% / >6.5%

This endpoint will be analyzed as described for the analysis of % CV < 36% / ≥ 36%, section 8.6.2.4.1.

HbA1c at D180 visit classified as follows: ≤7% / >7%

This endpoint will be analyzed as described for the analysis of % CV < 36% / ≥ 36%, section 8.6.2.4.1.

HbA1c at D180 visit classified as follows: ≤6.5% / >6.5%

This endpoint will be analyzed as described for the analysis of % CV < 36% / ≥ 36%, section 8.6.2.4.1.

8.6.2.11. Maintain of the Eversense effect on hypoglycemia between D150 and D180 for enabled group

This endpoint will be analyzed on patients from the FAS who were randomized in Enabled arm of Cohort 2.

A descriptive analysis will be provided for:

- Percentage of time spent in hypoglycemia <54mg/dL between D90 and D120 visit
- Percentage of time spent in hypoglycemia <54mg/dL between D150 and D180 visit
- Difference in percentage of time spent in hypoglycemia <54mg/dL between (D90-D120) and (D150-D180)

Note: Normality of distribution will be studied using a histogram with the normal probability density curve.

Main analysis (parametric model):

A restricted maximum likelihood (REML) estimation based on mixed effect model for repeated measures analysis will be used to obtain adjusted means. This model will include time (1="D90-D120", 2="D150-D180") and center as fixed classification effects and the level of hypoglycemia at baseline (percentage of time spent in hypoglycemia <54 mg/dl between D0 visit and D30 visit) as baseline covariates. An unstructured covariance structure will be used to model the within-patient measurements. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The comparison of interest will be the contrast between "D90-D120" and "D150-D180". Adjusted means with their 95% CI will be provided. P-values of each effects and covariates will be displayed.

The following template will be used.

	Cohort 2 – Enabled arm		
	Enabled D90-D120 N=XXX	Enabled D150-D180 N=XXX	Difference
Percentage of time spent in hypoglycemia <54mg/dL Adjusted mean 95% CI p value	 xx.x [xx.x;xx.x]	 xx.x [xx.x;xx.x]	 xx.x [xx.x;xx.x] p=0.xxx
From a mixed model for repeated measures including time (1="D90-D120", 2="D150-D180") and Center (p=0.xxx) as fixed classification effect and time spent in hypoglycemia <54 mg/dl between D0 visit and D30 visit (p=0.xxx) as baseline covariate.			

Sensitivity analysis #1:

A (non-parametric) Wilcoxon-Mann-Whitney test will be performed.

The following template will be used.

	Statistical test	Cohort 2		
		Enabled D90-D120 N=XXX	Enabled D150-D180 N=XXX	Difference
Percentage of time spent in hypoglycemia <54mg/dL: N Mean (SD) Median Q1 ; Q3 Min; Max	Wilcoxon p = x.xxx	xxx xx.x (xx.x) xx.x xx.x ; xx.x xx.x ; xx.x	xxx xx.x (xx.x) xx.x xx.x ; xx.x xx.x ; xx.x	xxx xx.x (xx.x) xx.x xx.x ; xx.x xx.x ; xx.x

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

This endpoint will be analyzed on patients from the FAS who were randomized in Control arm of Cohort 2.

The same analysis as described in section 8.6.2.11 will be provided.

The following template will be used.

	Cohort 2 – Control arm		
	Control D90-D120 N=XXX	Switch 150-D180 N=XXX	Difference (control-switch)
Percentage of time in hypoglycemia <54mg/dL Adjusted mean 95% CI p value	xx.x [xx.x;xx.x]	xx.x [xx.x;xx.x]	xx.x [xx.x;xx.x] p=0.xxx
From a mixed model for repeated measures including time (1="D90-D120", 2="D150-D180") and Center (p=0.xxx) as fixed classification effect and time spent in hypoglycemia <54 mg/dl between D0 visit and D30 visit (p=0.xxx) as baseline covariate.			

The following template will be used.

	Statistical test	Cohort 2		
		Control D90-D120 N=XXX	Switch D150-D180 N=XXX	Difference
Percentage of time spent in hypoglycemia <54mg/dL: N Mean (SD) Median Q1 ; Q3 Min; Max	Wilcoxon p = x.xxx	xxx xx.x (xx.x) xx.x xx.x ; xx.x xx.x ; xx.x	xxx xx.x (xx.x) xx.x xx.x ; xx.x xx.x ; xx.x	xxx xx.x (xx.x) xx.x xx.x ; xx.x xx.x ; xx.x

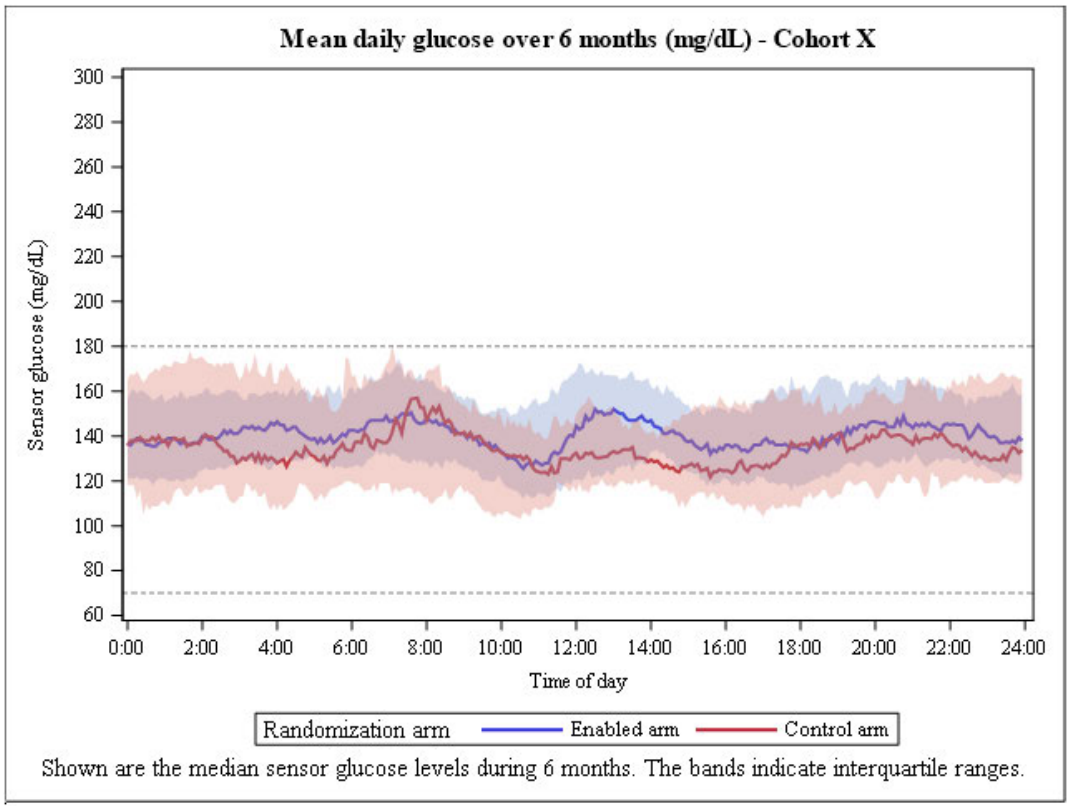
8.6.2.13. Analysis of Patient Reported Outcome Measures (PROMs)

A descriptive analysis will be provided by cohorts and intervention arm, on the FAS.

Free-text questionnaire will be listed.

8.6.2.14. Graphical representation of the mean daily glucose level over the 6-month period

The following figure will be provided by cohort.



8.7. Safety analysis

All safety analyses will be performed on the Safety Set.

8.7.1. Adverse events

8.7.1.1. Overall summary of adverse events

An overall summary of TEAEs will be provided by cohort and by intervention arm and overall, for all categories of AE defined in section 6.3.

The following template will be used.

	Cohort 1		
	Control N=xxx	**Enabled N=xxx**	**Total N=xxx**
Patient experiencing at least one AE [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patient experiencing at least one TEAE [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patient experiencing at least one Serious TEAE [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
TEAE by maximum severity:			
Mild TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Cohort 1		
	Control N=xxx	**Enabled N=xxx**	**Total N=xxx**
Patient experiencing at least one Fatal TEAE [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patient experiencing at least one TEAE leading to discontinuation of the investigational device [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patient experiencing at least one TEAE with possible or probable relationship with investigational device [n (%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patient experiencing at least one Symptomatic hypoglycemia	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patient experiencing at least one Severe hypoglycemia (SAEs)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patient experiencing at least one Serious Diabetic Ketoacidosis (SAEs)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Device Effect (ADE) as collected in eCRF	xx (xx.x)	xx (xx.x)	xx (xx.x)
ADEs as reported to the hotline	xx (xx.x)	xx (xx.x)	xx (xx.x)

This analysis will be done for:

- Cohort 1 from D0 to D180
- Cohort 2 from D0 to D120
- Cohort 2 from D120 to D180
- Cohort 2 from D0 to D180 (for enabled arm only)
- Follow-up arm from D0 to D180.

8.7.1.2. Analysis of adverse events by MedDRA coding

A descriptive analysis will be provided by MedDRA SOC and MedDRA PT, by cohort and by intervention arm and overall for the following categories of adverse events:

- AE
- TEAE
- Serious TEAE
- Fatal TEAE
- Related TEAE
- TEAE leading to discontinuation of the investigational device
- Mild TEAE
- Moderate TEAE
- Severe TEAE
- Symptomatic hypoglycemia
- Severe hypoglycemia (SAEs)
- Serious Diabetic Ketoacidosis

Tables will summarize the total number of events and the number and percentage of patients experiencing the event (i.e. in the case of patients experiencing the same event more than once during

the study, the patient will be counted only once in the same SOC/PT level). The SOC will be sorted by descending frequency and PT will be sorted by descending frequency (within SOC, on « total » column).

	Cohort 1								
	Control (N=xxx)			Enabled (N=xxx)			Total (N=xxx)		
System Organ Class / Preferred Term	Nb AE	Nb pat	% pat	Nb AE	Nb pat	% pat	Nb AE	Nb pat	% pat
TOTAL	x	x	x.x	x	x	x.x	x	x	x.x
SOC A	x	x	x.x	x	x	x.x	x	x	x.x
- PT 1	x	x	x.x	x	x	x.x	x	x	x.x
- PT 2	x	x	x.x	x	x	x.x	x	x	x.x
…	x	x	x.x	x	x	x.x	x	x	x.x
SOC B	x	x	x.x	x	x	x.x	x	x	x.x
- PT 1	x	x	x.x	x	x	x.x	x	x	x.x
- PT 2	x	x	x.x	x	x	x.x	x	x	x.x
…	x	x	x.x	x	x	x.x	x	x	x.x

Nb AE = number of adverse events.
Nb pat = number of patients experiencing the event
% pat = percentage of patients experiencing the event

This analysis will be done for:

- Cohort 1 from D0 to D180
- Cohort 2 from D0 to D120
- Cohort 2 from D120 to D180
- Cohort 2 from D0 to D180 (for enabled arm only)
- Follow-up arm from D0 to D180.

8.7.1.3. Analysis of adverse events per 100 patient years

Incidence rates of all AEs and of 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, by cohort and by intervention arm.

This analysis will be done for:

- Cohort 1 from D0 to D180
- Cohort 2 from D0 to D120
- Cohort 2 from D120 to D180
- Cohort 2 from D0 to D180 (for enabled arm only)
- Follow-up arm from D0 to D180.

The following template will be used.

Cohort 1	**Control**					**Enabled**				
	N	%	IC 95%	Time at risk (pt-years)	Rate/100 pt-years	N	%	IC 95%	Time at risk (pt-years)	Rate/100 pt-years
Number of patients	x	100				x	100			
Patient with any AE	x	xx.x	[xx.x;xx.x]	x.x	xxx.x	x	xx.x	[xx.x;xx.x]	x.x	xxx.x
Patient with serious AEs	x	xx.x	[xx.x;xx.x]	x.x	xxx.x	x	xx.x	[xx.x;xx.x]	x.x	xxx.x
Patients with investigator defined investigational related AEs	x	xx.x	[xx.x;xx.x]	x.x	xxx.x	x	xx.x	[xx.x;xx.x]	x.x	xxx.x
Patients with AEs leading to discontinuation of investigational device	x	xx.x	[xx.x;xx.x]	x.x	xxx.x	x	xx.x	[xx.x;xx.x]	x.x	xxx.x
		xx.x					xx.x			
Adverse Device Effect (ADE) as collected in eCRF	x	xx.x	[xx.x;xx.x]	x.x	xxx.x	x	xx.x	[xx.x;xx.x]	x.x	xxx.x
Anticipated ADE as collected in eCRF	x	xx.x	[xx.x;xx.x]	x.x	xxx.x	x	xx.x	[xx.x;xx.x]	x.x	xxx.x
Unanticipated ADE as collected in eCRF	x	xx.x	[xx.x;xx.x]	x.x	xxx.x	x	xx.x	[xx.x;xx.x]	x.x	xxx.x

Note:
Percentages are calculated using total number of patients per intervention arm as the denominator.
Incidences rates are calculated using number of patients with the respective events per intervention arm divided by time at risk expressed as 100 patient-years.
Patients with AE(s): time at risk = start of first AE – date of first sensor insertion + 1 day.
Patients without AE: time at risk = end of time at risk – date of first sensor insertion + 1 day.
End of time at risk is defined as date of end of studied period (i.e. D120 or D180) or date of premature discontinuation (if it occurs earlier).

8.8. Individual data listings

All data collected in the CRF will be listed. Individual data listings will be provided in statistical appendices. The following templates will be used.

8.8.1. Disposition of patients – all patients

ID	Sex	Cohort	Date of informed consent	Date of randomization	Date of first sensor insertion	Date of last sensor insertion	Date of completion/ Discontinuation	Completed study?	Reason for not performing following-up	Extent of exposure (days)
CxxPxxx	M	1	yyyy-mm-dd	yyyy-mm-dd	yyyy-mm-dd	yyyy-mm-dd	yyyy-mm-dd	Yes		xxx
CxxPxxx	F	2	yyyy-mm-dd	yyyy-mm-dd	yyyy-mm-dd	yyyy-mm-dd	yyyy-mm-dd	No	Lost to follow-up	xxx
...										
...										
Number of patients = xxx										

8.8.2. Protocol deviations – all patients

ID		IN/EX criteria not respected or missing		
Center	Patient	Criterion number	Criterion label	Value
[redacted]		IN 2	Male and female patients at least 18 years of age	No
		EX 3	History of hepatitis B, hepatitis C, or HIV	Yes
		(...)	(...)	(...)
		(...)	(...)	(...)
(...)	(...)	(...)	(...)	(...)

8.8.3. Analysis sets and cohorts analyzed – all patients

ID		Cohort	Analysis sets				
Center	Patient		Screened Set	Randomized Set	Safety Set	Full Analysis set	Per Protocol
[redacted]		1	Yes	Yes	Yes	Yes	Yes
[redacted]		2	Yes	Yes	No	No	No
(…)	(…)						
(…)	(…)						

8.8.4. Demographic data and other baseline characteristics, including medical history and therapies – all patients

Center-Patient	Sex	Diabetes type	Of childbearing capacity	Urine pregnancy test done	Result	Date of birth	Weight (kg)	Height (cm)	BMI (kg/m²)
CxxPxxx	Male	1	Y	Y	Negative	mmyyyy	xxx	xxx	xxx
CxxPxxx	Female	2	N	.	.	mmyyyy	xxx	xxx	xxx
...									
...									

The same template as above will be used for:

- Diabetes history (i.e. diabetes duration, type of diabetes, usual self-monitoring blood glucose: capillary blood glucose monitoring or flash glucose monitoring, etc.)
- Diabetes complications
- Last HbA1c analysis
- Diabetes Family History
- Diabetes Medication
- Medical history - diseases other than Diabetes
- Previous medications for diseases other than Diabetes
- Training at sensor insertion (D0) (arm chosen for insertion, trainer, etc.)
- Training to the device after randomization (at D30) – for Enabled group

- Age (years)
- BMI
- Time since start of diabetes (years)
- Time since last blood test for HbA1c (days)
- Duration of insertion procedure (minutes)
- Duration of removal procedure (minutes)

8.8.5. Extent of exposure and treatment compliance

Individual data listings will be provided on the SAF.

8.8.6. Primary efficacy endpoint

8.8.6.1. Cohort 1: HbA1c (%) level - RS

ID	Cohort	FAS	PP	SAF	HbA1c (%) level		
					D0	D120	D180
CxxPxxx	1	Y	Y	Y	xx	xx	xx
CxxPxxx	1	Y	Y	Y	xx	xx	xx
Etc.	Etc.	..	..	..	..	..	..

8.8.6.2. Cohort 2: percentage of time in hypoglycemia <54mg/dL between D90 visit and D120 visit - RS

ID	Cohort	RS	FAS	PP	SAF	Time (%) between D90 and D120				
						<54 mg/dL	<70 mg/dL	Euglycemia	>180 mg/dL	>250 mg/dL
CxxPxxx	2	Y	Y	Y	Y	xx	xx	xx	xx	xx
CxxPxxx	2	Y	Y	Y	Y	xx	xx	xx	xx	xx
Etc.	Etc.	..	..	..	..	..	..	..	..	..

8.8.7. Secondary efficacy endpoint

The same template as above will be used for all secondary efficacy endpoints.

8.8.8. Adverse events

All AEs will be listed on the RS.

9. ALGORITHMS

9.1. Handling of missing CGM data

Fig.1 is designed to understand how the algorithm operates for the replacement of missing CGM data.

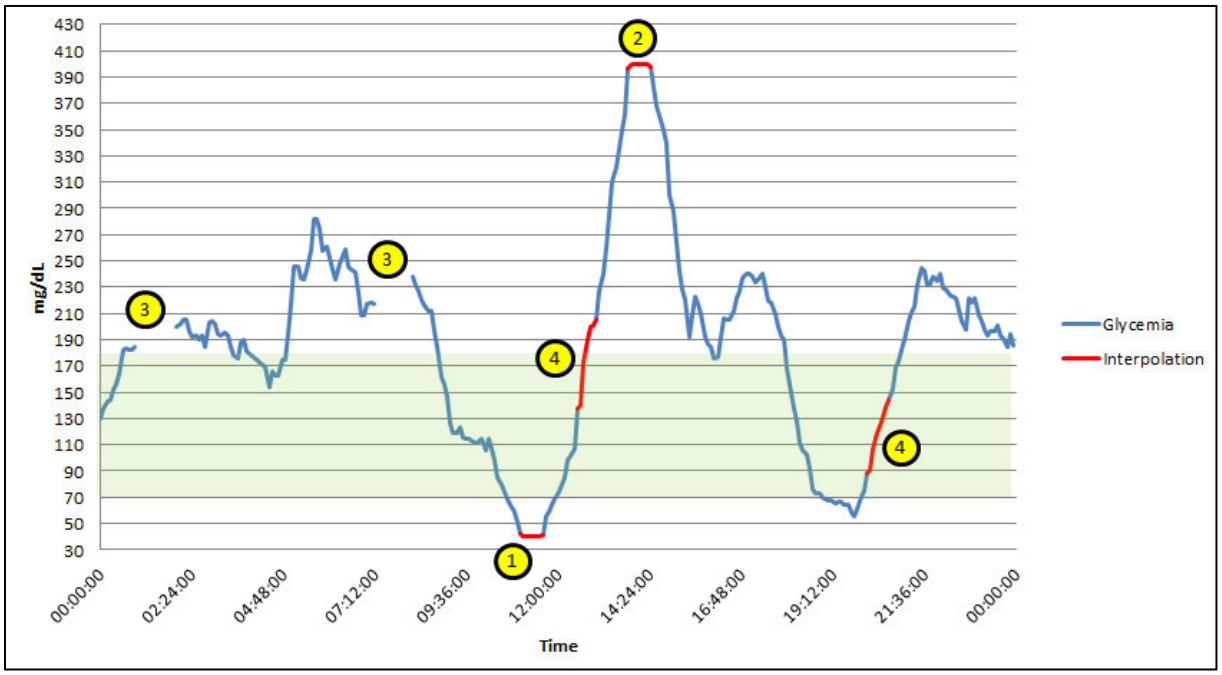


Figure 1. Daily Glucose

Case 1:

Glycemia values below 40 mg/dL are marked as "Out of Physiological Range" in the CGM files and recorded as missing values. In addition, the first record below 40 mg/dL is marked as "Out of Range Low Glucose". The following records are only marked as "Out of Physiological Range" without further details, until glycemia values returns within detection range.

These missing data will be replaced as described below:

1. Missing data flagged as "Out of Range Low Glucose" by CGM system will be imputed to **40 mg/dL**
2. Missing data flagged as "Out of Physiological Range" by CGM system will be imputed to **40 mg/dL** under the following conditions:
    a. If the "Out of Physiological Range" missing data is within 30 minutes **after** an available value that is smaller than 70 mg/dL,
    b. If the "Out of Physiological Range" missing data is within 30 minutes **before** an available value that is smaller than 70 mg/dL,
    c. If the "Out of Physiological Range" missing data is within 30 minutes **after** an "Out of Physiological Range" value already imputed to 40 mg/dL,
    d. If the "Out of Physiological Range" missing data is within 30 minutes **before** an "Out of Physiological Range" value already imputed to 40 mg/dL.

Case 2:

Glycemia values above 400 mg/dL are marked as "Out of Physiological Range" in the CGM files and recorded as missing values. In addition, the first record above 400 mg/dL is marked as "Out of Range High Glucose". The following records are only marked as "Out of Physiological Range" without further details, until glycemia values returns within detection range.

These missing data will be replaced as described below:

1. Missing data flagged as "Out of Range High Glucose" by CGM system will be imputed to **400 mg/dL**
2. Missing data flagged as "Out of Physiological Range" by CGM system will be imputed to **400 mg/dL** under the following conditions:
    a. If the "Out of Physiological Range" missing data is within 30 minutes **after** an available value that is greater than 180 mg/dL,
    b. If the "Out of Physiological Range" missing data is within 30 minutes **before** an available value that is greater than 180 mg/dL,
    c. If the "Out of Physiological Range" missing data is within 30 minutes **after** an "Out of Physiological Range" value already imputed to 400 mg/dL,
    d. If the "Out of Physiological Range" missing data is within 30 minutes **before** an "Out of Physiological Range" value already imputed to 400 mg/dL.

Note: an "Out of Physiological Range" data that can be imputed both to 40 mg/dL according to rule 1 and 400 mg/dL according to rule 2 will not be replaced.

Cases 3 and 4:

It is expected that glycemia values are recorded every 5 minutes by CGM system. However, there can be more than 5 minutes between 2 consecutive records (e.g. temporary discontinuation, discharged battery, transmitter temporarily removed, etc.). A threshold of 30 minutes between 2 consecutive records has been defined. CGM data will be handled as described below whether there is more or less than 30 minutes between 2 consecutive records:

1. If 30 minutes or more between 2 consecutive records: this is considered as a temporary discontinuation of the CGM system (no interpolation nor any other approach of replacement).
2. If less than 30 minutes between 2 consecutive records: linear interpolation will be used for calculation of time spent (cf. next section).

9.2. Computation rules for time spent in-, below- and above- target ranges

The algorithm can be adjusted to:

- Targeted range of glucose values: lower and upper limit,
- Specified time interval: start time and end time for analysis.
- Maximum allowed duration (min) between 2 records (30 min by default)

After replacement of missing data flagged as "Out of Physiological Range", the algorithm will automatically compute time in-, below- or above- the targeted range of glucose values for the given duration.

Example 1: Referring to figure 2, for the period between the start point and the end point, the algorithm gives the following results:

- Hyperglycemia: 0.5 + 2 = 2.5 hours
- Euglycemia: 4 + 2 = 6 hours
- Hypoglycemia: 2 hours
- Non-replaced missing data: 2 hours

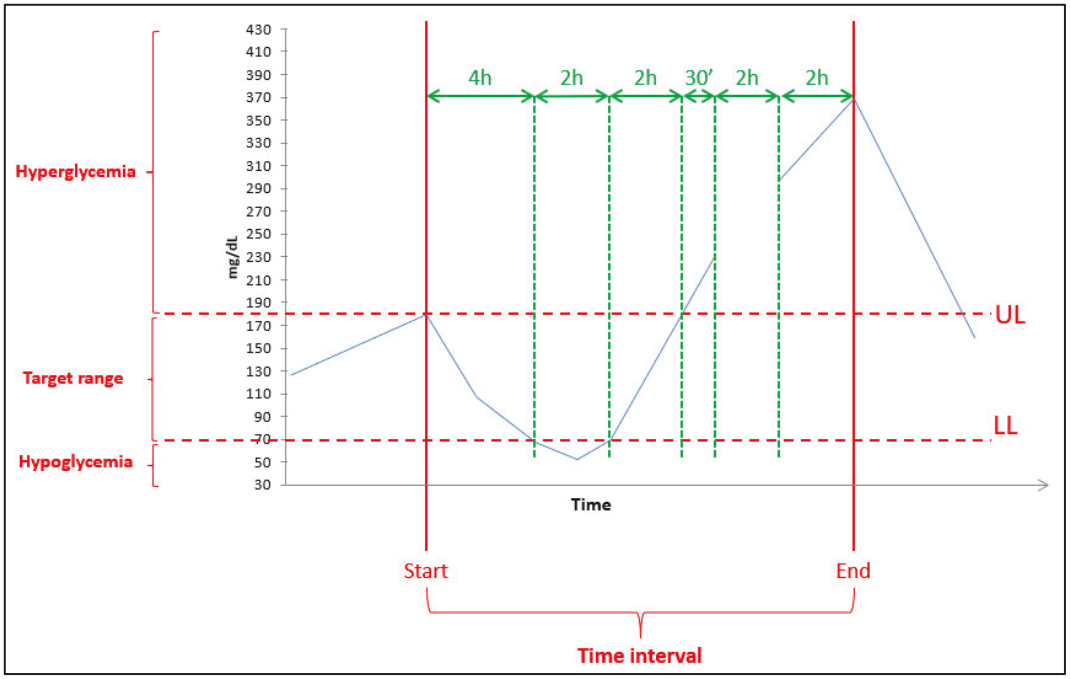


Figure 2. Pattern for computation rules

Example 2:

Assuming we have the following data for a patient after running the algorithm and for a period of 24h:

- Hyperglycemia: 4 hours
- Euglycemia: 14 hours
- Hypoglycemia: 2 hours
- Non-replaced missing data: 4 hours

Computation of time spent in range values gives the percentage of time in:

- Hyperglycemia: (4/20)*100 = 20%
- Euglycemia: (14/20)*100 = 70%
- Hypoglycemia: (2/20)*100 = 10%.

Availability of sensor data: (20/24)*100 = 83%.

10. CHANGES IN THE STATISTICAL METHODS FROM THOSE STATED IN THE PROTOCOL

This Statistical Analysis Plan is based on Protocol V5.0 dated of 11/12/2018 and CRF V2.0.1 dated 24/04/2019.

Clarification about Section 14.4 of the Protocol:

It is stated in the Protocol, Section 14.4 (Analysis of the primary endpoint for cohort 2) : "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".

Since the primary endpoint of cohort 2 is a continuous data, Poisson distribution is not appropriate (Poisson is appropriate for count data only).

Therefore, this sentence has been interpreted in the SAP as follows: "In case of non-normal distribution, a study will be done in order to use either a model based on **non-normal parametric distribution** or a non-parametric test approach".

Analysis planned in the Protocol not performed:

It is stated in the Protocol, Section 14.6 (Safety analysis): "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".

ADEs leading to replacement of device will not be analyzed, as it was not collected in the eCRF whether ADE led to replacement of device or not.

There are no other changes in the statistical methods from those stated in the protocol.

11. QUALITY CONTROL

A self-validation will be performed by the statistician in charge of the analysis as follows: each derived variables will be validated exhaustively (i.e. on all patients) whenever possible. Exhaustive controls can be performed using either contingency tables (i.e. displaying all qualitative variables and minimum/maximum values of quantitative variables involved in the derivation rules) or individual data listings that are considered as not too large (i.e. no more than 50 rows). An exhaustive control is considered possible when the corresponding output contains up to 50 rows. For validation outputs considered as too large (i.e. more than 50 rows), the validation can be performed on a minimum of 5% patients randomly drawn. If the validation output is still too large (i.e. more than 50 rows), the validation will be performed on a subset of 50 rows (minimum).

Validation outputs will be review by a third party (i.e. head of biostatistics or another statistician).

In particular, derivation of the primary endpoint will be double-checked by a third party (i.e. head of biostatistics or another statistician).

12. References

1. *Toward Defining the Threshold Between Low and High Glucose Variability in Diabetes.* **Louis Monnier, Claude Colette, Anne Wojtusciszyn, Sylvie Dejager, Eric Renard, Nicolas Molinari, David R. Owens.** 7, Diabetes Care Jul 2017, Vol. 40, pp. 832-838.

2. *Are risk indices derived from CGM interchangeable with SMBG-based indices?* **Fabris C, Patek SD, Breton MD.** 2015, J Diabetes Sci Technol., pp. 50-59.