SATURN – ALMED-19-001

Study Protocol

Title

Evaluation of satisfaction regarding home healthcare provider (PSAD) management of type 1 diabetic patients equipped with the "closed-loop" automated insulin delivery system (or "artificial pancreas"), under normal conditions of use.

NCT number

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PROTOCOL

Reference number: ALMED-19-001

Acronym: SATURN

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Evaluation of satisfaction regarding home healthcare provider (PSAD) management of type 1 diabetic patients equipped with the "closed-loop" automated insulin delivery system (or "artificial pancreas"), under normal conditions of use.

RCB-ID number: 2019-A02469-48

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Title of the study: Evaluation of satisfaction regarding home healthcare provider (PSAD) management of type 1 diabetic patients equipped with the "closed-loop" automated insulin delivery system (or "artificial pancreas"), under normal conditions of use.

Final version Protocol No. 3.0 of 01/19/2021 - English version of 04/19/2021

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Final Version Protocol 3.0 of 19/01/2021

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INVESTIGATOR'S OBLIGATION

Title of the study: Evaluation of satisfaction regarding home healthcare provider (PSAD) management of type 1 diabetic patients equipped with the "closed-loop" delivery system (or "artificial pancreas"), under normal conditions of use.

By signing below, I confirm that I agree:

- To conduct the study in accordance with the Protocol, the Clinical Best Practices (CBP), the study's specific procedures and the regulations in effect.
- To train the personnel involved in the study and document any delegation of tasks within the framework of this study. In the event of personnel changes during the course of the study, I undertake to inform the sponsor.
- To comply with the recommendations set forth in the user manuals for the "closed-loop" automated insulin delivery systems (or "artificial pancreas").
- To adhere to the procedures and regulations related to data recording, including serious adverse events.
- To authorise direct access to source data for monitoring purposes as well as for audit or inspection.
- To retain the essential documents relating to the study for a period of 15 years from the date of the last publication.
- Not to present or publish the study data without the prior authorisation of the sponsor.

In addition, I hereby confirm that I have and will have the human and material resources needed to conduct this study.

Name and Title	**Contact Information**
Date	**Signature**
___/___/_____	

CONTACT

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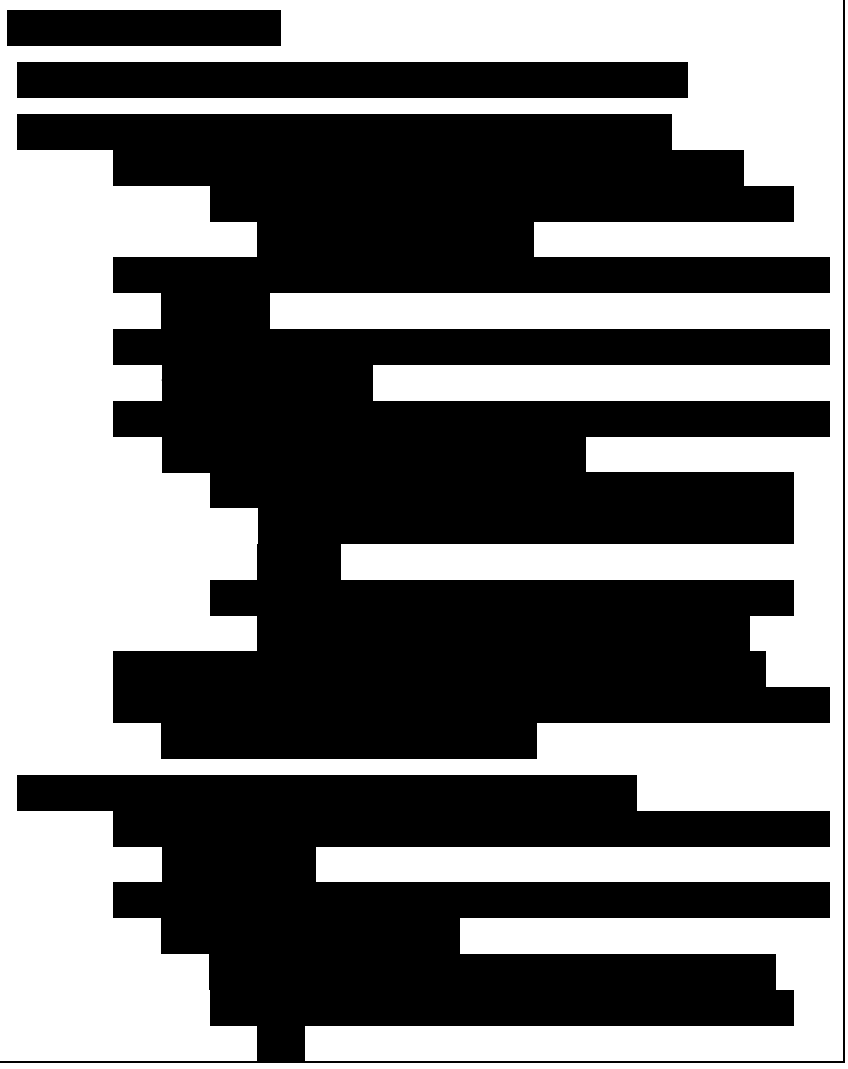
SYNOPSIS

Title	Evaluation of satisfaction regarding home healthcare provider (PSAD) management of type 1 diabetic patients equipped with the "closed-loop" automated insulin delivery system (or "artificial pancreas"), under normal conditions of use.
Acronym	SATURN
Protocol number	ALMED-19-001
Sponsor	AIR LIQUIDE SANTE INTERNATIONAL
Clinical Research Organisation (CRO)	[redacted]
Coordinating Investigator	Prof. Hélène Hanaire Hôpital de Rangueil Service de Diabétologie - Maladies métaboliques - Nutrition 1 Avenue du Professeur Jean Poulhès - TSA 50032 31059 Toulouse Cedex 9
Centres	2 hospital centres in France <u>List of investigators:</u> - Prof. Hélène Hanaire, Toulouse University Hospital Hôpital Rangueil, Toulouse - Dr Lucy Chaillous, Hôpital Nord, Nantes
Number of patients	35 patients included, in order to have 32 evaluable patients
Study context and rationale/ Medical Device	Type 1 diabetes is an auto-immune disease characterised by chronic hyperglycaemia (blood glucose levels are too high), caused by the destruction of pancreatic beta cells of islets of Langerhans, which therefore no longer produce insulin. The absence of insulin prevents the body from storing and using glucose, exposing the individual to a major risk of hyperglycaemia. The treatment of type 1 diabetes is based on insulin therapy. For patients, excessive injection of insulin causes an increased risk of hypoglycaemia, especially between meals. Insulin deficiency can lead to diabetes ketoacidosis or even coma. The treatment of type 1 diabetes is based on the administration of insulin multiple times a day to compensate for the body's lack of insulin production. Glucose levels must first be measured, and the doses to be administered must be calculated and adapted to the patient's activities, particularly meals and sporting activities. Glycaemic control is the primary objective in the management of

	patients with type 1 diabetes. The continuous adjustment of insulin doses aims to get as close as possible to normoglycaemia, to avoid hyper and hypoglycaemic surges on a daily basis, and to prevent chronic and degenerative micro and macrovascular complications over the long term, which are the major cause of morbidity and mortality for this pathology. The advent of innovative medical devices such as continuous glucose monitoring systems, which take regular measurements without patients having to prick their fingers, insulin pumps which allow insulin to be continuously delivered via a catheter, and algorithms for calculating the insulin dose, have expedited the development of "closed-loop" automated insulin delivery systems, or the "artificial pancreas". These systems are able to automatically adjust the insulin dose to be injected. The patient continues to record meals eaten and sequences of physical activity, but it is the algorithm that continuously determines the insulin flow rate adjustments. Teaching patients how to use these medical devices is essential and indispensable for their proper functioning, and includes proficiency in the system's three components (pump, sensor and control module/terminal), understanding the messages of the control module/terminal, and the ability to respond to system failures and switch to manual mode. In addition, providing support to diabetic patients throughout their treatment ensures the proper use of medical devices and guarantees their effectiveness in both the short and long term. This study will be used to assess the support given by home healthcare providers (PSADs) to type 1 diabetic patients using a "closed-loop" automated insulin delivery system (or "artificial pancreas"), and specifically the satisfaction of the various people involved (patients, PSADs, hospital healthcare teams) and their interactions. Among the "closed-loop" automated insulin delivery systems (or "artificial pancreas") that have obtained CE marking, the study will focus on: - [redacted]
Population concerned	Adult type 1 diabetic patients for whom the investigator proposes the use of a "closed-loop" automated insulin delivery system (or "artificial pancreas").

Methodology	National, multi-centre, longitudinal, non-comparative interventional study with minimal risks and constraints (RIPH2).
Objectives	Primary objective: To assess satisfaction and experience regarding home healthcare provider (PSAD) management after 1 and 3 months of follow-up (D30 and D90) of type 1 diabetic patients equipped with a "closed-loop" automated insulin delivery system (or "artificial pancreas"), under normal conditions of use. Secondary objectives: *Home healthcare provider (PSAD) management:* o To describe home healthcare provider management (number, type, time and reasons for interaction), according to the various phases of installing a "closed-loop" automated insulin delivery system (pre-installation, installation, post-installation). o To compare the management observed with the theoretical management set out in the opinion of the HAS (French National Authority for Health) dated 28 January 2020 for the [redacted] system using the reimbursement record for the "closed-loop" automated insulin delivery system (or "artificial pancreas"). This reference document will be extrapolated/applied to all the "closed-loop" systems used in the study. o To assess the knowledge acquired by the patient during their technical training, on D1/D3, D30 and D90. o To describe the satisfaction of the PSAD nurses at the end of the study. *Patient questionnaire:* o To describe the patient's profile in terms of their experience with medical devices, at the time of inclusion, and their feelings about their current and future state of health, at inclusion and on D90, in order to contextualise the level of patient satisfaction. o To describe the quality of life of patients and the daily constraints faced by the patient, at inclusion, on D30 and on D90, in order to measure the effects of management with a "closed-loop" automated insulin delivery system (or "artificial pancreas") and PSAD services on the patient's quality of life. o To describe the relation to the "closed-loop" automated insulin delivery system (or "artificial pancreas"), the benefits expected at inclusion and those perceived on D30 and D90, in order to measure the impact of the management on the patient's autonomy and the reduction of their mental load. *Investigator questionnaire:* o To describe the satisfaction, assessed at the end of the study, of hospital healthcare teams with patient management by PSADs in

	the pre-installation/installation and 3-month follow-up phases, under the conditions of use of a "closed-loop" automated insulin delivery system (or "artificial pancreas"). ○ To describe, at the end of the study, the interactions between hospital healthcare teams and PSADs in terms of frequency and satisfaction. ○ To describe, at the end of the study, the benefit of the data visualisation platform for investigators, in order to improve patient follow-up. *Safety:* ○ To describe the safety profile of patients after 3 months of follow-up with the "closed-loop" automated insulin delivery system (or "artificial pancreas"). *Clinical course:* ○ To describe the patient's clinical profile (metabolic balance) and its evolution, at inclusion, and on D30 and D90, in order to contextualise the study results. 

	[redacted]
Questionnaires	*Patient questionnaires:* *The following validated questionnaires will be used:* ○ **CSQ-8** Questionnaire: Measures patients' overall satisfaction with their management in general. ○ **EQ-5D-5L** Questionnaire: Measures the patient's quality of life in the context of using a "closed-loop" automated insulin delivery system (or "artificial pancreas"), in terms of the impact on their activities (mobility, self-care, usual activities, , pain/discomfort, anxiety/depression). ○ **HFS-II** (**Hypoglycaemia Fear Survey-II**) questionnaire: Measures quality of life and daily constraints with respect to hypoglycaemia-related behaviours and concerns in adults with type 1 diabetes. ○ **BMQ** (**Beliefs about Medicines Questionnaire**) Questionnaire: The specific section of this questionnaire will be used. It describes the patient's perception of the Medical Device (MD) in a wider sense. *The following ad-hoc questionnaires, developed by the French Federation of Diabetics (FFD), will be used:* ○ Questionnaire entitled "**You and medical devices**": This is used to determine the patient's profile with regard to their experience with medical devices. ○ Questionnaire entitled: "**You and your health**": This assesses the patient's feelings about their current and future state of health. ○ Questionnaire entitled: "**You and your daily constraints**": This assesses the daily constraints encountered by the patient in the past month based on a pre-established multiple-choice list. ○ Questionnaire entitled "**You and the "closed-loop" automated insulin delivery system (or "artificial pancreas")**": This assesses

	the expected and perceived benefits of the "closed-loop" automated insulin delivery system (or "artificial pancreas"). o Questionnaire entitled "**You and your management by your home healthcare provider**": This measures patients' targeted experience / satisfaction with their management by the PSADs during the follow-up period. *Investigator satisfaction questionnaire:* This is a five-part ad-hoc questionnaire developed by the sponsor: o General questions about the study and the "closed-loop" automated insulin delivery system (or "artificial pancreas") o Assessment of the follow-up conducted by the PSAD nurse during the initial period, i.e. before the patient returns home o Assessment of the follow-up conducted by the PSAD nurse after the patient returns home o Overall satisfaction o Access to data and use of the data visualisation platform. *PSAD satisfaction questionnaire:* The satisfaction of PSAD nurses is assessed using an ad-hoc questionnaire developed by the sponsor, which relates to the training received on the "closed-loop" automated insulin delivery system (or "artificial pancreas"), logistical aspects associated with the equipment, the quality of the products, use of the medical device, the relevance of the follow-up Protocol offered to the patient and relationships with the hospital service.
Evaluation criteria	<u>Primary criterion:</u> Patient satisfaction and experience are assessed by 2 questionnaires, on D30 and D90: the **CSQ-8** questionnaire and the "**You and your management by your home healthcare provider**" questionnaire. With the **CSQ-8**, the patients' overall satisfaction with their management in general is determined by a score above 20 points (on a scale from 8 to 32) on D30. Maintenance of satisfaction is measured on D90 by a score above 20 points which has not decreased by more than 4 points compared with D30. The safety profile with the questionnaire "**You and your management by your home healthcare provider**". The answers to all questions with 5 possible choices and the scores based on the scales from 1 to 10 will be described. <u>Secondary criteria:</u> *Home healthcare provider (PSAD) management:* o PSAD management is described during the different phases (pre-installation, installation, follow-up), by the number of interactions, their type (visits / telephone calls), the time spent, the reason for these interactions and, for the visits, by their location (home / hospital).

	○ The management observed is also described for all the "closed-loop" systems used in the study according to whether or not these interactions were set out in the opinion of the HAS (French National Authority for Health) dated 28 January 2020 for the [redacted] system, and is therefore compared with the management initially scheduled for conducting the study (number of visits or telephone calls made versus those scheduled). ○ The knowledge acquired by the patient during their initial training is evaluated by the PSAD nurse using the acquired knowledge assessment questionnaire on D1/D3, D30 and D90. ○ The satisfaction of the PSAD nurses is assessed with the **PSAD satisfaction questionnaire**. This questionnaire is completed once by each PSAD nurse at the end of the study (after the D90 of the last patient at the centre). It takes into account the PSAD nurse's opinion on all of the services they provide. *Patient questionnaires:* ○ The patient's profile in terms of their experience with medical devices is assessed by the "**You and medical devices**" questionnaire completed at the time of inclusion. ○ The patient's feelings about their current and future state of health are assessed by the "**You and your health**" questionnaire completed at inclusion and on D90. ○ The patient's quality of life is assessed by the **EQ-5D-5L** questionnaire, at inclusion, on D30 and D90. The daily constraints encountered by the patient are assessed based on the past month, with the question "**You and your daily constraints**", at inclusion, on D30 and on D90. ○ Quality of life and daily constraints related to the risk of hypoglycaemic episodes are assessed by the HFS-II questionnaire at inclusion, on D30 and D90. ○ The expected and perceived benefits with respect to the "closed-loop" automated insulin delivery system (or "artificial pancreas") are assessed by the questionnaire "**You and the "closed-loop" automated insulin delivery system (or "artificial pancreas")**", completed at inclusion, on D30 and D90. ○ The patient's beliefs related to the medical treatment are assessed by the specific section of the **BMQ** (**Beliefs about Medicines Questionnaire**) questionnaire, at inclusion, on D30 and D90. *Investigator satisfaction questionnaire:* This questionnaire is completed once by each investigator at the end of the study (after the last patient has left the centre). It takes into account the investigator's opinion on all of their included patients.

	Safety: The safety profile of patients with a "closed-loop" automated insulin delivery system (or "artificial pancreas") is described according to: ○ All serious adverse events (SAEs) and non-serious adverse events, both related and unrelated to the "closed-loop" automated insulin delivery system (or "artificial pancreas"), whether expected or unexpected. ○ Episodes of severe hypoglycaemia requiring the intervention of a third party for glucose administration. ○ Episodes of hyperglycaemia with ketosis. ○ All incidents related to the "closed-loop" automated insulin delivery system (or "artificial pancreas"). *Clinical course:* The patient's clinical profile and its evolution are described by the values of: ○ HbA1c, measured at the time of installation and on D90. ○ Daily average blood sugar level and its variability (standard deviation and coefficient of variation, if applicable) at inclusion, on D30 and D90. ○ Percentage of time spent over a 4-week period: in the blood sugar target [70-180 mg/dl], in hypoglycaemia (< 70 mg/dl) and in hyperglycaemia (> 180 mg/dl) at inclusion, on D30 and D90. ○ Percentage of time spent using a closed-loop system over a 4-week period, if available, on D30 and D90. [redacted]

	[redacted]
Selection of the patients	Inclusion criteria: 1. Type 1 diabetic patient diagnosed for at least 2 years 2. Patient treated with an external insulin pump for at least 6 months 3. Patient with an HbA1c level less than or equal to 10% in the past 4 months (assay performed in a medical analysis laboratory or equivalent) 4. Patient with U-100 rapid-acting insulin (Novorapid or Humalog) requirements between the upper and lower bounds set by the pump of the "closed-loop" automated insulin delivery system (or "artificial pancreas") 5. Patient who is not isolated, who does not live alone or who has a "resource" person living nearby with his/her own telephone and a key to the patient's house 6. Patient living in an area covered by a GSM (Global System for Mobile Communications) network and not planning to travel outside France or outside an area covered by a GSM network

	within 30 days of the "closed-loop" automated insulin delivery system (or "artificial pancreas") being installed 7. Patient at least 18 years old and whose age complies with the eligibility criteria for each medical device of the "closed-loop" automated insulin delivery system (or "artificial pancreas") 8. Patient registered with a Social Security scheme 9. Patient who has agreed to comply with the requirements of the study and has signed the free and informed consent form 10. Patient who the investigator deems capable of using a "closed-loop" automated insulin delivery system (or "artificial pancreas") under normal conditions of use <u>Exclusion criteria:</u> 1. Patient with any serious pathology that could affect their participation in the study 2. Patient undergoing treatment that could affect the physiology of diabetes, i.e., that leads to interactions with glucose and/or insulin, in the investigator's judgement 3. Patient benefiting from a legal protection measure 4. Pregnant or breastfeeding women 5. Absence of contraception deemed effective by the investigator for a woman of childbearing age 6. Psychological and/or physical state which could affect the proper monitoring of the study procedures 7. Severe hypoglycaemia which has led to convulsions or a loss of consciousness in the last 12 months 8. Decrease in the perceived sensation of hypoglycaemia, in the investigator's judgement 9. Impaired renal function (creatinine clearance < 30 ml/min measured in the last 6 months) 10. Patient who has had a pancreas or pancreatic islet transplant 11. Patient with serious uncorrected hearing and/or visual problems 12. Patient included in another clinical study or who has taken part in another clinical study in the last 30 days
Conduct of the study	Patients will be monitored for a period of 3 months, starting from the end of the device installation procedure. The management proposal consists of three distinct phases: pre-installation, installation and follow-up. During these three phases, the number and duration of interactions (visits/telephone calls) may vary according to the patient's needs, the investigator's judgement and practice, and the judgement of PSAD staff. Two French hospitals and their PSAD representatives, whose contact details are provided on the investigator list, will participate in the study. **Pre-installation phase:** The pre-installation phase will be conducted in two stages:

	- The patient inclusion visit in the hospital centre, when the patient will give their free and informed consent, and the investigator will submit the request for management and initiation by the PSAD. - Pre-installation visit(s) by a PSAD nurse at the investigator's request. This period corresponds to the patient's management by the PSAD via one or two home visits to introduce the patient to the system, and assess their motivation and their ability to use the medical device. **Installation phase:** The "closed-loop" automated insulin delivery system (or "artificial pancreas") will be installed during a scheduled hospital stay (or outpatient visits) in the hospital centre for a variable duration, estimated between 2 and 3 days. At the prescriber's request, the sensor can be installed prior to installing the complete "closed-loop" automated insulin delivery system (or "artificial pancreas"), and this can be done either in hospital by hospital staff or at the patient's home during a pre-installation visit by the PSAD nurse. The estimated number of visits carried out by the PSAD is between 1 and 3 during the installation phase, including at least one visit to the hospital centre. **The pre-installation and installation phases** include at least 2 patient visits to the hospital centre, and 2 to 5 visits by the PSAD (at home and in the hospital centre). The PSAD's role is to provide the patient with initial technical training. This training will be assessed by the PSAD (questionnaire) and will be followed by written feedback to the investigator (prescriber). The end of the patient's hospitalisation and their return home, i.e. the end of the installation phase, shall be considered to be D0 for patient follow-up. **Follow-up phase (post-installation):** - Post-installation early follow-up between D1/D3: This follow-up will be carried out by the PSAD nurse via a home visit or telephone call. It will be used to check that the patient has mastered how to use their device (thorough understanding and correct use of the "closed-loop" automated insulin delivery system (or "artificial pancreas")). - Home visit for the first sensor change by the PSAD nurse: The PSAD nurse will conduct this follow-up to provide refresher training on best practices for the use of the pump and sensor and to assist with changing the first glucose sensor. - Follow-up one month after installation (D30):

	This follow-up will be carried out by the PSAD nurse via a home visit or telephone call. It is recommended to provide refresher training and assess the patient's acquired knowledge. The investigator will also conduct a patient follow-up on D30 by visiting the patient in the hospital or consulting by telephone. They will collect the metabolic balance over a 4-week period and assess the patient's continued use of the system via the data visualisation platform. - <u>Follow-up at 3 months:</u> ▪ <u>Home visit on D90 by the PSAD nurse</u>: The PSAD nurse carries out this home visit to assess the patient's knowledge (continuous technical training and reminder of the initial technical training) and confirm their best practices. This visit should be carried out before the patient's end-of-study visit at the centre. ▪ <u>End-of-study visit (D90) by the investigator at the hospital centre:</u> The patient will visit the hospital service for the end-of-study visit, which will include a medical check-up (patient's metabolic balance, efficiency, safety), assessment of the continued use of the system and assessment of the patient's satisfaction and experience. In theory, 3 visits or telephone calls by PSAD staff are scheduled during the first month of post-installation follow-up as part of the patient's overall initial training, plus a visit at 3 months.
Duration of the study	• Planned start of the study: Q4 2019 • Inclusion of the patients: Q1 2021-Q4 2021 • Patient follow-up: 3 months from the date the device is installed, at the patient's home End of the study (last visit of the last patient to leave the study): Q1 2022
Justification for the number of subjects	For reasons of feasibility, the number of patients to be included in the study was set at 35, for a number of expected evaluable subjects fixed at 32. Should any patients leave the study between the time of inclusion and the beginning of the fitting with the closed-loop automatic insulin delivery system (or artificial pancreas), they shall be replaced. This number of patients will be sufficient to estimate the percentage of patients satisfied on D90 with their management by the PSAD (the primary objective of the study), with an accuracy of ≤ 12.4%. In fact, whatever the criterion considered (satisfaction estimated from the CSQ-8 and satisfaction assessed from the answers to the various questions in the questionnaire "You and your management by your home healthcare provider" on D90), the expected percentage

	of satisfied patients is ≥ 85%. The formula used to estimate the accuracy is obtained from the definition of the 95% bilateral confidence interval (CI 95%) for a proportion, with normal approximation $E = \sqrt{(1.96^2\ p\ (1\text{-}p)\ /\ n)}$ With n=32 evaluable patients, the accuracy will therefore be ≤ 12.4%.
Statistical methodology	The reference population for the statistical analysis will be all of the included patients, fitted with the device who meet all of the inclusion and exclusion criteria. <u>Analysis of the primary criterion:</u> The overall CSQ-8 score will be calculated at each time of assessment. The percentage of patients satisfied on D30 and D90 and the percentage of patients with continued satisfaction on D90 will be described. The 95% confidence intervals (CIs) will also be presented. The absolute variation of the overall CSQ-8 score and the relative variation in relation to D30 will also be described on D90. The answers to all the items in the "**You and your management by your home healthcare provider**" questionnaire will be described using percentages for the questions with 5 possible choices. Scores based on the scales from 1 to 10 will be presented using descriptive statistics. <u>Analysis of the secondary criteria:</u> A descriptive statistical analysis of all the secondary parameters will be carried out as a whole and according to the study phase when applicable (pre-installation, installation and follow-up). All questionnaire items will be described using descriptive statistics and scores where applicable. The evolution of HbA1C will be described at the end of the study. Blood sugar parameters will be described at inclusion, on D30 and D90. To describe patient safety, the incidence rate of all adverse events and serious adverse events (SAEs), and those related to the "closed-loop" automated insulin delivery system (or "artificial pancreas"), will be presented as a whole and by "System Organ Class" and "Preferred term" in the MedDRA terminology. The number of episodes of severe hypoglycaemia requiring the intervention of a third party for glucose administration and the number of episodes of hyperglycaemia with ketosis will also be described. In addition, the number of incidents associated with the device will be described.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADE	Adverse Device Effect
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé [French National Agency for Medicines and Health Products Safety]
CRA	Clinical Research Associate
BLE	Bluetooth Low Energy
BMQ	Beliefs about Medicines Questionnaire
CBP	Clinical Best Practices
CE	European Conformity
CGM	Continuous Glucose Monitoring
CNIL	Commission Nationale de l'Informatique et des Libertés [French Data Protection Authority]
CNOM	Conseil National de l'Ordre des Médecins [French National Medical Council]
CPP	Comité de Protection des Personnes [French Ethics Committee]
CRF	Case Report Form
CRO	Contract Research Organisation
CSP	Code de la Santé Publique [French Public Health Code]
CSQ-8	Client Satisfaction Questionnaire (Overall Satisfaction)
CV	*Curriculum Vitae*
[redacted]	[redacted]
MD	Medical Device
e-CRF	Electronic Case Report Form
SAE	Serious Adverse Event
EQ-5D-5L	Quality of life questionnaire
FFD	Fédération Française de Diabétologie [French Federation of Diabetics]
GSM	Global System for Mobile Communications
HbA1C	Glycated haemoglobin
HFS	Hypoglycaemia Fear Survey
CI	Confidence Interval
ICTA	International Clinical Trial Association
InVS	Institut de Veille Sanitaire [French National Institute for Public Health Surveillance]
MRI	Magnetic Resonance Tomography
ISF	Investigator Site File

D	Day
MedDRA	Medical Dictionary for Regulatory Activities
mg/dl	Milligram / Decilitre
ml/min	Millilitre/Minute
MR-001	Reference Methodology - 001
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedures
Pre-Inst.	Pre-Installation
PSAD	Prestataire de Santé à Domicile [Home Healthcare Provider]
GDPR	General Data Protection Regulation
RIPH	Recherche Impliquant la Personne Humaine [Research Involving Human Subjects]
SAS	Statistical Analysis System
TMF	Trial Master File
USADE	Unanticipated Serious Adverse Device Effect

I - INTRODUCTION

I.1 - BACKGROUND

Pathology

Type 1 diabetes is an auto-immune disease characterised by chronic hyperglycaemia (blood glucose levels are too high), caused by the destruction of pancreatic beta cells of islets of Langerhans, which therefore no longer produce insulin. The absence of insulin prevents the body from storing and using glucose, exposing the individual to a major risk of hyperglycaemia.

The treatment of type 1 diabetes is based on insulin therapy. For patients, excessive injection of insulin causes an increased risk of hypoglycaemia, especially between meals. Such hypoglycaemia can be severe and lead to coma.

In contrast, the absence of insulin followed by a meal or even an insufficient dose of insulin in relation to a meal containing carbohydrates can lead to a hyperglycaemic situation. Insulin deficiency can lead to diabetes ketoacidosis or even coma.

Type 1 diabetes accounts for approximately 10% of all diabetes cases and one half of the cases occur in children or young adults. In France, the incidence of type 1 diabetes is approximately 15 cases in 100,000 children under the age of 15. According to the projection model produced by the French National Institute for Public Health Surveillance (InVS) on the number of diabetic patients treated in 2006, the number of type 1 diabetic patients in metropolitan France in 2016 is estimated at between 130,000 and 139,000 (1).

The proportion of patients treated pharmacologically with antidiabetic medication is rising steadily in France, with 3,587,262 patients treated in 2016 and 3,638,223 in 2017, according to Open Data from France's National Health Insurance System (2) (3). Diabetes is now the second leading cause of cerebrovascular accidents in France and the leading cause of amputation (4). Mortality and the rate of sequelae related to complications from diabetes remain very high despite the optimisation of emergency care management (5). Indeed, with 11,675 deaths where diabetes was the main cause, this pathology accounted for 2.1% of all deaths in France in 2009. Cardiovascular pathologies are said to be responsible for two thirds of deaths, and renal complications are the second leading cause of death in diabetic patients (6). In economic terms, €19 billion of healthcare expenditure was allocated to diabetic patients (diabetes-related or not) in 2014, representing 15% of National Health Insurance expenditure (7). Therefore, owing to its prevalence, the complexity of its management, the frequency and severity of its short- and long-term complications and the associated mortality, diabetes has a major impact on public health (6). As such, diabetes is currently a priority for the development of innovative strategies to optimise its management and patient care pathway.

Treatment

The treatment of type 1 diabetes is based on the administration of insulin multiple times a day to compensate for the body's lack of insulin production. Glucose levels must first be measured, and the doses to be administered must be calculated and adapted to the patient's activities, particularly meals and sporting activities. Glycaemic control is the primary objective in the management of patients with type 1 diabetes. The blood sugar goal advised in most recommendations is an HbA1c level of less than 7% (8). The continuous adjustment of insulin doses aims to get as close as possible to normoglycaemia, to avoid hyper and hypoglycaemic surges on a daily basis, and to prevent chronic and degenerative microvascular (retinopathy, nephropathy, neuropathy, etc.) and macrovascular (coronary heart disease, cerebrovascular disease, peripheral arterial disease, etc.) complications over the long term, which are the major cause of morbidity and mortality for this pathology.

The best technique routinely available at present is continuous insulin pump therapy with a rapid-acting insulin analogue. Customised algorithms, whose patient-specific parameters are related to base flow rates, carbohydrate requirements and physical activity, have also been developed and are available. Nonetheless, these techniques cannot be used to manage what is often a very high level of variability from one day to the next, and it is currently difficult to achieve complete and prolonged glycaemic control (9); the risk of hypoglycaemia is reduced, but is not zero (10).

The pairing of innovative medical devices, such as insulin pumps with continuous glucose sensors, which take regular measurements without patients having to prick their finger, and algorithms for calculating insulin doses, has expedited the development of “closed-loop” automated insulin delivery systems (or “artificial pancreas"). Data from randomised studies comparing artificial pancreas systems to the standard pump and sensor treatment show that time spent in the normoglycaemic target is increased by around 10% and time spent in hypoglycaemia is halved (11) (12) (13).

I.2 - MEDICAL DEVICES

In this study, patients are fitted with a "closed-loop" automated insulin delivery system (or "artificial pancreas") that has obtained CE marking.

Several of these systems have been successfully developed and tested in patients with type 1 diabetes. Despite their varied clinical and technical factors, they have improved glycaemic control and helped reduce the time spent in hypoglycaemia (14).

Among the “closed-loop” automated insulin delivery systems (or “artificial pancreas”) that have obtained CE marking, the study will focus on:

[redacted]

[redacted]

I.3 - STUDY RATIONALE

As with any chronic disease, therapeutic adherence is one of the key aspects of patient management. The effectiveness of diabetes treatment requires the patients' therapeutic adherence. Management must therefore take into account psychological aspects, including patient satisfaction, well-being and quality of life, as well as their understanding of the disease.

Patients play a key role in diabetes treatment because they are responsible for adapting their daily activities to the constraints imposed upon them by the disease. Indeed, they must consider diet, physical activity, blood sugar levels and the administration of medication (comorbidities, etc.). This self-management is a complex activity since it involves being able to monitor one's state of health and having the cognitive, behavioural and emotional reactions necessary to maintain balance and a satisfactory quality of life. While care and education have become increasingly patient-centred, many patients still struggle to maintain an appropriate level of self-management (22).

Improving patient satisfaction through high-quality care and support is necessary to help patients and improve their capacity for self-reliance, their adherence to the treatment and therefore promote long-term glycaemic stability, with the aim of reducing the risk of developing diabetes-related complications.

In addition, for optimal effectiveness, devices must be well tolerated by patients. Some patients do not accept new technologically-advanced alternatives and many studies have reported either discontinued treatment or interrupted use. Possible reasons for discontinuing or interrupting use are the differences between the clinicians' and patients' perceptions of the associated advantages and disadvantages (23).

Teaching patients how to use the medical device is essential and indispensable to its proper functioning, and to limiting the risks of hypoglycaemia and/or hyperglycaemia. In addition, providing support to diabetic patients throughout their treatment ensures the proper use of the medical device and guarantees its effectiveness in both the short and long term.

This study will be used to assess the support given by PSADs to type 1 diabetic patients using a "closed-loop" automated insulin delivery system (or "artificial pancreas"), and specifically the satisfaction of the various people involved (patients, PSADs, hospital healthcare teams) and their interactions.

II - OBJECTIVES OF THE STUDY

II.1 - PRIMARY OBJECTIVE

The primary objective of the study is to assess the satisfaction and experience of type 1 diabetic patients equipped with a "closed-loop" automated insulin delivery system (or "artificial pancreas"), as regards home healthcare provider (PSAD) management after 1 and 3 months of follow-up (D30 and D90), under normal conditions of use.

II.2 - SECONDARY OBJECTIVES

The secondary objectives of this study are as follows:

Home healthcare provider (PSAD) management

- To describe home healthcare provider management (number, type, time and reasons for interaction), according to the various phases of installing a "closed-loop" automated insulin delivery system (pre-installation, installation, post-installation).
- To compare the management observed for all the “closed-loop” systems used in the study with the theoretical management described in the opinion of the HAS dated 28 January 2020 for the [redacted] system using the medical device's reimbursement record.
- To assess the knowledge acquired by the patient during their technical training, on D1/D3, D30 and D90.
- To describe the satisfaction of the PSAD nurses at the end of the study.

Patient questionnaires

- To describe the patient's profile in terms of their experience with medical devices, at the time of inclusion, and their feelings about their current and future state of health, at inclusion and on D90, in order to contextualise the level of patient satisfaction.
- To describe the quality of life of patients and the daily constraints faced by the patient, at inclusion, on D30 and on D90, in order to measure the effects of management with a "closed-loop" automated insulin delivery system (or "artificial pancreas") and PSAD services on the patient's quality of life.
- To describe the relation to the "closed-loop" automated insulin delivery system (or "artificial pancreas"), the benefits expected at inclusion and those perceived on D30 and D90, in order to measure the impact of the management on the patient's autonomy and the reduction of their mental load.

Investigator questionnaire

- To describe the satisfaction, assessed at the end of the study, of hospital healthcare teams with PSAD patient management in the pre-installation/installation and 3-month follow-up phases, under the conditions of use of a "closed-loop" automated insulin delivery system (or "artificial pancreas").
- To describe, at the end of the study, the interactions between hospital healthcare teams and PSADs in terms of frequency and satisfaction.
- To describe, at the end of the study, the benefit of the data visualisation platform for investigators, in order to improve patient follow-up.

Safety

- To describe the safety profile of patients after 3 months of follow-up with the "closed-loop" automated insulin delivery system (or "artificial pancreas").

Clinical course

- To describe the patient's clinical profile (metabolic balance) and its evolution, at inclusion, on D30 and on D90, in order to contextualise the study results.

[redacted]

III - STUDY MODEL

This is a national, multi-centre, longitudinal, non-comparative interventional study with minimal risks and constraints (RIPH2), conducted on patients with type 1 diabetes for whom a "closed-loop" automated insulin delivery system (or "artificial pancreas") has been prescribed.

This study will be conducted in two hospital centres in France. Each centre will work in close collaboration with a PSAD representative.

Investigators, hospital teams and PSAD nurses have been trained in the "closed-loop" automated insulin delivery system (or "artificial pancreas") by the system's supplier.

Patient recruitment will take place over a period of approximately 6 months. Recruitment will end once 35 patients are fitted with a "closed-loop" automated insulin delivery system (or "artificial pancreas").

The included patients will be monitored for a period of 3 months, starting from the end of the medical device installation procedure, or once the patient returns home. The management proposal consists of three distinct phases: pre-installation, installation and follow-up.

During these three phases, the number and duration of interactions (visits/telephone calls) may vary according to the patient's needs, the investigator's judgement and practice, and the judgement of PSAD staff.

IV - STUDY POPULATION

IV.1 - ELIGIBILITY CRITERIA

Patient selection is based on the following inclusion and exclusion criteria. Patients who meet all of the inclusion criteria and none of the exclusion criteria are eligible to participate in this study.

IV.1.1 - INCLUSION CRITERIA

1. Type 1 diabetic patient diagnosed for at least 2 years
2. Patient treated with an external insulin pump for at least 6 months
3. Patient with an HbA1c level less than or equal to 10% in the past 4 months (assay performed in a medical analysis laboratory or equivalent)
4. Patient with U-100 rapid-acting insulin (Novorapid or Humalog) requirements between the upper and lower bounds set by the pump of the "closed-loop" automated insulin delivery system (or "artificial pancreas")
5. Patient who is not isolated, who does not live alone or who has a "resource" person living nearby with his/her own telephone and a key to the patient's house
6. Patient living in an area covered by a GSM (Global System for Mobile Communications) network and not planning to travel outside France or outside an area covered by a GSM network within 30 days of the "closed-loop" automated insulin delivery system (or "artificial pancreas") being installed
7. Patient at least 18 years old and whose age complies with the eligibility criteria for each medical device of the "closed-loop" automated insulin delivery system (or "artificial pancreas")
8. Patient registered with a Social Security system
9. Patient who has agreed to comply with the requirements of the study and has signed the free and informed consent form
10. Patient who the investigator deems capable of using a "closed-loop" automated insulin delivery system (or "artificial pancreas") under normal conditions of use.

IV.1.2 - EXCLUSION CRITERIA

1. Patient with any serious pathology that could affect his/her participation in the study
2. Patient undergoing treatment that could affect the physiology of diabetes, i.e., that leads to interactions with glucose and/or insulin, in the investigator's judgement
3. Patient benefiting from a legal protection measure
4. Pregnant or breastfeeding woman
5. Absence of contraception deemed effective by the investigator for a woman of childbearing age
6. Psychological and/or physical state which could affect the proper monitoring of the study procedures
7. Severe hypoglycaemia which has led to convulsions or a loss of consciousness in the last 12 months
8. Decrease in the perceived sensation of hypoglycaemia, in the investigator's judgement
9. Impaired renal function (creatinine clearance < 30 ml/min measured in the last 6 months)
10. Patient who has had a pancreas or pancreatic islet transplant
11. Patient with serious uncorrected hearing and/or visual problems
12. Patient included in another clinical study or who has taken part in another clinical study in the last 30 days.

IV.2 - PATIENT STUDY PERIOD

The study is scheduled to begin in Q1 2021 and patient recruitment will be conducted over a period of approximately 6 months.

Patients will be monitored for a period of 3 months, starting from the end of the device installation procedure, at the patient's home and consequently upon the patient's return home, which is estimated as taking place within 15 ± 10 days of inclusion.

It is therefore estimated that the study will end with the last visit of the last patient to leave the study (Last Patient Last Visit) in Q3 2020.

IV.3 - EARLY TERMINATION OF THE STUDY

Temporary or definitive early termination of the study

The study may be stopped early, either temporarily or definitively, at any time at the request of the sponsor, the French Ethics Committee (CPP) or the relevant authority, the French National Agency for Medicines and Health Products Safety (ANSM). In such a case, the sponsor will inform the investigator of the decision to temporarily or definitively stop the study who must inform the patients as soon as possible. The investigator will complete the e-CRF with the data available on the day the study ends.

The sponsor must report the study's termination to the ANSM and the CPP, in accordance with national regulatory requirements, specifying the reason for this termination.

Early termination of the study for a patient

Patients have the right to withdraw from the study at any time and for any reason, without prejudice to their future medical monitoring. They will then have the device removed. All data collected up to the time they leave the study will be kept for analysis, but no other data concerning them will subsequently be collected.

For each patient, it will be specified whether they terminated the study early for any of the following reasons:

- Adverse event.
- Withdrawal of consent.
- Patient lost to follow-up.
- Non-compliance with at least one inclusion/exclusion criterion.
- Investigator's decision:
    - Patient considered unfit by the investigator
    - Other, to be specified
- Other, to be specified.

In the event of early termination of the study for a patient, the information (date and reason for leaving) will be reported by the investigator in the patient's medical file and entered in the e-CRF. In the event of early termination of the study due to an adverse event, the adverse event will be followed up until it is resolved or stabilised.

V - MEDICAL DEVICES

V.1 - PRESENTATION OF THE "CLOSED-LOOP" AUTOMATED INSULIN DELIVERY SYSTEM (OR "ARTIFICIAL PANCREAS")

In this study, patients will be fitted with a "closed-loop" automated insulin delivery system (or "artificial pancreas").

This system combines 3 medical devices:

- An insulin pump,
- A continuous glucose sensor (CGM),
- And an algorithm that continuously calculates the amount of insulin needed for glycaemic control and controls the insulin pump.

To help keep the patient's glucose levels as close to the desired value (e.g. 120 mg/dl) as possible, and within the target (e.g. between 70 and 180 mg/dl), the CGM measures the glucose concentration approximately every 5 minutes. The measured glucose value is transmitted from the sensor to the algorithm via Bluetooth. The algorithm compares this value with the set target value and calculates:

- Either the insulin requirement based on the difference between the glucose value and the target value. According to the result, the pump's base flow rate adapts to each measurement (increase or decrease).
  In this case, the insulin pump receives the command to deliver the specific quantity of insulin and the subcutaneous injection begins.
- Or the sugar requirement, if the glucose value is lower than the target value.
  The algorithm then prompts a patient alert on the control module/terminal, recommending they ingest a given quantity of sugar and asking them to confirm they have ingested the recommended quantity of sugar.

Glucose concentration measurements continue every 5 minutes and the system ensures the correct decision is made by continuously calculating the amount of insulin needed for glycaemic control and sending this command to the insulin pump. The system is thus able to automatically adjust the dose of insulin to be injected and only requires the patient's intervention for meals or exercise. The patient records their meals, and the algorithm recommends a bolus which they must confirm. The patient records their physical activity, and the algorithm factors this information in to adjust its calculation.

Among the “closed-loop” automated insulin delivery systems (or “artificial pancreas”) that have obtained CE marking, the study will use [redacted]

[redacted]

[redacted]

[redacted]

V.2 - MANAGEMENT AND DISPENSATION OF THE "CLOSED-LOOP"

AUTOMATED INSULIN DELIVERY SYSTEM (OR "ARTIFICIAL PANCREAS")

V.2.1 - DISTRIBUTION – PACKAGING – RECEIPT

Distribution

The sponsor orders the medical devices (MDs) and consumables required to operate the system from the supplier(s) of the "closed-loop" automated insulin delivery system (or "artificial pancreas").

The supplier of the "closed-loop" automated insulin delivery system (or "artificial pancreas") does not supply insulin; the patient must purchase it directly from their retail pharmacy. This also applies to the contents of the first aid kit.

The supplier sends the MDs and consumables to the PSADs in their commercial form with a unique identification number.

Packaging

The equipment (MDs and consumables) is packaged in boxes and identified by a serial and/or batch number.

Each of the components that make up the system can be supplied separately, as replacement equipment and/or consumables.

As such, throughout the study and according to patient needs and PSAD requests, the system supplier(s) will send the consumables and/or replacement equipment to the PSADs in their commercial form.

Receipt

Upon receipt, the PSADs electronically record the boxes received — identified by a unique number — in their information system. The date of receipt is also entered electronically. An acknowledgement of receipt will be sent to the sponsor or their representative and kept in the sponsor's Trial Master File (TMF).

In the event of a defect or damage to the boxes supplied, including the packaging, the PSADs shall inform the supplier within 24 working hours.

In the event of a batch recall, the supplier shall notify the PSADs and indicate the procedure to be followed. The PSADs will inform the sponsor and the investigator.

V.2.2 - LABELLING – STORAGE

Labelling

As the equipment (MDs, consumables and replacement equipment) will be received in its commercial form, the PSADs will label them for exclusive use in a clinical study as soon as they are received.

Storage

The equipment will then be stored in a ventilated room, in a location dedicated to the study and in accordance with their specific storage conditions (see storage conditions in the system's user manual).

The PSADs will document any temperature excursions and any non-compliance with the storage conditions required for the equipment supplied in their file, as well as corrective and preventive actions where applicable.

V.2.3 - PRESCRIPTION AND DISPENSATION

The investigator and PSAD nurse should only use the study MDs and consumables for patients who have consented to participate in the study. They shall neither use nor authorise use of the study MDs and consumables in circumstances other than those described in this Protocol.

During the inclusion visit, the investigator will submit the request for management and initiation by the PSAD. If the investigator considers the patient is motivated and able to use the "closed-loop" automated insulin delivery system (or "artificial pancreas"), the PSAD assigns the patient a "closed-loop" automated insulin delivery system (or "artificial pancreas").

Boxes previously labelled for use in a clinical study are brought by the PSAD nurse and given to the patients involved on the first day of installation in the hospital.

Nonetheless, at the investigator's request, the sensor can be fitted prior to installing the complete "closed-loop" automated insulin delivery system (or "artificial pancreas"), and this can be done at the patient's home, in the presence of the PSAD nurse. In this case, the PSAD nurse brings the assigned sensor box to the patient's home and helps the patient fit the sensor.

The PSADs maintain a record of the MDs and consumables assigned to the patients included in the study, with the following information:

- The study reference.
- The reference of the patient (including the patient's number in the study) to whom the "closed-loop" automated insulin delivery system (or "artificial pancreas") was distributed.
- Patient delivery dates, quantity and number of MDs and consumables delivered to the patient (initial shipment, replenishment or replacement).
- Return and destruction dates, quantity and number of MDs and consumables that were either used, partially used or never used by the patient (see V.2.4 management of used or unused equipment).

This information will also be recorded in the e-CRF.

V.2.4 - MANAGEMENT OF USED AND UNUSED EQUIPMENT

At the end of the study, the PSAD will collect any unused or partially used MDs and consumables supplied. As empty boxes or packaging will not be collected, they will be considered used. The PSAD will then conduct an accurate inventory and reconciliation of the MDs and consumables that were assigned to patients with the equipment that was used, partially used or unused.

Once the batch reconciliation is updated, and with the explicit agreement of the sponsor or the sponsor's representative, the equipment may then be destroyed and/or recycled according to the procedures the supplier has given to the PSAD.

During destruction and/or recycling, a destruction/recycling certificate must be completed and include the following information:

- The reference of the study equipment (MDs, consumables and/or replacement equipment) that was destroyed/recycled (batch number).
- Quantity destroyed/recycled.
- Date and method of destruction/recycling.
- Name and signature of the individual (or company) responsible for destroying/recycling the study equipment.

Batch reconciliation and destruction/recycling certificates will be kept in the PSAD's study file, the Investigator Site File (ISF) and the sponsor's Trial Master File (TMF).

At the end of the study, for each of the patients involved, the sponsor undertakes to take all possible measures towards ensuring continuity of the care chain.

V.3 - DURATION OF TREATMENT

The "closed-loop" automated insulin delivery system (or "artificial pancreas") will be used according to the instructions provided in the user manual and summarised above, during the 3-month follow-up period, unless the study is terminated early (see section IV.3).

V.4 - ADHERENCE/COMPLIANCE

Patient adherence and compliance are assessed using the "Patient acquired knowledge assessment" questionnaire (see section VI.10.5), completed by the PSAD nurse, at each visit/interaction during the patient's follow-up period, by asking the patient about their use of the "closed-loop" automated insulin delivery system (or "artificial pancreas"), including regular physical activity and meals.

The time spent in a "closed loop", which the investigator gathers via the data visualisation platform, also documents patient adherence and compliance.

V.5 - CONCOMITANT TREATMENTS / FIRST AID KIT / CONTRAINDICATIONS

V.5.1 - CONCOMITANT TREATMENTS

Since the purpose of this study is to assess PSAD support for patients equipped with an automated "closed loop" insulin delivery system (or "artificial pancreas"), and not to assess the effectiveness of the system itself, it is the clinical investigators' responsibility to establish the treatment(s) required for proper patient management in accordance with the rules of clinical best practices and the recommendations described in the user manual. Please note: treatments that could affect the physiology of diabetes, i.e. that lead to interactions with blood sugar and/or insulin and are thus liable to interfere with the action of “closed-loop” automated insulin delivery systems (or “artificial pancreas”), are not authorised for use in patients equipped with these systems (e.g. steroid treatment).

V.5.2 - FIRST AID KIT

In case one or more of the "closed loop" automated insulin delivery system (or "artificial pancreas") components fails, the patient must carry a first aid kit at all times. The contents of the first aid kit are described in the system user manual. It contains, at least:

- A spare insulin cartridge
- An infusion set
- A blood sugar meter with its test strips
- A lancing device
- A means of administering glucose
- Ketone test strips for measuring ketones

V.5.3 - CONTRAINDICATIONS

The "closed-loop" automated insulin delivery system (or "artificial pancreas") cannot be used in the presence of magnetic fields, including storage cabinets with magnet locks, MRIs, X-rays and CT scans. Magnetic fields can cause damage to sensors and induce display errors in glucose concentration values or block alerts.

The "closed-loop" automated insulin delivery system (or "artificial pancreas") cannot be used in the presence of ionising radiation or during radiotherapy.

Should any of these cases arise, the system must be removed beforehand to keep it safe.

The use of accessories other than those supplied with the system is prohibited.

VI - ASSESSMENT SCHEDULE

Management consists of three distinct phases: pre-installation, installation and follow-up. During these three phases, the number and duration of interactions (visits/telephone calls) may vary according to the patient's needs, the investigator's judgement and practice, and the judgement of PSAD staff.

The pre-installation and installation phases include 2 patient visits to the hospital centre, and 2 to 5 visits by the PSAD (at home and at least one in the hospital centre).

The end of the patient's hospitalisation and their return home, i.e. the end of the installation phase, shall be considered to be D0 for patient follow-up.

The follow-up phase (post-installation) includes 4 interactions with the PSAD, on the telephone and/or at home, and 1 hospital centre visit by the patient.

Based on the investigator's clinical judgement, a urinary pregnancy test may be performed, at any time during the study, to ensure that no pregnant patients have been involved or retained during the conduct of the study.

VI.1 - STUDY ORGANISATION CHART

The schedule of study procedures and assessments is summarised in the table below.

Study phase	**Pre-installation (Pre-Inst.)**			**Installation[a]**	**Post-installation**					
	Inclusion D-15	Pre-Inst. 1 / Pre-Inst. 2	Additional interaction	Installation (end = D0)	D1 / D3	1st sensor change	D30 (1 month)	Additional interaction	D90 (3 months)	End of the study: D90 (3 months) (or early withdrawal)
Day / Location	+/-10 days Hospital	Home	Home or Telephone:	Hospital	Home or Telephone	Home	+/-15 days Home/ Hospital or Telephone	Home or Telephone	+/-15 days Home	+/-15 days Hospital
Number of PSAD scheduled interactions	0	1 to 2 pre-installation visits + 1 to 3 installation visits			4 interactions					
Information and signed consent	X									
Inclusion and exclusion criteria[b, c]	X									
Demographic data	X									
Socio-professional data	X									
Medical history	X									
HbA1c	(X[d])			X[d]						X
Metabolic balance[e]	X						X			X
Urinary pregnancy test	X[b]									
Creatinine or creatinine clearance	X[c]									
Sensor fitting		(X[f])		X[f]						
Installation of the "closed-loop" automated insulin delivery system (or "artificial pancreas")				X						
Evaluation of the patient's continued use of the system							X			X
Replenishment of consumables requested by the patient, if necessary								X[g]		
Adverse events (adverse events, SAEs) / Incidents	X[h]	X[h]	X[h]	X	X	X	X	X	X	X
Patient acquired knowledge assessment questionnaire, completed by the PSAD					X		X		X	
Hospital healthcare team satisfaction questionnaire										X[i]
PSAD satisfaction questionnaire									X[i]	
Patient questionnaires	X						X			X

[a]: The installation is performed in hospital, during a scheduled hospital stay or outpatient visit, over a period of 2 to 3 days. D0 represents the end of the installation, i.e. the day the patient returns home with the "closed-loop" automated insulin delivery system (or "artificial pancreas") installed.
[b]: Including a urine pregnancy test for women of childbearing age.
[c]: If a creatinine clearance measurement from less than 6 months ago is not available in the patient's medical file, the assay must be performed at inclusion to confirm the patient's participation in the study.
[d]: If an HbA1c measurement (performed in a medical analysis laboratory or equivalent) that is less than 4 months old is not available in the patient's medical file, the inclusion criterion will be confirmed by an assay performed at the inclusion visit. In this case, the HbA1c assay will not be repeated at the time of installation, and the value of the inclusion assay will be used as a reference at installation.
[e]: Metabolic balance includes the daily average blood sugar level and its variability, the time spent in hyperglycaemia (>180 mg/dl, [180-250 mg/dl] and > 250 mg/dl), normoglycaemia [70-180 mg/dl] and hypoglycaemia (<70mg/dl, [54-70 mg/dl] and < 54 mg/dl), and % of time spent in closed loop (if available).
[f]: At the prescriber's request, the sensor can be installed prior to installing the complete "closed-loop" automated insulin delivery system (or "artificial pancreas"), and this can be done either in hospital by hospital staff or at the patient's home during a pre-installation visit by the PSAD nurse.
[g]: At the patient's request.
[h]: Collection of adverse events only (unless the sensor is installed during the pre-installation phase).
[i]: Completed once, at the end of the study (after the last patient has left the centre).

Details of the patient questionnaires

	Inclusion	D30	End of the study - D90 (or early withdrawal)
You and the "closed-loop" automated insulin delivery system (or "artificial pancreas") (Expected benefits / Perceived benefits)	X	X	X
You and your quality of life with diabetes (EQ-5D-5L (24) (25) (26))	X	X	X
You and your beliefs about the medical treatment (BMQ (27) – specific section only)	X	X	X
You and medical devices (Patient profile / MD experience)	X		
You and your health (Patient profile / state of health)	X		X
You and your daily constraints	X	X	X
You and your management in general (CSQ-8 (28) (29): Overall satisfaction)		X	X
You and your management by your home healthcare provider (Proactiveness / availability / PSAD advice)		X	X
You and your quality of life and daily constraints linked to the risk of hypoglycaemia episodes (HFS-II) (30) (31)	X	X	X

VI.2 - INCLUSION VISIT (DAY -15 ± 10 DAYS)

An investigator carries out the patient's inclusion visit in the hospital centre.

Patients meeting the eligibility criteria are invited to participate in the study.

The investigator then gives the patient an information leaflet and explains the study (procedure, objectives, benefits and risks, etc.) and answers any questions they may have. If the patient agrees to participate in the study, they give their free and informed consent by dating and signing the consent form. The information will be transferred to the patient's source file, and the study procedures described below can begin (see details in section VI.10):

- Demographic data
- Socio-professional data
- History of diabetes including date of diagnosis and complications
- Medical history / Comorbidities

- Diabetes management including the date of first pump use, daily U-100 rapid-acting insulin requirement, prior use of an automated "closed loop" insulin delivery system ("artificial pancreas") and, where relevant, whether there was a change of healthcare provider at inclusion
- Urinary pregnancy test for women of childbearing age
- Creatinine blood test, if a value taken less than 6 months ago is not available in the patient's medical file
- HbA1c blood test, if a test value taken from a medical analysis laboratory or equivalent less than 4 months ago is not available in the patient's medical file
- Metabolic balance over a period of 4 weeks including (see section VI.10.9):
    - Daily average blood sugar level and its variability (standard deviation and coefficient of variation, if applicable)
    - Time spent if available (as a percentage):
        - In hyperglycaemia (> 180 mg/dl), [180-250 mg/dl] and > 250 mg/dl
        - In the blood sugar target [70-180 mg/dl]
        - In hypoglycaemia (< 70 mg/dl), [54-70 mg/dl] and < 54 mg/dl
- Patient Inclusion Booklet including the following questionnaires:
    - You and the "closed-loop" automated insulin delivery system (or "artificial pancreas") (Expected benefits)
    - You and your quality of life with diabetes (EQ-5D-5L)
    - You and your beliefs about the medical treatment (BMQ – specific section only)
    - You and medical devices (Patient profile / MD experience)
    - You and your health (Patient profile / state of health)
    - You and your daily constraints
    - You and your quality of life and daily constraints linked to the risk of hypoglycaemia episodes (HFS-II)
- Adverse events, data collection begins as soon as the patient agrees to participate in the study

The data are recorded in the e-CRF by the investigator or a member of the hospital team delegated by the investigator at the time of the visit, so that the sponsor and their representative are informed of the patient's inclusion.

The investigator makes the request for management and initiation by the PSAD.

This inclusion visit is the first stage of the pre-installation phase.

VI.3 - PRE-INSTALLATION VISIT(S) BY A PSAD NURSE (PRE-INST. 1 / PRE-INST. 2)

The second stage of the pre-installation phase is the patient's management by the PSAD through one or two home visits to present the "closed-loop" automated insulin delivery system (or "artificial pancreas") to the patient, and assess their motivation and ability to use such a system.

The interview includes:

- The patient’s initial technical training, including:
    - Learning how the system works as a whole, with both simple and advanced functions, including how each component works, and how to use the platform.
    - How to use the consumables and knowledge of the safety rules.
    - How to respond to alarms and equipment malfunctions.
    - Routine maintenance of the equipment.
    - Precautions for use.

  - Ways of wearing the pump and sensor.
  - Knowledge of the medical on-call procedure, including the various telephone numbers, the replacement scheme and emergency kit.
- Assessment of the patient's ability to use the control module/terminal with which the system's algorithm works.
- The collection of any adverse events that have occurred since the inclusion visit. If an adverse event is reported, the PSAD nurse passes the information on to the investigator for patient assessment and monitoring if necessary.

After the visit(s), the PSAD nurse sends the investigator a written report with their assessment of the patient's motivation and ability to use the "closed-loop" automated insulin delivery system (or "artificial pancreas"). If the investigator ultimately deems the patient unfit to use this "closed loop" system, it will be considered a selection failure and the patient will be discharged from the study.

After each interaction with the patient, the PSAD nurse electronically records this interaction in the PSAD files and also completes the e-CRF. If additional interactions, either at home or by telephone, are required between the patient and the PSAD nurse during the pre-installation phase, these will also be electronically recorded in the PSAD files and entered in the e-CRF in compliance with the PSAD management procedure (VI.10.3).

VI.4 - INSTALLATION VISIT(S) AT THE HOSPITAL CENTRE

Once the patient's motivation and ability to use the medical device have been established, the installation phase begins.

The "closed-loop" automated insulin delivery system (or "artificial pancreas") will be installed during a scheduled hospital stay (or outpatient visits) in the hospital centre for a variable duration, estimated between 2 and 3 days.

The estimated number of installation visits carried out by the PSAD is between 1 and 3 during the installation phase, including at least one visit to the hospital centre.

The boxes (medical devices and consumables), which have already been labelled for use in a clinical study, are brought into the hospital by the PSAD nurse.

The procedures below are performed exclusively by the hospital teams:

- HbA1c blood test, unless the test had to be performed at inclusion. In this case, the HbA1c assay will not be repeated at the time of installation, and the value of the inclusion assay will be used as a reference at installation.
- Installation of the "closed-loop" automated insulin delivery system (or "artificial pancreas") (including the insulin pump).
- Collection of any adverse events and SAEs / incidents.

The following procedures may be fully or partially delegated to the PSAD:

- Assistance with sensor installation, if not previously installed. At the prescriber's request, the sensor can be installed prior to installing the complete "closed-loop" automated insulin delivery system (or "artificial pancreas"), and this can be done either in hospital by hospital staff or at the patient's home during a pre-installation visit by the PSAD nurse.
- Technical training on how to use the "closed-loop" automated insulin delivery system (or "artificial pancreas") and associated consumables.
- Assistance with signing up to the platforms for the closed-loop systems and pairing their medical devices.

The data are written down in the patient's source file and recorded in the e-CRF by the investigator or a member of the hospital team delegated by the investigator. The PSAD nurse electronically records their hospital visits in the PSAD files and also completes the e-CRF.

Once the "closed loop" automated insulin delivery system (or "artificial pancreas") has been installed, the patient does not keep their previous equipment and contacts the PSAD who usually monitors them to arrange its return.

The patient received the system and associated consumables for a period of time established between the patient and the PSAD nurse. Replenishment will be based on the patient's needs, as explained in section V.2.

However, should any problems arise with a defective system, the investigator will check the equipment and, if necessary, provide a prescription for the replacement scheme. The investigator also provides instructions for completing the questionnaires on D30 and gives the patient the corresponding booklet and pre-paid envelope for returning the completed questionnaires.

The end of the patient's hospitalisation and their return home, i.e. the end of the installation phase, shall be considered to be D0 for patient follow-up.

On-call technical support and maintenance support by the PSAD is available 24 hours a day, 7 days a week.

VI.5 - POST-INSTALLATION EARLY FOLLOW-UP BETWEEN D1/D3

This follow-up, between D1 and D3, will be carried out by the PSAD nurse via a home visit or telephone call. It will be used to check that the patient has mastered how to use their device (thorough understanding and correct use of the "closed-loop" automated insulin delivery system (or "artificial pancreas")).

Remote technical monitoring takes place throughout the follow-up period. The PSAD nurse views the patient's data on the platform of the "closed-loop" automated insulin delivery system (or "artificial pancreas") to detect any technical problems and checks the technical data is transmitted correctly.

The interview includes:

- Refresher and/or additional technical training on how to use the "closed loop" automated insulin delivery system (or "artificial pancreas") and associated consumables
- A check that the "closed-loop" automated insulin delivery system (or "artificial pancreas") is functioning properly
- A check that the patient still has their replacement scheme in case of a system failure and whether it has been used
- The collection of any adverse events / SAEs / incidents. If an adverse event is reported, the PSAD nurse passes the information on to the investigator for patient assessment and monitoring if necessary
- Assessment of the training by the PSAD nurse using the patient acquired knowledge assessment questionnaire.

After this visit, written feedback will be provided to the investigator (prescriber), including an assessment of the patient's training and any adverse events. This information will also be recorded in the PSAD service files and added to the e-CRF.

VI.6 - HOME VISIT FOR THE FIRST SENSOR CHANGE BY THE PSAD NURSE:

This visit will be made by the PSAD nurse at the patient's home to help the patient change the first glucose sensor. This visit takes place at the latest on the last day of use of the sensor. During this visit, the PSAD nurse

provides refresher training on best practices for using the "closed loop" automated insulin delivery system (or "artificial pancreas").

The interview includes:

- Assistance with changing the glucose sensor for the first time
- Refresher and/or additional technical training on how to use the "closed loop" automated insulin delivery system (or "artificial pancreas") and associated consumables
- A check that the "closed-loop" automated insulin delivery system (or "artificial pancreas") is functioning properly and being correctly maintained by the patient, according to the user manual
- A check that the patient still has their replacement scheme in case of a system failure and whether it has been used
- An evaluation of the consumption of consumables
- The collection of any adverse events / SAEs / incidents. If an adverse event is reported, the PSAD nurse passes the information on to the investigator for patient assessment and monitoring if necessary

The PSAD nurse records the interaction in the PSAD files and completes the e-CRF. The PSAD nurse will send the investigator a written report and list the adverse events, where applicable.

VI.7 - FOLLOW-UP ON D30 (D30 ± 15 DAYS)

VI.7.1 - FOLLOW-UP ON D30 BY THE PSAD NURSE

This follow-up, one month after the "closed-loop" automated insulin delivery system (or "artificial pancreas") has been installed, will be carried out by the PSAD nurse, by a visit to the patient's home or by a telephone call. This interaction is recommended to provide refresher training and assess the patient's acquired knowledge (end of initial technical training).

Remote technical monitoring takes place throughout the follow-up period. The PSAD nurse views the patient's data on the platform of the "closed-loop" automated insulin delivery system (or "artificial pancreas") to detect any technical problems and checks the technical data is transmitted correctly.

The interview includes:

- Refresher and/or additional technical training on how to use the "closed loop" automated insulin delivery system (or "artificial pancreas") and associated consumables
- The patient acquired knowledge assessment questionnaire, completed by the PSAD nurse
- A check that the "closed-loop" automated insulin delivery system (or "artificial pancreas") is functioning properly and being correctly maintained by the patient, according to the user manual
- A check that the patient still has their replacement scheme in case of a system failure and whether it has been used
- An evaluation of the consumption of consumables
- The collection of any adverse events / SAEs / incidents. If an adverse event is reported, the PSAD nurse passes the information on to the investigator for patient assessment and monitoring if necessary

At the end of the interview, the PSAD nurse reminds the patient to complete the J30 patient booklet and return it in the pre-paid envelope they were given during their hospital stay or hand it to the investigator if the 1-month follow-up takes place during a hospital visit. They record this visit in the PSAD files and complete the e-CRF. They send a written report to the investigator with their assessment of the patient's training and the list of adverse events (where applicable).

At the end of their interview with the PSAD nurse, the patient completes the D30 patient booklet, which consists of the following questionnaires:

- You and the "closed-loop" automated insulin delivery system (or "artificial pancreas") (Perceived benefits)
- You and your quality of life with diabetes (EQ-5D-5L)
- You and your beliefs about the medical treatment (BMQ – specific section only)
- You and your daily constraints
- You and your management in general (CSQ-8: Overall satisfaction)
- You and your management by your home healthcare provider (Proactiveness / availability / PSAD nurse advice)
- You and your quality of life and daily constraints linked to the risk of hypoglycaemic episodes (HFS-II)

The patient sends the completed D30 patient booklet to the investigator as soon as possible using a pre-paid envelope provided to the patient or gives it to the investigator if the 1-month follow-up takes place during a hospital visit. Once received, patient questionnaires will be entered in the e-CRF by the investigator or a member of the hospital team delegated by the investigator and filed in the patient's source file.

VI.7.2 - FOLLOW-UP ON D30 BY THE INVESTIGATOR

This follow-up can be performed during a hospital visit or by remote consultation at the investigator's discretion. The investigator will retrieve data on the patient's metabolic balance over the last 4 weeks from the data visualisation platform:

- Daily average blood sugar level and its variability (standard deviation and coefficient of variation, if applicable)
- Time spent (as a percentage):
  - In hyperglycaemia (> 180 mg/dl), [180-250 mg/dl] and > 250 mg/dl
  - In the blood sugar target [70-180 mg/dl]
  - In hypoglycaemia (< 70 mg/dl), [54-70 mg/dl] and < 54 mg/dl
- % of time spent in closed loop (if available)
- The D30 patient booklet, including the following questionnaires if follow-up takes place in the hospital:
  - You and the "closed-loop" automated insulin delivery system (or "artificial pancreas") (Perceived benefits)
  - You and your quality of life with diabetes (EQ-5D-5L)
  - You and your beliefs about the medical treatment (BMQ – specific section only)
  - You and your daily constraints
  - You and your management in general (CSQ-8: Overall satisfaction)
  - You and your management by your home healthcare provider (Proactiveness / availability / PSAD nurse advice)
  - You and your quality of life and daily constraints linked to the risk of hypoglycaemic episodes (HFS-II)

The investigator ensures that the patient meets the criteria for continued use of the system (patient follows the technique; sufficient use of the [redacted] "closed-loop" systems [redacted] (minimum use time 75% for semi-closed-loop) and regular observation of results in real-time) and does not present any discontinuation criteria (choice of the patient and/or their family; poor tolerance; use time for the closed-loop system less than 75%; failure to comply with the follow-up consultation instructions; misuse of or damage to the equipment). If necessary, use of the system must be discontinued and the reasons for the discontinuation given.

VI.8 - VISIT ON D90 BY THE PSAD NURSE (D90 ± 15 DAYS)

This visit, three months after the "closed-loop" automated insulin delivery system (or "artificial pancreas") is installed, will be carried out by the PSAD nurse at the patient's home. It should be used to assess the patient's knowledge (continuous technical training and reminder of the initial technical training) and confirm their best practices. This visit should be carried out before the patient's end-of-study visit at the centre.

Remote technical monitoring takes place throughout the follow-up period. The PSAD nurse views the patient's data on the platform of the "closed-loop" automated insulin delivery system (or "artificial pancreas") to detect any technical problems and checks the technical data is transmitted correctly.

The interview includes:

- An assessment of the patient's knowledge at both the beginning and end of the training and the patient acquired knowledge assessment questionnaire, completed by the PSAD nurse in the e-CRF.
- A point-by-point review of the initial technical training by having the patient repeat the necessary operations.
- A reminder of the safety rules.
- A review of anything that has not been understood.
- A check of the terminal, including its proper maintenance and the patient's correct understanding of how it works.
- A check of the pump and its proper maintenance.
- A check of the interstitial glucose measurement system and its proper maintenance.
- Verification that the patient still has their replacement scheme and whether it has been made use of, as well as the expiration dates for the insulin, pen and emergency kit.
- An evaluation of the consumption of consumables
- The collection of any adverse events / SAEs / incidents. If an adverse event is reported, the PSAD nurse passes the information on to the investigator for patient assessment and monitoring if necessary
- Collection of partially used and unused boxes by the PSAD nurse. However, used boxes are not collected.

At the end of the interview, the PSAD nurse records this visit in the PSAD files and completes the e-CRF. The PSAD nurse sends the investigator a written report with an assessment of the patient's training and a list of adverse events (where applicable).

After the last follow-up of the last patient included on D90 in the hospital centre, the PSAD nurse completes the PSAD Satisfaction Questionnaire in the e-CRF.

VI.9 - END-OF-STUDY VISIT

The end-of-study visit is carried out approximately 3 months (± 15 days) after the "closed loop" automated insulin delivery system (or "artificial pancreas") is installed. An end-of-study visit will be carried out for all patients. If the patient ends their participation in the study before its scheduled end, the patient's condition, date and the reason for termination will be documented in the patient's medical file and reported in the e-CRF.

For this end-of-study or early discharge visit, the patient will attend the hospital and undergo the following procedures (if possible):

- HbA1c blood test

- Metabolic balance over the last 4 weeks:
  - Daily average blood sugar level and its variability (standard deviation and coefficient of variation, if applicable)
  - Time spent (as a percentage):
    - In hyperglycaemia (> 180 mg/dl), [180-250 mg/dl] and > 250 mg/dl
    - In the blood sugar target [70-180 mg/dl]
    - In hypoglycaemia (< 70 mg/dl), [54-70 mg/dl] and < 54 mg/dl
  - % of time spent in closed loop (if available)
- D90 patient booklet including the following questionnaires:
  - You and the "closed-loop" automated insulin delivery system (or "artificial pancreas")
  - You and your quality of life with diabetes (EQ-5D-5L)
  - You and your beliefs about the medical treatment (BMQ – specific section only)
  - You and your health (Patient profile / state of health)
  - You and your daily constraints
  - You and your management in general (CSQ-8: Overall satisfaction)
  - You and your management by your home healthcare provider (Proactiveness / availability / PSAD nurse advice)
  - You and your quality of life and daily constraints linked to the risk of hypoglycaemic episodes (HFS-II)
- Collection of any adverse events / SAEs / incidents

At this visit, as well as at the 1-month visit, the investigator will assess the continued use of the system, which will apply both to patients followed up after 3 months in accordance with the protocol and to those discharged prematurely. This assessment will be based on the above-mentioned criteria plus a clinical evaluation of the objectives set in advance (severe hypoglycaemia, diabetes ketoacidosis, time spent above or below the set threshold values) and/or a biological (HbA1c) evaluation.

The data, including the date and reason for discharge from the study (see section IV.3 in the event of early termination), are written down in the patient's source file and recorded in the e-CRF by the investigator or a member of the hospital team delegated by the investigator.

Furthermore, after the last end-of-study visit of the last patient included in the hospital centre, each investigator who participated in fitting at least one patient in the study completes the investigator Satisfaction Questionnaire in the e-CRF.

VI.10 - ASSESSMENTS AND PROCEDURES

VI.10.1 - GENERAL ASSESSMENT

Patient demographics, medical history and clinical characteristics

The following data are collected at inclusion and reported in the e-CRF:

- Demographic data: age, weight, height, gender and, for women, fertility and contraceptive method.
- The diabetes history including the date of first diagnosis, and any micro- and macro-vascular complications associated with diabetes.
- Metabolic balance (see section VI.10.9).
- Other relevant history and comorbidities.

Socio-professional data

Socio-professional data: level of education, socio-professional category, urban unit bracket and lifestyle, are recorded in the e-CRF at inclusion.

Diabetes management

The date the patient was first put on the pump and their daily U-100 rapid-acting insulin requirements (NovoRapid® or Humalog®) are recorded in the e-CRF at inclusion. The investigator also records in the e-CRF whether the patient has already been fitted with a "closed loop" automated insulin delivery system (or "artificial pancreas") and whether their inclusion in the study leads to a change in home healthcare provider.

Pregnancy test

At inclusion, a urinary pregnancy test is performed in women of childbearing age.

VI.10.2 - LABORATORY WORK-UP

Creatinine / Creatinine Clearance

If a creatinine measurement and creatinine clearance calculation performed less than 6 months ago are not available in the patient's medical file at inclusion, the creatinine blood test must be carried out and clearance calculated at inclusion to confirm the patient's participation in the study.

HbA1c

An HbA1c blood test is carried out at inclusion if an HbA1c measurement (performed in a medical analysis laboratory or equivalent) less than 4 months old is not available in the patient's medical file. In this case, the value of the assay at inclusion will be used as a reference at installation.

If an HbA1c measurement (performed in a medical analysis laboratory or equivalent) less than 4 months old is available in the patient's medical file, the HbA1c blood test is performed at installation.

The HbA1c blood test is also performed at the end of the study.

VI.10.3 - HOME HEALTHCARE PROVIDER (PSAD) MANAGEMENT

The activities of the PSADs in this study are consistent with their normal practices. The only difference in terms of everyday practice is having to complete questionnaires specific to the study.

During each interaction set out in the Protocol, the following information is recorded:

- Type of interaction: visits / telephone calls
- Study phases: pre-installation, installation, follow-up
  For visits:
  - Location: home / hospital
- Date of interaction
- Time spent: start time and end time
- The usefulness and necessity of the interaction to the patient; if none, please specify in what way
- New visit to be scheduled
- Adverse event where applicable
- Written report to the prescriber

Depending on whether the interaction is for pre-installation, installation or follow-up, the following information may be requested:

- Primary and secondary reasons for the interaction:
  - Training / need for additional training
  - Motivational support or need to be reassured
  - Information on the patient's lifestyle (holidays, going abroad, etc.)
  - Medical situation requiring contact with the doctor / other
  - Support installing the sensor
  - Other

Any interaction not set out in the Protocol is also recorded in the e-CRF. In addition to the above, the following information is collected:

- Person who initiated the interaction (patient, investigator, PSAD or other)
- In addition to the above-mentioned reasons:
  - Fault, and if so, the type and nature of the fault
  - Difficulty assessing/reporting an event (meals, physical activity, etc.)
  - Failure to understand one of the algorithm's proposals
  - Alarm or alert management
  - Replenishment needs (ordering pumps, sensors, etc.)
  - Other
- Additional information on the nature and reason for the call, namely:
  - Problem resolved after the interaction
  - Home intervention required, and if so, for which actions and for what reason
  - Medical device vigilance case identified
  - Information on the patient's use of the system (management, replacement scheme, closed loop, etc.)

In the follow-up phase, during each home visit the PSAD nurse checks:

- That the "closed-loop" automated insulin delivery system (or "artificial pancreas") is functioning properly and being correctly maintained by the patient
- The patients' adherence, by asking about their use of the system and through their consumption of the consumables (keeping an inventory of boxes (MDs and consumables) provided, unused or partially used, see section V.2.4).

VI.10.4 - DESCRIPTION OF THE STUDY QUESTIONNAIRES

In addition to the patient acquired knowledge assessment questionnaire used in the PSADs' day-to-day practice, 11 study-specific questionnaires will be used: 9 patient questionnaires, 1 investigator questionnaire and 1 PSAD questionnaire.

VI.10.5 - PATIENT QUESTIONNAIRES

Each questionnaire completed by the patient will be recorded in the e-CRF by a hospital centre member delegated by the investigator.

You and the "closed-loop" automated insulin delivery system (or "artificial pancreas") (Expected benefits / Perceived benefits)

This is an ad-hoc questionnaire developed by the FFD, entitled "You and the "closed-loop" automated insulin delivery system (or "artificial pancreas")". It measures the difference between the patient's expectations and their experience with the MD and how the PSAD helped reduce this discrepancy during follow-up; it describes the impact of management on the patient's autonomy (ability to use the MD independently and to increase their competence) and on the reduction of their mental load.

It is composed of:

- 11 questions with two possible answers:
  - During the first assessment, the patient assesses the expected benefits of the "closed-loop" automated insulin delivery system (or "artificial pancreas"), and the possible answers are: "Yes, I hope so " or "I don't have any expectations regarding this matter".
  - In the subsequent assessments, the patient assesses the perceived benefits of the "closed-loop" automated insulin delivery system (or "artificial pancreas"), and the possible answers are: "Yes, I have noticed this" or "I have not noticed anything regarding this matter ".
- 1 scale from 1 (no confidence at all) to 10 (complete confidence) concerning the level of confidence in the technical use of the "closed loop" automated insulin delivery system (or "artificial pancreas").

There is no specific score, the answers are evaluated independently of each other.

You and your quality of life with diabetes (EQ-5D-5L)

The patient's quality of life is assessed by the EQ-5D-5L questionnaire (24) (25) (26). This is a validated French-language questionnaire that measures the patient's quality of life in the context of using a "closed-loop" automated insulin delivery system (or "artificial pancreas"), in terms of the impact on their activities (mobility, autonomy, daily activities, pain/discomfort, anxiety/depression), and is used to describe the effect PSAD management has on this quality of life during follow-up. It is composed of:

- 5 items each corresponding to a specific dimension (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and divided into 5 levels of perception (1. no problem, 2. slight problems, 3. moderate problems, 4. severe problems, 5. extreme problems/incapacity).
- 1 scale from 0 (worse health than the patient can imagine) to 100 (best health than the patient can imagine) representing the patient's state of health on the day the questionnaire is completed.
  The patient reports their state by ticking the number on the scale, giving a value between 0 and 100.

You and your quality of life and daily constraints linked to hypoglycaemia (HFS-II)

The original "Hypoglycaemia Fear Survey (HFS)" was developed to assess hypoglycaemia-related behaviours and concerns in adults with type 1 and type 2 diabetes (30). The original version of the HFS (HFS-I) and the revised version (HFS-II) are composed of 33 items divided into two sub-categories: Behaviour (HFS-B) and Worry (HFS-W):

- HFS-B: 15 questions that outline behaviours patients may adopt to avoid hypoglycaemic episodes and/or their negative consequences (keeping blood glucose above 150 mg/dl, ensuring other people are present and limiting physical activity).
- HFS-W: 18 questions that outline specific concerns patients may have about their hypoglycaemic episodes (being alone, having episodes while sleeping or having an accident).

The questionnaire uses a Likert scale with 5 response options ranging from "never" to "always". The scores are then aggregated to obtain scores from the two sub-categories and the total score.

The HFS-II is a valid and reliable questionnaire (31) for assessing the fear of hypoglycaemia. It has been validated for use in many languages and countries, including France.

You and your beliefs about the medical treatment (BMQ – specific section only)

The patient's beliefs about the medical treatment is assessed by the specific section of the BMQ (Beliefs about Medicines Questionnaire), validated in French for diabetes (27), which describes the patient's perception of the MD in a wider sense; it is used to describe the effect PSAD management has on the patient's perception of the MD during the follow-up.

The specific BMQ consists of two parts:

- Part one contains five questions related to the need for the treatment.
- Part two contains five questions on concerns about the prescription.

The 10 questions are answered using a 5-point scale (: 1. strongly disagree, 2. disagree, 3. uncertain, 4. agree and 5. strongly agree.

The results of the specific BMQ therefore take the form of two scores ranging from 5 to 25.

You and medical devices (Patient profile / MD experience)

The patient's profile in terms of their experience with medical devices is assessed by an ad-hoc questionnaire entitled: "You and medical devices", developed by the FFD. It is used to contextualise the satisfaction score obtained for PSAD management, based on the patient's actual experience of "medical devices" (history of use and level of competence with "connected medical devices") over the course of the follow-up.

It consists of 5 questions including:

- 2 scales from 1 (no confidence at all) to 10 (complete confidence)
- 3 multiple-choice questions.

There is no specific score, the answers are evaluated independently of one another.

You and your health (Patient profile / state of health)

The patient's feelings about their current and future state of health are assessed by an ad-hoc questionnaire entitled: "You and your health", developed by the FFD. It is used to contextualise the satisfaction score

obtained for PSAD management, based on the patient's portrayal of their current and future state of health over the course of the follow-up.

It consists of 2 questions:

- One on the current state of health with 5 possible answers: excellent, very good, good, poor, very poor
- The other looking ahead at the diabetic patient's future, with 4 possible answers: with great confidence, with confidence, with concern, with great concern.

There is no specific score, the answers are evaluated independently of each other.

You and your daily constraints

The patient's everyday constraints are assessed based on the past month, with a question proposed by the FFD in the form of a pre-established multiple-choice list. This question is used to measure the patient's quality of life in the context of using a "closed-loop" automated insulin delivery system (or "artificial pancreas"), by describing the effect the PSAD's management has on how the patient perceives the constraints caused by their disease throughout the follow-up.

The list includes the following 12 items:

- Managing other people's perceptions of my diabetes
- Anticipating my activities
- Thinking about my diabetes all the time
- Dealing with my diabetes all the time
- Fear of experiencing hypoglycaemia
- Fear of experiencing hyperglycaemia
- Uncertainties about my future health
- Carrying one or more treatment devices on me at all times
- Handling my continuous glucose sensor
- Handling all my treatment equipment (pump, glucose sensor, etc.)
- Determining my insulin doses several times a day
- Hearing the audible alarms of my treatment equipment (pump, glucose sensor, etc.)

There is no specific score, the answers are evaluated independently of one another.

You and your management in general (CSQ-8: Overall satisfaction)

The patient's overall satisfaction with their management is assessed by the CSQ-8 (Client Satisfaction Questionnaire) (28) (29). This is a validated French-language questionnaire, which consists of 8 questions. It measures the patient's direct satisfaction with specific services provided and received within a given time frame and specific service framework. It is used to describe the effect of PSAD management on this overall patient satisfaction during the follow-up. Each question is answered using a 4-point scale (e.g. 1. poor, 2. average, 3. good, 4. excellent).

The score ranges from 8 to 32, with higher values indicating higher satisfaction[22, 23].

You and your management by your home healthcare provider (Proactiveness / availability / PSAD advice)

The patient's targeted experience / satisfaction is assessed by an ad-hoc questionnaire entitled: "You and your management by your home healthcare provider" developed by the French Diabetes Federation (FFD).

The questionnaire assesses the proactiveness, availability and PSAD nurse advice. It is used to measure patients' overall satisfaction with their management by the PSAD during the follow-up.

It is composed of:

- 13 questions answered using a 5-point scale
- 3 scales from 1 (no confidence at all) to 10 (complete confidence).

There is no specific score, the answers are evaluated independently of each other.

VI.10.6 - PATIENT ACQUIRED KNOWLEDGE ASSESSMENT QUESTIONNAIRE

The knowledge acquired by the patient is assessed via an ad-hoc questionnaire, developed by the sponsor. The questionnaire is completed by the PSAD nurse and each item is recorded in the e-CRF.

The questionnaire is divided into 2 parts:

- Learning the basic functions
- Learning the advanced open-loop functions/settings.

Part one contains 12 sections, each evaluating between 4 and 12 items. The 12 sections relate to knowledge on:

- Precautions for use of the components
- Data visualization software
- Initialisation of the control module/terminal
- Reading the control module/terminal screen
- Control module/terminal menu
- Remote-control mode
- Use of the pump
- Cartridge
- Catheter
- Sensor
- Alarms/Alerts/Information
- Various knowledge (on-call support, procedure to follow, etc.).

Part two contains 4 sections, each assessing between 1 and 4 items. The 4 sections relate to the following:

- Advanced settings
- Use of reminder alarms
- Programming specific boluses
- Functional insulin therapy.

Each item is evaluated as: not addressed, not acquired, in progress, acquired.

VI.10.7 - INVESTIGATOR SATISFACTION QUESTIONNAIRE

The investigators' satisfaction is assessed via an ad-hoc questionnaire, developed by the sponsor. Each investigator who participated in fitting at least one patient in the study completes the questionnaire once only, after the last patient in the study has left the centre, in order to obtain their overall satisfaction with all of their included patients rather than their satisfaction with each patient.

The questionnaire is divided into 5 parts:

- General questions about the study and the "closed-loop" automated insulin delivery system (or "artificial pancreas")
- Assessment of the follow-up conducted by the PSAD nurse during the initial period, i.e. before the patient returns home
- Assessment of the follow-up conducted by the PSAD nurse after the patient returns home
- Overall satisfaction
- Access to data and use of the data visualisation platform.

The answers are evaluated independently of one another; no score is provided for this questionnaire. Each item will be completed directly in the e-CRF.

VI.10.8 - PSAD SATISFACTION QUESTIONNAIRE

The satisfaction of the PSAD nurses is assessed by an ad-hoc questionnaire, developed by the sponsor. Each PSAD nurse completes the questionnaire once only after the D90 of their last patient, in order to obtain their overall satisfaction with all of their included patients rather than their satisfaction with each patient.

The questionnaire is divided into 7 parts:

- Training received on the "closed-loop" automated insulin delivery system (or "artificial pancreas")
- Equipment (logistical aspects)
- Quality of the products
- Use of the system
- Services provided by the PSAD nurse (relevance of the follow-up Protocol proposed to the patient)
- Reception of the system by the patient
- Relations with the hospital service.

The answers are evaluated independently of one another; no score is provided for this questionnaire.

Each item will be recorded in the e-CRF.

VI.10.9 - METABOLIC BALANCE

The patient's clinical course is assessed on the basis of their metabolic balance at inclusion, on D30 and at the end of the study (D90) and described by the following values:

- HbA1c (see section VI.10.2; not collected on D30)
- Metabolic balance over the last 4 weeks:
    - Daily average blood sugar level and its variability (standard deviation and coefficient of variation, if applicable)
    - Time spent (as a percentage):
        - In hyperglycaemia (> 180 mg/dl), [180-250 mg/dl] and > 250 mg/dl
        - In the blood sugar target [70-180 mg/dl]
        - In hypoglycaemia (< 70 mg/dl), [54-70 mg/dl] and < 54 mg/dl
    - % of time spent in closed loop (if available)

These values are available via the data visualisation platform, provided the patient gives the investigator access to this platform.

VI.10.10 - SAFETY ASSESSMENT

Safety assessments consist of recording all adverse events, serious or non-serious, related or unrelated to the "closed-loop" automated insulin delivery system (or "artificial pancreas"), expected or unexpected, occurring from the time signed consent is obtained until the end of the study for the patient.

Adverse events may be spontaneously reported by the patient or may come to light following a discussion with hospital staff. The occurrence and follow-up of adverse events and, if applicable, pregnancy should be assessed at each visit.

All of these adverse events are documented in the patient's source file and then recorded in the e-CRF, in accordance with section VIII.

In addition, the following parameters are incorporated into the assessment of the safety profile for patients fitted with a "closed-loop" automated insulin delivery system (or "artificial pancreas"):

- Episodes of severe hypoglycaemia requiring the intervention of a third party for glucose administration

- Episodes of hyperglycaemia with ketosis.
- All incidents related to the "closed-loop" automated insulin delivery system (or "artificial pancreas").

These parameters are documented in the patient's source file and reported in the e-CRF, after discussion with the patient and connection to the data visualisation platform.

[redacted]

VII - EVALUATION CRITERIA

VII.1 - PRIMARY CRITERION

The primary assessment criterion concerns patient satisfaction and experience, which are assessed by questionnaires on D30 and D90.

The **CSQ-8** questionnaire assesses patients' overall satisfaction with their management in general. Satisfaction is confirmed by a score above 20 points (on a scale of 8 to 32) on D30. Maintenance of satisfaction is measured on D90 by a score above 20 points which has not decreased by more than 4 points compared with D30.

The targeted experience / satisfaction is assessed with the questionnaire "**You and your management by your home healthcare provider**" (Proactiveness / availability / PSAD advice). The percentage of patients in each category and the scale scores are assessed independently.

VII.2 - SECONDARY CRITERIA

The secondary assessment criteria are described below:

Home healthcare provider (PSAD) management

- PSAD management is described during the different phases (pre-installation, installation, follow-up) by:
    - The number of interactions.
    - Their type (visits / telephone calls).
    - The time spent.
    - The reason for these interactions and, for the visits, by their location (home / hospital). The reason for an interaction is selected from:
        - Training
        - Motivational support or need for reassurance
        - Malfunction
        - Difficulty assessing / reporting an event (meal, physical activity, etc.)
        - Failure to understand one of the algorithm's proposals
        - Alarm or alert management
        - Replenishment needs (ordering pumps, sensors, etc.)
        - Information on the patient's lifestyle
        - Medical situation requiring contact with the doctor
        - Other.
- The management observed is also described for all the “closed-loop” systems used in the study according to whether or not these interactions were set out in the opinion of the HAS (French National Authority for Health) dated 28 January 2020 for the [redacted] system, and is therefore compared with the management initially scheduled for conducting the study (number of visits or telephone calls made versus those scheduled).
- The knowledge acquired by the patient during their initial training is evaluated by the PSAD nurse using the acquired knowledge assessment questionnaire on D1/D3, D30 and D90.
- The satisfaction of the PSAD nurses is assessed with the **PSAD satisfaction questionnaire**. This questionnaire is completed once by each PSAD nurse at the end of the study (after the D90 of the last patient at the centre). It takes into account the PSAD nurse's opinion on all of the services they provide. For each question, the response rate for each category is described.

Patient questionnaire

- The patient's profile in terms of their experience with medical devices is assessed by the "**You and medical devices**" questionnaire completed at the time of inclusion. For each question, the response rate for each category is described.

- The patient's feelings about their current and future state of health are assessed by the "**You and your health**" questionnaire completed at inclusion and on D90. For each question, the response rate for each category is described.
- The patient's quality of life is assessed by the **EQ5D-5L** questionnaire, at inclusion, on D30 and D90.
- Quality of life and daily constraints related to the risk of hypoglycaemic episodes are assessed by the HFS-II questionnaire at inclusion, on D30 and D90.
- The daily constraints encountered by the patient are assessed based on the past month with the question "**You and your daily constraints**", at inclusion, on D30 and D90. For each item, the percentage of patients is estimated. In addition, the number of items ticked per patient is also assessed to estimate a level of constraints for each patient.
- The expected and perceived benefits of the "closed-loop" automated insulin delivery system (or "artificial pancreas") are assessed by the questionnaire "**You and the "closed-loop" automated insulin delivery system (or "artificial pancreas")**", completed at inclusion, on D30 and D90. The percentage of patients who have expected and perceived benefits is described for each item on the whole.
- The patient's beliefs related to the medical treatment is assessed by the specific section of the **BMQ** (**Beliefs about Medicines Questionnaire**) questionnaire, at inclusion, on D30 and D90. The scores related to the need for treatment and prescription concerns are described, as well as the difference between need and concern.

Investigator satisfaction questionnaire

This questionnaire is completed once by each investigator at the end of the study (after the last patient has left the centre). It takes into account the investigator's opinion on all of their included patients.

For each question, the response rate for each category is described.

Safety

The safety profile of patients with a "closed-loop" automated insulin delivery system (or "artificial pancreas") is described according to:

- All serious adverse events (SAEs) and non-serious adverse events, both related and unrelated to the "closed-loop" automated insulin delivery system (or "artificial pancreas"), whether expected or unexpected, including:
    - Episodes of severe hypoglycaemia requiring the intervention of a third party for glucose administration.
    - Episodes of hyperglycaemia with ketosis.
- All incidents related to the "closed-loop" automated insulin delivery system (or "artificial pancreas").

Clinical course

The patient's clinical profile and its evolution are described by the values of:

- HbA1c, measured at the time of installation and on D90.
- Daily average blood sugar level and its variability (standard deviation and coefficient of variation, if applicable) at inclusion, on D30 and D90.

- Percentage of time spent over a 4-week period: in the blood sugar target [70-180 mg/dl], in hypoglycaemia (< 70 mg/dl, [54-70 mg/dl] and < 54 mg/dl) and in hyperglycaemia (> 180 mg/dl, [180-250 mg/dl] and > 250 mg/dl) at inclusion, on D30 and D90.
- Percentage of time spent using a closed-loop system over a 4-week period, if available, on D30 and D90.

[redacted]

VIII - VIGILANCE

VIII.1 - DEFINITIONS

VIII.1.1 - ADVERSE EVENT

An adverse event is any untoward event that occurs in an individual participating in research involving human subjects, whether or not the event is connected to the research or the product to which the research relates.

VIII.1.2 - ADVERSE DEVICE EFFECT

An adverse device effect (ADE) refers to any untoward and unintended reaction to a medical device or any incident that could have caused such a reaction if appropriate action had not been taken, in an individual participating in research or in the user of the medical device, or any effect related to a malfunction of or damage to a medical device and harmful to the health of a person participating in research.

VIII.1.3 - UNEXPECTED ADVERSE EFFECT

An unexpected adverse effect is defined as any adverse effect of the medical device whose nature, severity, or development is not consistent with the information available in the applicable version of the medical device's safety reference document.

The safety reference document for the "closed loop" automated insulin delivery system (or "artificial pancreas") is the current version of this system's user manual.

VIII.1.4 - INCIDENT

An incident is due to an accident or error, which may lead to an adverse effect in the patient.

VIII.2 - CLASSIFICATION

VIII.2.1 - INTENSITY

The intensity of the adverse events will be assessed by the investigator as follows:

- Mild: The event causes discomfort without disrupting normal daily activities.
- Moderate: The event causes discomfort that disrupts normal daily activities.
- Severe: The event prevents the patient from carrying out their normal daily activities or significantly affects their clinical condition.

VIII.2.2 - CAUSALITY

For each adverse event, the investigator should assess whether or not they consider the event to be related to the "closed-loop" automated insulin delivery system (or "artificial pancreas").

Assessment of causality according to five levels:

The causal link between the adverse event and the medical device will be classified according to the 5 levels below:

- Unrelated: an adverse event whose link to the use of the investigational medical device has been ruled out definitively.
- Unlikely: an adverse event that, after careful examination at the time of the assessment, is considered to be due to external causes (such as disease, environment, treatments, etc.) and does not meet the causality criteria of "Possible", "Probable" and "Definite causal relationship" (listed below) with the investigational medical device.
- Possible: an adverse event whose link to the use of the investigational medical device cannot be ruled out after careful examination at the time of assessment.
- Probable: an adverse event whose link to the use of the investigational medical device appears with a high degree of certainty, after careful examination at the time of assessment.
- Definite causal relationship: an adverse event that has been proven without a doubt to be entirely linked to the use of the investigational medical device, after careful examination at the time of assessment.

If a "Possible" or "Probable" causal link or "Definite causal relationship" is suggested, the adverse event corresponds to the definition of an adverse device effect (ADE).

VIII.2.3 - SEVERITY

Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as an adverse event that meets one or more of the following criteria:

- Fatal (results in death; note that death is a development and not an event).
- Is life-threatening (Note: a life-threatening event refers to an event for which the patient was in danger of death at the time the event occurred; it does not refer to an event that could have led to death if it had been more serious).
- Requires hospitalisation or prolongation of hospitalisation.
- Causes significant or lasting incapacity or disability.
- Results in a congenital anomaly or defect.
- Is a medically significant event (if the event does not meet any of the above criteria).

Unanticipated Serious Adverse Device Effect

A suspected unanticipated serious adverse device effect (USADE: is an adverse event that is considered to be related to the "closed loop" automated insulin delivery system (or "artificial pancreas") and is considered both serious and unanticipated (see above-mentioned medical device safety reference document).

VIII.3 - RECORDING AND DECLARING ADVERSE EVENTS AND INCIDENTS

VIII.3.1 - REGISTERING ADVERSE EVENTS

All adverse events (related or unrelated to the "closed loop" automated insulin delivery system (or "artificial pancreas"), expected or unexpected) that occur during the study, from the time signed informed consent is obtained until the end of the study for the patient (final assessment carried out as part of the study), will be noted in the patient's source file and recorded in the e-CRF by the investigator. If an adverse event is recorded by the PSAD nurse during an interaction (visit or telephone contact) with the patient, the PSAD nurse transmits the information to the investigator in a written report.

The following information will be recorded: the nature of the event (sign, symptom or preferably a diagnosis), intensity, date of occurrence, development (with date resolved if applicable), severity, causal link to the "closed loop" automated insulin delivery system (or "artificial pancreas"), corrective medical treatment and action taken with respect to the "closed loop" automated insulin delivery system (or "artificial pancreas").

Should an adverse event occur during a study visit, it will be monitored during subsequent visits.

Any adverse events considered as possibly related to the "closed loop" automated insulin delivery system (or "artificial pancreas") will be monitored until it is resolved or stabilised.

VIII.3.2 - RECORDING INCIDENTS

Should an incident with the "closed-loop" automated insulin delivery system (or "artificial pancreas") occur, it will be recorded in the PSAD file and reported in a specific e-CRF form by the PSAD. If the investigator identifies any MD incidents, they will report them to the PSAD within 24 hours of learning about the event.

The PSAD also informs the supplier of any incident with the "closed loop" automated insulin delivery system (or "artificial pancreas").

VIII.3.3 - DECLARATION OF SERIOUS ADVERSE EVENTS

Initial Declaration

All serious adverse events (related or unrelated to the "closed loop" automated insulin delivery system (or "artificial pancreas"), expected or unexpected) occurring during the study, from the time signed informed consent is obtained until the end of the study for the patient (final assessment carried out as part of the study), will be declared by the investigator in the e-CRF **within 24 hours** of being informed about the event.

If a causal link with the MD is established, an automatic notification is sent to the PSAD service and the sponsor.

If the PSAD service is the first to be informed of an SAE, it will immediately inform the investigator.

Following notification of an SAE, the PSAD service may request additional data relating to this SAE from the investigator, who must respond to these requests for additional information as soon as possible.

All SAEs must be documented in the patient's file (hospital and PSAD).

The PSAD service will be responsible for making the medical device vigilance declaration to the ANSM, as is standard practice.

Some events will not be considered SAEs. This includes the following cases:

- Hospitalisation for elective surgery or a procedure/treatment that was scheduled prior to inclusion in the study for a pre-existing condition/disease which has not worsened since the beginning of the study.

- Hospitalisation for comfort or social reasons.

- Emergency outpatient hospital consultation (without hospitalisation), unless one of the severity criteria described above applies.

Monitoring of Serious Adverse Events

The investigator will inform the PSAD service about any new information concerning an SAE **within 24 hours** of learning about it.

All SAEs should, as much as possible, be monitored until they are resolved or stabilised (in the event of sequelae) within the limitations of the patient's participation in the study.

Serious Adverse Events and Incidents Occurring After the Study

All serious adverse events and incidents occurring after the patient's participation in the study, and considered to be related to the "closed loop" automated insulin delivery system (or "artificial pancreas"), will be managed by the PSAD service as standard medical device vigilance.

Pregnancy

Pregnancy is an exclusion criterion for the study. However, if a patient gets pregnant during the study period (from the time of signed informed consent until the patient's last assessment in the study), the pregnancy should be reported in the e-CRF as an adverse event. The patient will leave the study early. Partners of male patients included in the study are not affected by this process.

New Facts

A new fact is defined as any new piece of data that may lead to:

- Reassessment of the benefit-risk ratio of the research or the investigational medical device.
- Changes in the use of this medical device, in the conduct of the research, or in research-related documents.
- Suspension, interruption or amendment of the Protocol of the research or similar research.

Any new fact will be reported promptly to the ANSM and CPP by the PSAD, who will pass the information on to the investigator. The investigator will then take the necessary measures for the patient in relation to this new fact.

IX - PROCESSING OF DATA

IX.1 - CASE REPORT FORM (CRF)

The data will be collected using an e-CRF, by the investigator or a member of the hospital team delegated by the investigator and by the PSAD nurse, with different connection profiles. The patient questionnaires will be entered in the e-CRF by the hospital team.

Patients participating in the study will be identified by an 8-digit numeric patient code, consisting of the centre number prefixed by FR followed by 3 digits, and the 3-digit chronological order of inclusion number for the centre (FRYYY-XXX where FRYYY represents the centre number and XXX the patient number in chronological order of inclusion at the centre).

For the clinical component, the patient's data will be collected from the source documents contained in the patient's medical file (original files, hospital reports, laboratory tests, various correspondence, investigator questionnaire, patient questionnaires, etc.) under the investigator's responsibility.

The investigator or a person delegated from the centre should complete the e-CRF at the inclusion visit, during installation of the medical device and during the follow-up. All original source documents from which information is reported in the e-CRFs, should be kept up to date and be readily available.

Data entry updates should be made by the investigator or a delegated person from the centre as soon as possible after each visit.

All corrections relating to the clinical component of the e-CRF will be made by the investigator or a delegated person.

After performing the data entry and resolving any requests for correction in the e-CRF, the investigator will validate all of the recorded data concerning the patient's clinical component, with their signature using their login details and access code.

For the home healthcare service component, the PSAD nurse will complete the patient file contained in the PSAD's information system for each interaction (home visit, hospital visit or telephone contact) with the patient. The PSAD nurse will enter this data in the e-CRF as soon as possible after each interaction (home visit, hospital visit or telephone call), to keep the information up to date and readily available. All corrections relating to the home healthcare service component of the e-CRF will be made by the PSAD nurse.

After performing data entry and resolving any requests for correction in the e-CRF, the PSAD nurse will validate all of the recorded data concerning the home healthcare service, with their signature using their login details and access code.

The data collected in the e-CRF will be partially verified against the source data during follow-up visits by a Clinical Research Associate (CRA) from the CRO provider in the centre.

IX.2 - DATA MANAGEMENT

At the initiation of the study, the data manager will write all the Data Management steps to be followed and the applicable procedures in a manual. It will provide details on the data management system, users, applicable procedures, data flow, requests for corrections, organisation of data collection and coding methods.

An electronic database specific to the study will be developed. Its characteristics will be described by an annotated CRF and dictionary of variables, which will be validated prior to the development of the electronic data collection tool.

The e-CRF will be developed and validated before its entry into production.

Check procedures for the reliability and validity of the data collected with the e-CRF will be defined and described in a data validation plan. These procedures will be defined to ensure the validity of the data in relation to the study's objectives and context. These checks will focus on the completeness and plausibility of the recorded values (bounds checking) and the compatibility of the various data (consistency checking). These checks will generate requests for clarification at the end of data entry on each page of the e-CRF.

After performing data entry and resolving any requests for correction in the e-CRF, the investigator and PSAD nurse will validate all of the recorded data. They will each sign once per patient the data recorded in the e-CRF for which they are responsible, using their login details and access code.

After entering the data for all patients in the e-CRF, a data review meeting will be organised using tables, listings and graphs representing the database content. The strategy for factoring in missing, inconsistent or other problematic data will be determined in collaboration with the sponsor. All deviations from the Protocol will also be described, in particular the list of erroneously included patients. If it becomes necessary to define different patient populations for analysis, these populations will also be described. All decisions made during the data review, prior to analysis, will be recorded in a specific report kept in the Trial Master File.

Once this report has been approved, the patient database will be locked and sent to the statistician for analysis.

X - STATISTICAL ANALYSIS

X.1 - THE SAMPLE SIZE

For reasons of feasibility, the number of patients to be included in the study was set at 35, for a number of expected evaluable subjects fixed at 32. Should any patients leave the study between the time of inclusion and the beginning of fitting the "closed-loop" automated insulin delivery system (or "artificial pancreas"), they will be replaced.

This number of patients will be sufficient to estimate the percentage of patients satisfied on D90 with their management by the PSAD (the primary objective of the study), with an accuracy of ≤ 12.4%.

In fact, whatever the criterion considered (satisfaction estimated from the CSQ-8 and satisfaction assessed from the answers to the various questions in the questionnaire "You and your management by your home healthcare provider" on D90), the expected percentage of satisfied patients is ≥ 85%. The formula used to estimate the accuracy is obtained from the definition of the 95% bilateral confidence interval (CI 95%) for a proportion p, with normal approximation

$$E = \sqrt{(1.96^2\, p\,(1-p)\,/\,n)}$$

With n=32 evaluable patients, the accuracy will therefore be ≤ 12.4%.

X.2 - ANALYSIS POPULATIONS

X.2.1 - DEFINITION OF THE POPULATIONS

The following analysis populations will be defined:

- **Included patients**: all patients included in the study who have signed a consent form
- **Intent-to-treat patients**: all of the included patients fitted with the device who meet all of the inclusion and exclusion criteria
- **PSAD nurses**: all PSAD nurses who answered the PSAD satisfaction questionnaire
- **Investigators**: all investigators in the study

X.2.2 - DEVIATION FROM THE PROTOCOL

Before the database is frozen, deviations from the Protocol related to the inclusion/exclusion criteria will be reviewed.

Patients who do not meet all of the inclusion/exclusion criteria will not be included in the intent-to-treat patient population.

[redacted]

X.3 - STATISTICAL ANALYSES

A Statistical Analysis Plan (SAP) will be drafted by the CRO in charge of the study and validated by the sponsor before the database is frozen. Statistical analyses will be carried out in SAS® version 9.2 or higher (SAS institute, North Carolina, USA).

X.3.1 - GENERAL CONSIDERATIONS

The continuous variables will be described in terms of mean, standard deviation, median, 1st and 3rd quartiles and extreme values. The categorical variables will be described in terms of absolute frequency and percentage per category. Ordinal variables will be described using the most appropriate method (continuous variables or categorical variables). Open-ended responses to questionnaires developed on an ad-hoc basis will be presented in the form of a list.

95% bilateral confidence intervals (CI 95%) of percentages and/or averages will be calculated when deemed relevant. The confidence intervals of the percentages will be calculated using the Agresti-Coull method. For averages, the Wald 95% CIs will be calculated.

The number of patients is small and the proportion of expected missing or invalid data is small and randomly distributed. Consequently, no imputation procedure for missing or invalid data will be applied. If necessary, the replacement of some of these data will be detailed in the SAP on a case-by-case basis.

X.3.2 - AVAILABILITY OF THE PATIENTS

The number of patients included, fitted with the device, prematurely discharged before being fitted and prematurely discharged after being fitted will be described. The reasons for early discharge will also be described.

The analysis populations and number of patients per sub-group will also be described.

X.3.3 - DEMOGRAPHICS AND INCLUSION CHARACTERISTICS

Descriptive statistics (number, mean, standard deviation, median, Q1, Q3, minimum and maximum) will be used to present the inclusion characteristics and demographic data of intent-to-treat patients.

X.3.4 - ANALYSIS OF THE PRIMARY ASSESSMENT CRITERION

To meet the main objective, the overall CSQ-8 score will be calculated at each time of assessment. The percentage of patients satisfied on D30 and D90 and the percentage of patients with continued satisfaction on D90 will be described. The 95% CIs will also be presented.

The absolute variation of the overall CSQ-8 score and the relative variation in relation to D30 will also be described on D90.

Each item of the questionnaire "You and your management by your service provider" will be described at each time of assessment. Scores based on the scales from 1 to 10 will be presented using descriptive statistics.

X.3.5 - ANALYSIS OF SECONDARY ASSESSMENT CRITERIA

Home healthcare provider (PSAD) management

Management description
For each phase of the study (pre-installation, installation and follow-up), the number of interactions will be described. The type of interaction (visits/telephone calls), the time spent per interaction, the main reason and secondary reason for making contact will also be presented.

To verify whether the PSAD patient follow-up is consistent with the follow-up expected, the number and percentage of patients who required increased follow-up/support, identical follow-up/support and reduced follow-up/support in relation to what was recommended in the opinion of the HAS dated 28 January 2020 for the [redacted] system will be described. The theoretical aspects of management recommended in this HAS opinion will be extrapolated/applied to all the "closed-loop" systems used in the study. The 95% CIs of the percentages will be calculated.

Knowledge acquired by the patient
For each item of the patient acquired knowledge assessment questionnaire, the percentage of patients for whom the item is not addressed/not acquired/in progress/acquired will be described on D1/D3, D30 and D90.

PSAD nurse satisfaction
Responses to all items in the PSAD satisfaction questionnaire will be described for the PSAD nurse population. The answers to text entry fields will be presented in a list.

Patient questionnaire

Patient's profile in relation to their experience with devices
Each item of the "You and medical devices" questionnaire will be described qualitatively and/or quantitatively at inclusion.

Patient's feelings about their current and future state of health
At inclusion and on D90, the percentage of patients who think their health is Excellent/ Very Good / Good / Poor / Very Poor and who look ahead at their future life with diabetes With great confidence / With Confidence / With concern / With great concern will be described.
On D90, the percentage of patients whose feelings about their state of health improved will be described.

Quality of life and daily constraints
The EQ-5D score will be calculated at inclusion, on D30 and D90 together with the absolute and relative variations on D30 and D90 compared to the time of inclusion.
For each of the 5 dimensions in the questionnaire, the percentage of patients for each perception level will be presented at inclusion, on D30 and D90. In addition, the levels will be dichotomised into no problems (level 1) and problems (levels 2 to 5). The percentage of patients with no problems / with problems will be presented for each dimension.
The EQ-VAS score at inclusion, on D30 and D90, as well as the absolute and relative variations of the EQ-VAS score will be presented.

For each item in the "You and your daily constraints" questionnaire, the percentage of patients with this constraint will be described at inclusion, on D30 and D90. The number of constraints ticked by the patient will also be presented.

The total HFS-II score and the scores from the two sub-categories, "HFS-B" and "HFS-W", will be presented at inclusion, on D30 and on D90, along with the absolute and relative variations on D30 and D90 compared with the time of inclusion.

Expected and perceived benefits

For each item in the "You and the "closed-loop" automated insulin delivery system (or "artificial pancreas")" questionnaire, the percentage of patients who answered "Yes, I hope so " or "I don't have any expectations regarding this matter" will be described at inclusion. The confidence level score for the technical use of the system will also be prepared.

On D30 and D90, for each item of the questionnaire, the percentage of patients who answered "Yes, I perceived benefits" or "I didn't perceive any benefits" will be described. The confidence level score on D30 and D90, as well as the absolute and relative variation compared to the time of inclusion will also be described.

Beliefs about the medical treatment
For each BMQ-specific question, the percentage of patients who answered: strongly disagree / disagree / uncertain / agree / strongly agree will be described.
The BMQ-specific score related to the need for the treatment and the score relating to concerns will be described at inclusion, on D30 and D90. The absolute and relative variations in these two scores compared to the time of inclusion will be calculated on D30 and D90.

Investigator questionnaire

Responses to all items in the investigator questionnaire will be described for the investigator population. The answers to text entry fields will be presented in a list.

Clinical course

The average HbA1C value will be described at installation and on D90. The percentage of patients with an HbA1C < 7% will also be calculated at installation and on D90.

The parameters below will be presented using descriptive statistics:

- Percentage of time spent over a 4-week period (if available) in the blood sugar target, hypoglycaemia and hyperglycaemia, at inclusion, on D30 and on D90.
- Percentage of time spent using a closed-loop system over a 4-week period (if available) on D30 and D90.
- Daily average blood sugar level and its variability (standard deviation and coefficient of variation, if applicable) at inclusion, on D30 and D90.

Safety

The incidence rate of adverse events, SAEs, as well as those related to the "closed-loop" automated insulin delivery system (or "artificial pancreas"), will be presented as a whole and by "System Organ Class" and "Preferred term" in the MedDRA terminology.

The percentage of patients with at least one episode and the average number of episodes will be described for the following:

- Episodes of severe hypoglycaemia requiring the intervention of a third party for glucose administration.
- Episodes of hyperglycaemia with ketosis.

In addition, the number of incidents associated with the device will be described.

[redacted]

[redacted]

X.4 - MANAGING CHANGES TO THE INITIAL METHODS OF STATISTICAL ANALYSIS

Any changes made to the initial statistical methodology, along with the reasons for such changes, will be described in a specific section of the Statistical Analysis Plan (SAP) and in the clinical study report.

XI - QUALITY CONTROL/MONITORING

Monitoring involves keeping track of the study as it progresses, to ensure it is being conducted and that data are collected and reported in accordance with the Protocol, Standard Operating Procedures (SOP), Clinical Best Practices (CBP) and applicable laws and regulations.

The main responsibilities of the Clinical Research Associate (CRA) are ensuring the investigators comply with the Protocol and that informed consent is obtained and recorded before any study procedure is implemented.

Continuous monitoring of the centre:

During the study, the CRA will regularly contact the centre (investigator and hospital team) to monitor patient recruitment, to check that a centre staff member is completing the e-CRF and entering the patient questionnaires, and to monitor patient safety and the resolution of any correction requests

The CRA will participate in explaining the study Protocol and procedures to all centre staff members involved, including the investigator. If new employees become involved during the course of study, additional training sessions will be organised by the investigator and the CRA.

Monitoring visit:

For each active centre, the CRA, assigned by the sponsor, will contact the investigator to conduct monitoring visits.

During these site visits, the CRA will compare the data recorded in the e-CRF against the medical files, the questionnaires completed in the e-CRF, the patient questionnaires entered in the e-CRF and other documentation through direct access. They will ensure that the data recorded in the e-CRF are complete, consistent and accurate. The data will be verified in accordance with a Monitoring Plan.

As part of the study monitoring, certain sponsor or CRO staff may accompany the CRA during their on-site visit. The investigator and members of their team undertake to cooperate with the CRA to resolve any problems, corrections or possible misinterpretations identified during these monitoring visits.

XII - RESPONSIBILITIES

XII.1 - The SPONSOR'S RESPONSIBILITIES

The sponsor will submit the study to the CPP for their opinion, inform the ANSM of this study and provide it with the CPP's positive recommendation. The CPP's positive recommendation must have been received by the sponsor before the study began.

In accordance with the regulations and CBP, the sponsor will take out civil liability insurance to cover any damage that may result from the research.

XII.2 - THE INVESTIGATOR'S RESPONSIBILITIES

The investigator must ensure the accuracy, completeness, legibility and timeliness of the reported data. All source documents must be completed legibly and carefully and kept up to date to ensure accurate interpretation of the data.

The investigator will maintain up-to-date appropriate and accurate records in accordance with CBP to ensure the study's conduct is properly documented and the data can subsequently be verified during the study's monitoring, audits and regulatory inspections.

The investigator must inform and train all members of their team involved in the study or in patient management, including the PSAD nurses involved in the study, before any procedure is implemented and throughout the study (e.g. if a new member becomes involved).

The investigator will maintain an up-to-date record of all staff members involved in the study (physician, hospital nurse, PSAD nurse and others) and will specify the delegated tasks of each member for the study. The investigator is responsible for ensuring the privacy, health and well-being of patients both during and after the study.

The investigator should be familiar with the context and requirements of the study and must comply with the recommendations set out in the user manuals for the "closed-loop" automated insulin delivery systems (or "artificial pancreas").

By signing the Protocol's signature page, the investigator undertakes to fulfil their assigned responsibilities.

XIII - CONFIDENTIALITY AND ARCHIVING

XIII.1 - PROTECTION OF PERSONAL DATA AND CONFIDENTIALITY

The investigator must ensure that patients' personal data, including their identity and medical information, are kept confidential at all times.

Patients will be identified by a number on the case report form (centre number-patient number in order of inclusion). On other study documents provided to the sponsor (patient questionnaires, etc.), patients will only be identified by the above-mentioned number.

By signing this Protocol, the investigator agrees that this Protocol and all accompanying information are and will remain confidential. The investigator accepts that after providing this Protocol and the necessary information to the staff involved, they remain responsible for their complete confidentiality.

In accordance with local regulations and ethical considerations, the investigator consents to allowing a representative of the sponsor or the ANSM to directly consult and/or copy any study document, ensuring that the patient's identity remains confidential, while allowing the representative to check the case report form.

The investigator undertakes to manage all patient data used or disclosed in the study in accordance with local legislation and European data protection laws.

The investigator must maintain an up-to-date confidential correspondence list for the included patients, including their number, name and date of birth.

The data will be recorded and analysed in accordance with the CNIL's compliance undertaking MR-001 (Reference Methodology 001) (see section XIV.5.1).

The sponsor has the right to use and analyse all anonymous data collected in this study. The data are inspected, in accordance with the regulations in force and in particular Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation - GDPR), in addition to the current version of Law No. 78-17 of 6 January 1978 on information technology, data files and civil liberties.

The contact details of the Data Protection Officer appointed by the sponsor are:

Air Liquide

Déléguée à la Protection des Données

75, Quai d'Orsay

75007 Paris - France

https://www.airliquide.com/fr/groupe/contactez-nous-rgpd

The data may be transmitted to companies acting on behalf of the sponsor and located in countries inside or outside the European Union that would be able to guarantee an adequate level of personal data protection for the administration of the study.

XIII.2 - RETENTION OF STUDY DOCUMENTS

The investigator must maintain the study records in an adequate and accurate manner to ensure that the study's documentation is complete and correct and can be duly verified. Study documents, including case report forms, will be filed in the investigator file.

The investigator file will contain the Protocol, its amendments, the CPP's recommendation along with the relevant correspondence, the informed consent form, records relating to the MD, staff CVs, task delegations and correspondence, etc.

The investigator must keep the study file for 15 years from the date of the last publication concerning the study.

In the event that the investigator wishes to transfer the study file to a third party or move it to another location, the sponsor must be informed in advance.

XIV - ETHICAL AND REGULATORY CONSIDERATIONS

XIV.1 - PATIENT INFORMATION LEAFLET AND INFORMED CONSENT FORM

The investigator (or any other person designated by the investigator in accordance with regulatory requirements) will provide patients with the information leaflet, which must be easy to understand, before any acceptance or refusal of participation in accordance with local regulations and Clinical Best Practices.

This information is based on the principles set out in the Declaration of Helsinki and CBP recommendations. It must also describe the measures in place to protect the privacy and personal data of patients, in accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation - GDPR), in addition to the current version of Law No. 78-17 of 6 January 1978 on information technology, data files and civil liberties.

The investigator (or the person designated by the investigator in accordance with regulatory requirements) must provide patients with an easy to understand oral explanation of the study in which they are invited to participate, which includes a discussion of the investigational medical device, the expected benefits and any potential risks or disadvantages that could be encountered during the study, the implications and any other aspect of the study that is relevant to the patients' decision to participate, and they must also answer any questions patients may have regarding the study. The investigator must ensure that patients have understood the information and give them enough time to carefully consider whether or not they wish to participate in the study.

The investigator should explain to patients that they are completely free to refuse to participate in the study or to discontinue their participation in the study at any time, without having to justify their decision and without this affecting their relationship with the investigator or their future medical care.

Each patient will be informed that part of their original medical file and baseline data related to the clinical study will be reviewed by the Clinical Research Associate (CRA), and possibly by an auditor appointed by the sponsor or a regulatory authority, in accordance with the applicable local regulatory requirements.

The patient gives their free and informed consent by dating and signing the consent form before any study procedure is implemented.

A copy of the informed consent form will be made: the original is kept by the investigator and the copy is given to the patient.

If any new information becomes available during the course of the study that may affect the patient's willingness to participate in the study, they should be given a new and updated informed consent form so they can give their consent to their continued participation.

XIV.2 - ACCESS TO SOURCE DATA

The investigator must provide the CRA with direct access to any source documents relating to the patient that may be required to verify the data recorded in the case report form.

With regard to electronic patient records, if they do not come from validated software with an audit trail and if access cannot be limited to the patients in the study, the investigator must provide a signed hard copy of the electronic medical records during the CRA's visits.

If so requested by the relevant authorities, the investigator must provide access to all study data.

In accordance with the regulations and CBP recommendations, the patient will be informed in writing of the need to verify their data in the medical file for quality control, audit or inspection.

XIV.3 - CONDUCT OF THE STUDY

The study will be conducted in accordance with Clinical Best Practices (CBP), the Declaration of Helsinki and applicable European and/or local laws and regulations related to the proper conduct of clinical studies.

XIV.4 - ETHICS COMMITTEE AND RELEVANT AUTHORITY

The sponsor will submit this Protocol along with the other essential study documents to the CPP. Before starting the study, the investigator should have received a positive recommendation from the CPP for the Protocol and the patient informed consent form. This positive recommendation from the CPP will be forwarded to the ANSM as soon as it has been received.

The CPP and the ANSM will be informed of the implementation and completion of the study.

During the course of the study, the sponsor must inform the CPP of any changes to the Protocol and/or essential documents (see section XIV.6).

Medical device vigilance cases will be reported to the relevant authorities (see section VIII).

XIV.5 - SPECIFIC NATIONAL PROCEDURES

XIV.5.1 - COMMISSION NATIONALE DE L'INFORMATIQUE ET DES LIBERTES [FRENCH DATA PROTECTION AUTHORITY] (CNIL)

In accordance with the current version of the French Law 78-17 called"Informatique et Libertés" of 6 January 1978 and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation - GDPR), the sponsor has undertaken to comply with the CNIL's MR-001 Reference Methodology.

Patients will be informed that their personal data, collected as part of the study, will be kept confidential and will be processed electronically in countries inside or outside the European Union under the responsibility of the sponsor. They will also be informed of their rights regarding the processing of their data. They will be given an information leaflet and an informed consent form that must be signed prior to any study procedure taking place.

XIV.5.2 - CONSEIL NATIONAL DE L'ORDRE DES MEDECINS [FRENCH NATIONAL MEDICAL COUNCIL] (CNOM)

In accordance with article R1121-3-1 of the French Public Health Code, a tripartite financial agreement, called the "Convention Unique", will be signed by the sponsor, the healthcare facility, the investigator and the PSAD, and will be sent to the CNOM for information purposes.

In accordance with French Act No. 2011-2012 of 29 December 2011 and its implementing Decree No. 2013-414 of 21 May 2013 relating to the transparency of potential conflict of interests, the sponsor will publish the existence of this agreement as well as the benefits, in cash or in kind, provided directly or indirectly to the investigator.

XIV.6 - AMENDMENTS

Neither the investigator nor the sponsor may amend the Protocol without the consent of the other party. Any amendments that are likely to be issued must be dated and signed by both parties and must appear as amendments to the Protocol before implementation.

Substantial amendments must be submitted to the CPP for its opinion before the changes are implemented. The positive recommendation(s) obtained will be sent to the ANSM for information purposes.

A substantial amendment is an amendment that has a significant impact on the safety integrity of the study's patients, the scientific value or conduct of the study, or the quality or safety of the medical device.

Substantial amendments pertaining to safety measures will be submitted to the CPP for its opinion but may be implemented immediately under specific conditions defined by the sponsor.

Non-substantial amendments are not submitted to the CPP, but the related changes, whose documentation is kept by the sponsor are highlighted upon submission of any subsequent substantial amendments.

XIV.7 - AUDIT AND INSPECTION

The investigator must consent to making the study source documents available to the auditors (qualified personnel of the sponsor or its representative) or health authority inspectors. The investigator will make themselves available to answer any questions raised by the auditors/inspectors and will do everything possible to facilitate the audit/inspection process.

In the event of an inspection, the investigator may inform the sponsor.

XV - PUBLICATION OF DATA

All data and results from the study are the exclusive property of the sponsor. They must be neither communicated nor published without the prior authorisation of the sponsor.

The sponsor reserves the right to publish or use them in any form whatsoever, to submit them for registration to the health authorities of any country, on its own behalf or on behalf of its subsidiaries.

The investigators should inform the sponsor of any plans to publish or present the study data. Any publication or presentation of the results (abstracts in scientific journals or reviews, oral presentations, etc.), in whole or in part, by the investigators or their representatives should be reviewed by the sponsor before submission.

In the event that the study generates patentable results, the sponsor will be authorised to file such a patent, on their own behalf and at their own expense.

The final clinical study report will be prepared in accordance with applicable regulations.