DEMONSTRATION STUDY OF THE INTEREST OF THE MEDTRUM A7+ TOUCHCARE INSULIN PATCH PUMP VERSUS INSULET OMNIPOD® PATCH PUMP

Interventional study protocol

Final version 1.3 of 13/05/2020

ID-RCB : 2019-A02566-51
Sponsor reference: MedInPS

Study sponsor

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PROTOCOL VALIDATION PAGE

Demonstration Study of the Interest of the MEDTRUM A7+ TouchCare Insulin Patch Pump Versus INSULET Omnipod® Patch Pump

Protocol final version 1.3 of 13/05/2020 (ID-RCB 2019-A02566-51)

Sponsor's Representative:

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Julien le Dall Project Manager jledall@axonal.com	Signature:  Date: 13/05/2020

SCIENTIFIC COMMITTEE

For this clinical study, MEDTRUM, the Sponsor, has chosen a Scientific Committee made up of experts in diabetes who regularly prescribe insulin pumps to their patients. This Scientific Committee will be responsible for validating the relevance of this study: objectives, methodology and scientific quality of the project. It will provide support in the design of the study, contribute to the drafting of the protocol, organize meetings and write publications on the study.

Members of the Scientific Committee :

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PROVIDER COMPANY:

The *contract research organization (*CRO) is responsible for writing the protocol, the electronic case report form (eCRF), regulatory submissions, study logistics and follow-up, data management, statistical analysis and clinical reporting.

CRO	**AXONAL-BIOSTATEM S.A.S.** 215, avenue Georges Clemenceau 92024 Nanterre Cedex, France Tel : + 33 (0)1 56 38 21 50
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INVESTIGATOR SIGNATURE PAGE

I have read and approved the protocol, version 1.3 dated 05/13/2020 entitled, "**Demonstration Study of the Interest of the MEDTRUM A7+ TouchCare Insulin Patch Pump Versus INSULET Omnipod® Patch Pump**".

I am aware of my responsibilities as an Investigator under applicable local regulations and the study protocol.

I agree to conduct the study in accordance with these responsibilities and to appropriately direct and assist the personnel under my control who will be involved in the study.

I will discuss the medical device with patients to ensure that they are fully informed about the device being investigated and the conduct of the study. I will use only the sponsor-approved informed consent form and assume all responsibilities for presenting the information.

I agree that the confidential information contained in this document will not be used for any purpose other than the evaluation of the clinical study without the prior written consent of MEDTRUM.

I agree that the Research Associate/Clinical Research Officer (CRA) and/or other representatives of the Sponsor or its delegated agents may have access to any data source from which case information may have been generated, as well as any audit or inspection.

Name:	Contact information:
_____	_____
Signature:	Date:
_____	_____

SUMMARY OF THE PROTOCOL

Title of the study	**Demonstration Study of the Interest of the MEDTRUM A7+ TouchCare Insulin Patch Pump Versus INSULET Omnipod® Patch Pump**
Developer	MEDTRUM France
Principal Investigator	Pr Alfred PENFORNIS Head of the Endocrinology, Diabetology and Metabolic Diseases Department at the Centre Hospitalier Sud-Francilien in Corbeil-Essonnes (91), France
Scientific Committee	- Pr Alfred PENFORNIS, Endocrinology, Diabetology and Metabolic Diseases Department of the Centre Hospitalier Sud-Francilien de Corbeil-Essonnes (91) - Dr Vincent MELKI, Diabetology, Metabolic Diseases and Nutrition Department, Rangueil Hospital, Toulouse (31) - Dr Jennifer ALLAIN, Endocrinology and Metabolic Diseases Department, Hôpital d'Instruction des Armées Begin, Saint-Mandé (94)
Medical device under study	The A7+ TouchCare® Insulin Management System (MEDTRUM) insulin pump. CE mark n° HD 601 357 110001 of 19/02/2019 (TUV Rheinland). Alternative to treatment with multi-daily insulin injections (basal-bolus regimen) for patients with insulin-requiring type 1 or 2 diabetes.
Comparator	Omnipod® (INSULET) which is reimbursed in France and registered on the LPPR under brand name since 23/02/2016.
Type of study	Randomized, open-label, two-group, parallel, 1:1, national, multicenter, prospective clinical trial with a non-inferiority methodology versus the reimbursed comparator already used by the patient for insulin administration.
Rationale for the study	*The treatment of patients with type 1 diabetes and type 2 insulin-requiring diabetes is based on insulin therapy that mimics the physiological secretion of the pancreas through a basal/bolus regimen, obtained either by multi-injections or by pump. The objective of this basal/bolus regimen is to approach normoglycemia in order to prevent :* *- in the long term, chronic complications of diabetes;* *- In the short term, acute complications of diabetes that are metabolic emergencies (including coma): related either to hyperglycemia associated with ketoacidosis or hypoglycemia.* *Diabetes is a serious disease because of its complications. However, these complications can be prevented and/or mitigated with sustained metabolic control of blood glucose. This control aims to achieve an A1C level of less than 7 or 7.5% (the percentage being different depending on the recommendation and the type of patient) without increasing hypoglycemic episodes. A position paper from the Société Francophone du Diabète published in 2009 states that external insulin pumps have proven their effectiveness for years as an intensive treatment of diabetes by improving glycemic control and reducing hypoglycemia.* *Overall, the indications for pump therapy can be summarized as follows:* *- need for an intensive program (at least 3 injections per day, 3 self-monitoring of blood glucose per day)* *- poor glycemic control despite intensive treatment (A1C > 7.5%, 2 episodes of severe hypoglycemia or unexplained coma within a year and/or 4 moderate hypoglycemia per week)* *- variability of insulin requirements.* *Absolute contraindications are rare and include severe psychiatric disorders, rapidly progressing ischemic or proliferative retinopathy (prior to laser treatment), and high magnetic field exposure.*

	In the current decades, there have been several innovations in diabetes management. Pumps have become smaller, less invasive and easier to use. They also have the potential to have sensors and algorithms built into them to be part of a loop that should lead, in the longer term, to an artificial pancreas. *In addition, the latest models of so-called "patch-p pumps" can detect an early occlusion resulting in the absence of insulin injection. All pumps are built with an occlusion alarm, but it often goes off too late on conventional pumps. The long catheters of conventional pumps have some elasticity, which means that they can expand, storing insulin and thus delaying the moment of "hyperpressure", which is triggered only when 5 to 7 units of insulin have not been delivered. This delay can be dangerous, especially for children. In the new patch pump design, this alarm is more immediate in case of occlusion due to the absence of a catheter.* *Today, in France, there are two types of insulin pumps for continuous external subcutaneous infusion (CSII):* *1. the so-called "durable" insulin pumps (also called "conventional") which deliver insulin continuously using a tube and an external catheter. These models are listed on the LPPR (Liste des Produits et Prestations Remboursables) on a generic line. The LPPR provides for the reimbursement of insulin pumps and consumables by means of complete packages. The conditions for registration of portable insulin pumps and associated services are set by decree.* *External insulin pumps, called "patch pumps", which cannot be reused and are designed without external tubing. These patch pumps also deliver insulin continuously, but the insulin delivery system itself is not durable and is managed by a remote control - a PDM (Personal Diabetes Manager). This type of device does not include external tubing and does not require the installation of a catheter. The insulin delivery reservoirs adhere to the skin with an adhesive patch that lasts 3 days. They are changed regularly but do not require long-term maintenance. The absence of tubing reduces the number of catheter and tubing incidents (skin tolerance, obstruction). In addition, they allow for early detection of occlusion and these systems are lighter, allowing for less clutter and more daily comfort. These models are listed on the LPPR under their own name (brand).* *The LPPR provides for the reimbursement of insulin pumps and services associated with their installation, monitoring and training. The conditions for registration of insulin pumps and associated services are also set by decree.* *The available epidemiological data do not allow for a precise determination of the target population. According to CNAMTS databases, the average number of patients using an external insulin pump was estimated at 41,600 in 2013, with an 18% increase over the previous year.* *Insulin pump administration has a different penetration rate depending on the type of diabetes and age group (estimated penetration rate in adults: 16%, in children: 50%). However, while penetration is increasing more rapidly with newer devices, there is still a drop-off each year. Indeed, if we consider the SNITEM (Syndicat National de l'Industrie des Technologies Médicales) data combined with the above sources, we can estimate the population of patients treated with external insulin pumps at about 50,000 patients in 2019.*
Objectives	• <u>Main Objective:</u> **The primary endpoint is the estimate of HbA1c based on the mean of continuous glucose measurements obtained over the past 10 weeks for each pump use.** The patient's glucose level (averaged over 10 weeks in each arm) will be calculated from measurements automatically recorded by a Continuous Glucose Measurement sensor that the patient already uses: the FreeStyle Libre (Abbott). • <u>Secondary Objectives</u>: o HbA1c values measured at the medical and biological laboratory at the beginning and end of the study o Glucose measurements (minimum, maximum, mean/median, standard deviation, out-of-range value, time in range[Time in Range] , variability) o Glycemic events (hypo- and hyperglycemia - as defined by the ADA, coma, other complications) o Skin and general tolerance o Technical incidents with the device

	○ Overall patient satisfaction, out of the total study population, in each arm and the comparison between the two arms ○ Insulin treatment compliance
Study population	**Type 1 or 2 diabetic patients already equipped with an Omnipod® insulin patch pump (Insulet) and a FreeStyleLibre® blood glucose sensor (Abbott).**
Number of patients	75 diabetic patients (type 1 & 2) recruited in 3 months.
Duration of follow-up per patient	3 months from randomization. Follow-up visits at 4 weeks and 12 weeks. Patients randomized to the control arm (Omnipod) will be allowed to use an A7+Touchcare® pump for 1 full month after the 3-month visit if they wish, to facilitate recruitment by the centers and to allow for a satisfaction measure for both pumps.
Number of centers	8 centers in France (CHU and CHG).
Inclusion and exclusion criteria	<u>Inclusion criteria</u> • Patient with type 1 or type 2 diabetes, 18 years of age and older • Patient already equipped with an Omnipod® insulin patch pump (Insulet) and a FreeStyleLibre ® blood glucose sensor (Abbott). • A1C >= 6.5% to <= 9.5% • Treated with any type of rapid insulin except FIASP (which can be substituted as needed) with 60 IU maximum per day (no use of insulin supplements by pen injector allowed). • Patient able to receive and understand study information, give written informed consent, and readily participate in the study. <u>Exclusion Criteria</u> • Patient already participating in another study • Patient under the protection of the court or under guardianship or curatorship • Type 2 diabetic patient requiring a daily dose of insulin greater than 60 IU per day • Patients unable to continue using an insulin pump for reasons such as: severe psychiatric disorders, rapid progression of ischemic or proliferative retinopathy prior to laser treatment, exposure to magnetic fields • Patient allergic to nickel or adhesive • Patient not affiliated to a social security system • Pregnant or breastfeeding woman • Or any other criteria as determined by the investigator.
Primary endpoint	**The primary end point is the estimation of HbA1c from the mean of continuous glucose measurements obtained during the last 10 weeks of follow-up.** Glucose measurements will be derived from continuous measurements obtained with the FreeStyle Libre sensor, and extracted from the application provided by the manufacturer (already used in routine) and reported by the investigator in the eCRF.
Secondary endpoints	○ HbA1c measurements at D0 and 3M (lab values) ○ Glucose measurements (minimum, maximum, mean/median, standard deviation, off-target values, time in range, variability)

	○ Glycemic events (hypo- and hyperglycemia -ADA definition, coma, other complication) ○ Skin tolerance and overall tolerance ○ Technical incidents with the device ○ Overall patient satisfaction, out of the total study population, in each arm, and comparison between arms ○ Compliance with insulin treatment
Randomization Method	Randomization using e-CRF. It will determine the type of pump to be used in the study (Omnipod® or A7+Touchcare®).
Description of the devices	The Medtrum A7+ TouchCare® Patch Pump is indicated for the continuous subcutaneous delivery of insulin at fixed and variable rates for the management of diabetes in insulin-dependent patients. The pump is one component of a complete system: the Medtrum A7+ TouchCare® Insulin Management System, indicated for patients with diabetes (2 years and older). The complete system includes (in addition to the pump) a sensor that provides continuous glucose monitoring (CGM) by measuring glucose levels in the interstitial fluid. This combination also includes algorithms that allow for alerts (detection of hypoglycemia and hyperglycemia) and automatic suspension of insulin administration to prevent hypoglycemic episodes. The A7+ TouchCare® pump is a Class IIB medical device. The medical device is composed of: - A pump base containing the electronic elements and a system for attaching to the insulin reservoir. This base allows the storage of programs and injected doses in memory. - A "personal remote control" of the pump (or *Personal Diabetes Manager* -PDM-) with a color touch screen. The PDM controls the pump and delivers insulin continuously (wireless radio frequency transmission). It can record data for the last 90 days. - The removable part of the pump consists of insulin reservoirs (adhesive consumable that can be worn for up to 3 days) that can hold 200 units of insulin. This pump features a bolus calculator, a technology that has been used in pumps for many years. It is a deterministic system. **The hypoglycemia or hyperglycemia prediction algorithms built into the pump will be disabled during the study.** Pump data can be shared with healthcare professionals and caregivers through a mobile application (Medtrum EasyTouch®) and a web portal (EasyView®).
Conduct of the study and procedures	<u>Site recruitment procedure</u> • Feasibility of the study by the center, validation of the potential to recruit patients in 3 months, previous experience of participation in a clinical trial. • On-site training by a qualified Medtrum representative on the use of the 2 pump models and the sensor provided to patients, to the center's investigation team (physicians, nurses, CRAs). <u>Patient recruitment procedure</u> • Offer to patients seen in the clinic or hospital to participate in the study if they meet the study eligibility criteria, with an information and informed consent form (see V0) • Planned short-term consultation after a cooling-off period (7 days) to sign consent and randomize the pump to be used by the patient, and to train the patient in its use (V1 visit). • In the Omnipod arm, patients will continue to use their usual treatment: their FreeStyle Libre sensor and their Omnipod pump (to minimize the risk of error by using 2 identical pump and sensor models).

	• In the Medtrum arm the active group, all consumables will be provided for the duration of the study in: That is, the Medtrum pump and its consumables. They will be recovered at the end of the study. Chronology of the visits • Visit V2: after 4 weeks of use of the pump to evaluate the results and the conditions of use;. • Visit V3: after 12 weeks of pump use to evaluate the results at the end of the study; • Patients in the Omnipod group will be able to use the Medtrum pump for 1 month after the 3-month visit (V3). This will allow us to measure satisfaction with the use of both pump models. Glycemic measurements Glucose measurements from the FreeStyle Libre sensor and insulin delivery information from the two patch pumps will be integrated into the study database by the center's investigative team, using software provided by the manufacturers.
Data collected	*Inclusion visit (V1)* ○ Signature of informed consent ○ Socio-demographic data ○ Age of diabetes, type, start of insulin therapy ○ HbA1c at time of current pump prescription ○ Current pump model ○ Patient satisfaction ○ Type of insulin ○ Last HbA1c measurement ○ Glycemic parameters ○ Number of major glycemic events (ADA definition) in the past month, in the past 6 months ○ Randomization of the pump model *First follow-up visit (V2): 4 weeks* ○ Local tolerance and any adverse events ○ Time-stamped recording of blood glucose values and events, hypo- and hyperglycemia, insulin doses administered. ○ Glycemic parameters ○ Technical incidents with the device (catheter occlusion, alarms, detachment, pain, etc.) ○ Patient satisfaction *End of study visit (V3): 12 weeks* ○ Local tolerance and any adverse events ○ Time-stamped recording of blood glucose values and events, hypo- and hyperglycemia, insulin doses administered. ○ Glycemic parameters ○ Technical incidents with the device (catheter occlusion, alarms, detachment, pain, etc.) ○ Patient satisfaction *An additional 1 month of testing for the Omnipod group = V4 visit at month 4 to assess their satisfaction after using the Medtrum pump.* ○ Local tolerance and any adverse events ○ Time-stamped recording of blood glucose values and events, hypo- and hyperglycemia, insulin doses administered.

	○ Glycemic parameters ○ Technical incidents with the device (catheter occlusion, alarms, detachment, pain, etc.) ○ Patient satisfaction
Vigilance management	Expected complications of pump use in the study. All events that occurred during the study: medical device incident, serious or non-serious adverse event, serious or non-serious adverse event related to insulin injection.
Risk assessment	Each patient is already using an insulin pump at the time of inclusion in the study. The use of another pump model (CE marked and already used in other countries) does not present any additional potential risk.
Justification of the number of subjects needed	The objective of a non-inferiority study is to demonstrate that the mean difference between the 2 devices remains small and clinically insignificant. The average blood glucose level achieved in real life with the Omnipod pump is 7.8% according to the experience of the three centers in the scientific committee of the study, which is consistent with the literature. We can assume that the average blood glucose level on the Medtrum pump is the same as on the Omnipod pump. Setting the Δ threshold for non-inferiority at +0.4%, in accordance with FDA guidance (Guidance for Industry Diabetes Mellitus (Developing Drugs and Therapeutic Biologics for Treatment and Prevention), if the upper bound of the IC95% difference between the 2 pumps (Medtrum-Omnipod) exceeds Δ (i.e., 0.4), non-inferiority will not be demonstrated. Otherwise, the superiority of the Medtrum pump over the Omnipod pump can be tested, with a Δ' threshold set at -0.3%. Based on these assumptions, based on the so-called "Less is better" design with α = 2.5%, β = 20%, and a standard deviation (SD) set at 0.55, the calculation of the necessary number of (analyzable) subjects is 60 patients (30 in each group). Assuming that 20% of patients cannot be analyzed (major discrepancies, missing data, lost to follow-up), the **number of patients to be randomized is 75**. The number of centers to be recruited in 3 months maximum is 6. **To confirm our standard deviation hypothesis, a descriptive analysis of the baseline HbA1c data for the entire population will be performed blinded at the end of the inclusion period**. If a large difference from our hypotheses is found, the sample size will be recalculated to maintain 80% statistical power for this study.
Statistical analysis	Data processing and statistical analysis will be carried out by the service provider, Axonal-Biostatem. The statistical analyses will be described in a Statistical Analysis Plan (SAP) validated by the Sponsor and the Scientific Committee, prior to the freeze-in. Statistical analyses will be performed after baseline freezing of the data with SAS® software (SAS Institute, NC, Cary, USA), version 9.4 or later. Demographic and efficacy/performance analyses will be performed in the ITT population. The primary endpoint will be analyzed in PP (Per Protocol) and then validated in the ITT (intention to treat) population. The safety analyses will be performed in the safety population. For quantitative variables, the usual statistics (n, missing n, mean, standard deviation (SD), median, first and third quartiles (Q1 and Q3), minimum and maximum) will be presented. IC95% may be

	presented if relevant (especially for the primary endpoint). For categorical variables, the usual statistics (n, missing n, frequency and percentage) for each modality will be provided. Descriptive statistics will be provided in aggregate and by pump group. The type 1 error, α, is set at 5% when the tests used will be two-sided (superiority) and α will be set at 2.5% when the tests will be one-sided in the case of Noninferiority (IC95%). *Analysis of the main objective* The non-inferiority analysis will be produced via an Ancova or mixed model on the Per-Protocol population and then on an intention-to-treat basis. If non-inferiority is demonstrated, a superiority analysis will be conducted. *Analysis of secondary objectives* The secondary criteria will be described and then be the subject of mixed or Ancova models. A non-inferiority analysis on HbA1c data and superiority analyses on Time in range, number of glycemic events, patient satisfaction will be performed.
Regulatory framework	ID-RCB number, CPP opinion, CNIL MR001 and RGPD compliance, information to the ANSM, approval of investigator contracts by the CNOM, transparency obligations
Logistics	CRO Axonal-Biostatem (Nanterre, France)
Study schedule	Regulatory submissions (PPC): October 2019 Estimated date for obtaining all agreements: December 2019 Implementation of the centers: January to October 2020 Patient Recruitment: January to November 2020 Last patient visit: March 2021 Final base freeze: June 2021 Results on primary endpoint: September 2021 Validated clinical report: December 2021 Total duration of participation for each center = 7 months

ABBREVIATIONS

ANSM	National Agency for the Safety of Medicines and Health Products
ARC	Clinical Research Associate
ATC	Anatomical, Therapeutic and Chemical Classification
BPC	Good Clinical Practices (ISO 14155)
GMP	Good Manufacturing Practices
CNIL	National Commission for Information Technology and Civil Liberties
CNOM	National Council of the Order of Physicians
CPP	Committee for the Protection of Persons
CRO	Company Provider (*Contract Research Organization*)
eCRF	Electronic *Case Report* Form
EI	Undesirable Event
EIG	Serious Adverse Event
EIGI	Unexpected Serious Adverse Event
SD	Standard deviation
EVA	Visual Analog Scale
FAS	Full Analysis Set
HAS	High Authority for Health
HbA1c	Glycated Hemoglobin
ITT	Intent-to-treat
J	Day
M	Month
MEdDRA	Regulatory Medical Dictionary
NRS	Numerical scale score (0 to 10)
PP	Per Protocol
PT	Preferred Term
Q	Quartile
QoL	Quality of Life
RGPD	European General Data Protection Regulation (GDPR)
RIPH	Research Involving the Human Person
SOC	Organ System Classification
WHO	World Health Organization

CONTENTS

« MEDINPS » study: Demonstration Study of the Interest of the MEDTRUM A7+ TouchCare Insulin Patch Pump Versus INSULET Omnipod® Patch Pump

1 INTRODUCTION

1.1 INTRODUCTION AND RATIONALE FOR THE STUDY

The treatment of patients with type 1 diabetes and some type 2 diabetics is based on insulin therapy that mimics the physiological secretion of the pancreas through a basal/bolus regimen, obtained either by daily multi-injections or by external insulin pump. The objective of this basal/bolus regimen is to approach normoglycemia in order to prevent :

- in the long term, chronic complications of diabetes;

- in the short term, acute complications of diabetes which are metabolic emergencies (including coma): related either to hyperglycemia and ketoacidosis or to hypoglycemia.

Diabetes is a serious disease because of its complications. However, these complications can be prevented and/or mitigated with sustained metabolic control of blood glucose. This control aims to achieve an A1C level of less than 7 or 7.5% (the percentage being different depending on the recommendation and the type of patient) without increasing hypoglycemic episodes. A position paper from the Société Francophone du Diabète published in 2009[14] states that external insulin pumps have proven their effectiveness for years as an intensive treatment of diabetes by improving glycemic control and reducing hypoglycemia.

Overall, the indications for pump therapy can be summarized as follows:

- need for an intensive program (at least 3 injections per day, 3 self-monitoring of blood glucose per day)

- poor glycemic control despite intensive treatment (A1C > 7.5%, 2 episodes of severe hypoglycemia or unexplained coma within a year and/or 4 moderate hypoglycemia per week)

- variability of insulin requirements.

Absolute contraindications are rare and include severe psychiatric disorders, rapidly progressing ischemic or proliferative retinopathy (prior to laser treatment), and high magnetic field exposure.

In the current decades, there have been several innovations in diabetes management. Pumps have become smaller, less invasive and easier to use. They also have the potential to have sensors and algorithms built into them to be part of a loop that should lead, in the longer term, to an artificial pancreas.

In addition, the most recent models of pumps called "patch pumps" can detect an early occlusion resulting in the absence of insulin injection. All pumps are built with an occlusion alarm, but it often goes off too late on conventional pumps. The long catheters of conventional pumps have some elasticity, which means that they can expand, storing insulin and thus delaying the moment of "hyperpressure", which is triggered only when 5 to 7 units of insulin have not been delivered. This delay can be dangerous, especially for children. In the new patch pump design, this alarm is more immediate in case of occlusion due to the absence of a catheter[15] .

Today, in France, there are two types of insulin pumps for continuous external subcutaneous infusion[16] :

1. the so-called "durable" insulin pumps (also called "conventional") which deliver insulin continuously using a tube and an external catheter. These models are listed on the LPPR (Liste des Produits et Prestations Remboursables) on a generic line. The LPPR provides for the reimbursement of insulin pumps and consumables by means of complete packages. The conditions for registration of portable insulin pumps and associated services are set by decree.

2. External insulin pumps, called "patch pumps", which cannot be reused and are designed without external tubing. These patch pumps also deliver insulin continuously, but the insulin delivery system itself is not durable and is managed by a remote control - a PDM (Personal Diabetes Manager). This type of device does not include external tubing and does not require the installation of a catheter. The insulin delivery reservoirs adhere to the skin with an adhesive patch that lasts 3 days. They are changed regularly but do not require long-term maintenance. The absence of tubing reduces the number of catheter and tubing incidents (skin tolerance, obstruction). In addition, they allow for early detection of occlusion and these systems are lighter, allowing for less clutter and more daily comfort. These models are listed on the LPPR under their own name (brand). The LPPR provides for reimbursement of insulin pumps for services associated with installation, follow-up and training. The conditions for registration of insulin pumps and associated services are also set by decree.

The available epidemiological data do not allow for a precise determination of the target population. According to CNAMTS databases, the average number of patients using an external insulin pump was estimated at 41,600 in 2013, with an 18% increase over the previous year.

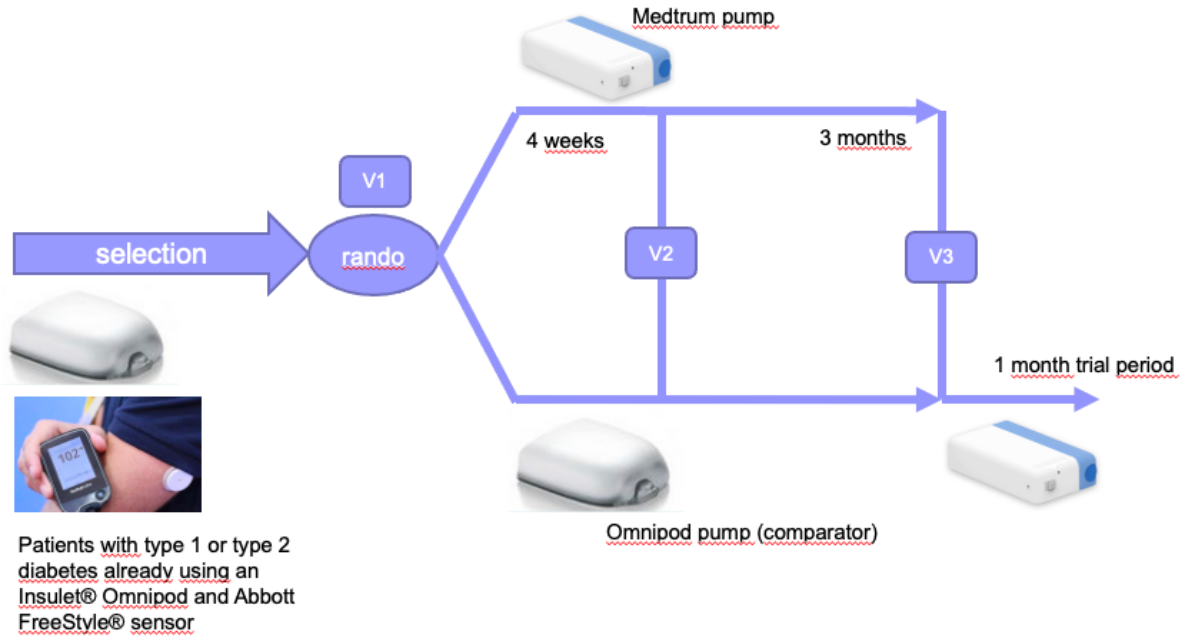
Insulin pump administration has a different penetration rate depending on the type of diabetes and age group (estimated penetration rate in adults: 16%, in children: 50%). However, while penetration is increasing more rapidly with newer devices, there is still a drop-off each year. Indeed, if we consider the SNITEM (Syndicat National de l'Industrie des Technologies Médicales) data combined with the above sources, we can estimate the population of patients treated with external insulin pumps to be more than 50,000 patients in 2019[16] . These figures have yet to be confirmed and refined in the light of the 2020 Expenses and Revenues Report.

2 METHODOLOGY

2.1 STUDY DESIGN

This is a longitudinal, **randomized, comparative** interventional study of type 1 or 2 diabetic patients requiring insulin treatment delivered by a patch pump. The study is multicenter in France, prospective, randomized in two parallel groups 1:1, open-label, with a non-inferiority methodology versus a comparator device (Omnipod® pump marketed by the company Insulet and which is already reimbursed in France since 23/02/2016).

75 type 1 or 2 diabetic patients will be included in the study by 8 hospital centers specialized in diabetes.



In order to facilitate the recruitment of patients already using an Omnipod® pump who would be randomized to the Omnipod group (thus without changing their pump), it is proposed that these patients be able to use a Medtrum pump at the end of the study for one month. Thus all patients in the study will have the opportunity to use the new A7+ TouchCare® pump.

The duration of the study will be: 1 month of set-up, 3 months of patient recruitment, 12 weeks of follow-up per patient, 1 additional month for patients in the Omnipod group to test the Medtrum pump, 3 months of data management, i.e. approximately 11 months of study.

2.2 RATIONALE FOR THE STUDY DESIGN

The objectives of this study are to generate specific data on the use of the insulin pump model A7+ TouchCare® from MEDTRUM (CE marked medical device), to collect safety, tolerance and performance data.

3 MEDICAL DEVICE

3.1 IDENTIFICATION AND DESCRIPTION OF THE MEDICAL DEVICE OF THE STUDY

3.1.1 Mechanism of action of an insulin pump

The external insulin pump is a discreet device that continuously delivers small amounts of rapid insulin, thanks to a user-programmed and disconnectable external infusion device (catheter and tubing) to be changed regularly.

Thanks to the user's programming, the insulin pump reproduces what the body does naturally:

- Deliver small doses of rapid insulin at regular intervals (basal rate) throughout the day.
- Delivering an additional dose of insulin (bolus) at mealtime to cover carbohydrates absorbed at mealtime, during a snack or to correct hyperglycemia.

Thus, the insulin pump is an alternative to treatment with multiple insulin injections using pens and promotes better glycemic control.

Patch pumps are pumps without a catheter or external tubing that are attached directly to the skin with an adhesive.

3.1.2 Medical device under review: A7+ TouchCare Medtrum insulin patch pump

The A7+ TouchCare® insulin patch pump (medical device from the manufacturer MEDTRUM) that will be used in the study is the version that has obtained the CE mark n° HD 601 357 110001 dated 19/02/2019 (Notified Body TUV Rheinland).

Figure 1. Appearance of the A7+ TouchCare® Pump

The A7+ TouchCare® pump is a Class IIB medical device.

The medical device is composed of:

An insulin delivery unit that requires 2 elements:

- The pump base, which is a durable part of the system containing the electronic elements. It is the real memory of the insulin administration unit and allows the

memorization of the programs and the injected doses. It is attached to a consumable, the Patch Reservoir

- The Reservoir Patch is the removable part of the pump that contains the insulin reservoir. It is equipped with a needle (cannula) to administer the insulin. It is an adhesive consumable that can be worn for up to 3 days and contain up to 200 units of insulin.

- A Personal *Diabetes Manager (*PDM) with a color touch screen. The PDM controls the pump and delivers insulin continuously (wireless radio frequency transmission). It can record data for the previous 90 days.

This pump features a bolus calculator. The algorithm is a technology that has been used in pumps for many years. It is a deterministic system.

The hypoglycemia or hyperglycemia prediction algorithms built into the pump will be disabled during the study.

Pump data can be shared with healthcare professionals and caregivers through a computer application (Medtrum EasyTouch®) and a web portal (EasyView®).

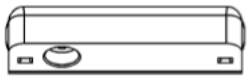
Detailed description of the A7+ TouchCare® pump

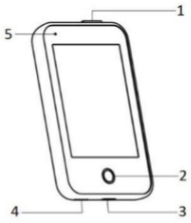
The Medtrum A7+ TouchCare® Patch Pump is indicated for the continuous delivery of subcutaneous insulin at fixed and variable rates for the management of diabetes in insulin dependent patients. The pump is one component of a complete system called the **Medtrum A7+ TouchCare® Insulin Management System**, indicated for patients with diabetes (2 years and older). The complete system combines a continuous glucose monitor (CGM) indicated for continuous monitoring of interstitial fluid glucose levels and detection of potential hypoglycemic or hyperglycemic episodes, and an automatic insulin shut-off system for the prevention of hypoglycemia.

The Medtrum A7+ TouchCare® Patch Pump as a stand-alone pump is designed for continuous subcutaneous delivery of insulin. The patch pump consists of two main components and three medical devices:

Insulin delivery unit **PDM**

Pump base

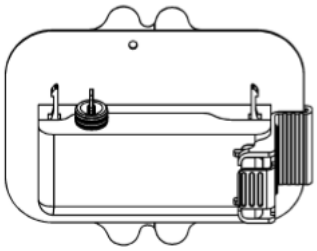




1. Bouton d'alimentation
2. Touche d'accueil
3. Port de chargement
4. Orifice de sortie de son
5. Voyant

✓ Gestionnaire Personnel de Diabète (FM-018)
(Personal Diabetes Manager, PDM)

Reservoir Patch



1/ Insulin delivery unit is a combination of 2 devices:

- A durable part called the **pump base** which contains the electronics and stores the programming of the insulin delivery unit. It must be attached to the consumable, to the Reservoir-Patch, to allow insulin delivery.
- The **Patch Reservoirs** are the consumables. They are disposable and contain up to 200 units of rapid insulin. The reservoir of the A7+ device must be changed every 3 days.

It is the combination of these two elements that allows for the continuous delivery of insulin through a system without external tubing or catheters.
Then, to manage the pump, the patient will have to equip himself :

2/The remote control or ***Personal Diabetes Manager*** **(PDM)** has a color touch screen. The PDM allows programming and control of the pump (and continuous glucose monitoring system if applicable) via wireless radio frequency (RF) communication. The PDM also stores pump (and sensor) data for up to 90 days. The PDM is AC powered and does not require batteries.

The Medtrum A7+ TouchCare® pump (versus the Insulet Omnipod® pump) is a stand-alone component of a complete insulin management system. The system also provides interstitial fluid glucose measurement and the ability to set up hyper and hypoglycemia prevention alarms and predictive suspension of insulin delivery to avoid hypoglycemia.

It also provides patients with flexibility, including the ability to customize the insulin flow rate, or even reduce it to 0 units/hour, allowing it to be used in pediatrics in particular. In addition, the Medtrum A7+ TouchCare® pump comes with a cloud-based management system that can be operated from an app and laptop providing real-time information to caregivers and enabling remote patient monitoring.

Table 1. Administrative characteristics of the medical device under study

Name of the product under study	A7+ TouchCare® Insulin Pump
Indication	Insulin-dependent diabetes
Presentation / Composition	Permanent pump base associated with its consumable, the insulin patch reservoir (disposable) Individual remote control (PDM)
Class	Class IIB
Holder of the medical device	MEDTRUM
CE marking	19/02/2019

3.1.3 Procedure for using the device

Initial training for each center in the use of the Medtrum device will be conducted by an authorized representative of the manufacturer.

Medtrum is providing physicians with a data management system via an online portal to view data collected by the A7+ TouchCare® pump. Investigating centers will be able to extract data for study purposes (data reported on the eCRF), as they already do with data from an Omnipod® pump and an Abbott FreeStyle Libre sensor.

3.1.4 Possible adverse events related to the use of the device

Investigators should report any events that occur during the study (see Chapter 13).

Tolerance problems have already been reported with the patches of insulin sensors and pumps already on the market. These are essentially events of the type of local skin allergy at the location of the adhesive used to attach the pump.

Other side effects, the severity and appearance of which are not known at this time, may occur and will be reported during the study.

3.1.5 Packaging and labeling

Labels will be prepared in accordance with Good Manufacturing Practices (GMP) and clinical trial regulatory requirements to ensure complete traceability of device use from the beginning to the end of the study. Devices will be individually and uniquely numbered.

3.1.6 Conservation and storage

Study devices should be kept at room temperature, and in a secure location under appropriate storage conditions.

3.1.7 Supply of devices

The study devices will be provided by the sponsor and sent to each center (hospital pharmacist) who will acknowledge their receipt.

3.1.8 Randomization

Randomization will be performed using the eCRF provided to the investigators for the study. It will determine which arm the patient will be assigned to: either the "Omnipod" group (the patient will continue to use his current Omnipod pump) or the "Medtrum" group (the patient will have to switch to a Medtrum model).

3.1.9 Dispensing of devices

The study devices provided will be used only as specified in the study protocol. Study site personnel will be responsible for all devices delivered to the patient.

The date of dispensing, patient identification number, and lot number of the medical device should be recorded in the appropriate sections of the investigator record. The traceability label shall be retained in the investigator record or patient's medical record.

The investigator's medical team will provide initial training in the use of the pump for each patient and provide associated documentation.

Patients included in the study will already be users of the other devices used in the study (Omnipod® pump and FreeStyle blood glucose meter), and will use them in the study. No intervention on insulin and its administration is planned as part of the protocol.

3.1.10 Return of the devices

Unused study devices should not be discarded or used for any purpose other than this study. They should be kept in their original packaging.

The Clinical Research Associate (CRA) in charge of monitoring will collect the distribution forms for the medical devices under study at the end of the study and will verify all returns before making arrangements for direct repatriation to the Sponsor or its provider.

3.2 COMPLIANCE

The insulin treatment will be delivered by the pump, and the doses determined by the patient and injected by the pump are recorded by the device. This data can then be viewed and downloaded by the center using the online application provided by the manufacturer.
A measure of compliance with continuous glucose measurements by the patient will be collected using the data recorded in the FreeStyle Libre device.

3.3 EXPECTED SERIOUS ADVERSE EVENTS

As with any Class IIB medical device, risks associated with use cannot be excluded.

Each patient will already be using an Omnipod® insulin pump at the time of inclusion in the study. The use of another pump model (CE marked and already used in other countries) does not present any additional potential risk.

Any serious adverse event, whether or not related to the device under study or its use, must be reported in accordance with the instructions in Chapter 13.

3.4 OTHER DEVICES USED IN THE STUDY

In this study, in addition to the A7+ TouchCare® Medtrum pump, the patient will be given the following:

3.4.1 FreeStyle Libre continuous glucose monitor

The FreeStyle Libre meter is a Continuous Glucose Monitoring (CGM) system for patients with diabetes (Class IIb medical device). It displays glucose level data collected by the associated sensor that measures glucose levels in the interstitial fluid. Unlike existing CGMs on the market, the FreeStyle LIbre uses NFC technology and requires the sensor to be scanned regularly for continuous glucose readings.

It records and stores up to 90 days of glucose data. To obtain a complete view of glucose levels over the past 3 months, the sensor must be replaced every 14 days and scanned by the patient at least once every 8 hours. The sensor should be removed before undergoing an MRI.


The functions of this player are as follows:

- Continuous glucose measurement on the interstitial liquid thanks to a sensor placed on the epidermis with the help of an adhesive base (maximum 14 days of use)
- Data display on a Reader (Wireless handheld terminal) for patient viewing. The FreeStyle LibreLink application is also available as a medical device to replace the FreeStyle Libre reader. It is possible to scan the FreeStyle Libre sensor using either the LibreLink app on Android or iOS, or the FreeStyle Libre reader, or both.
- Data from the system can be downloaded to a computer and then transmitted to the manufacturer's cloud so that the physician can view the information

Abbott is providing physicians with an online application to view the data collected by the FreeStyle Libre reader. Investigating centers already equipped with this software will be able to extract the data for the study (data to be reported on the eCRF).

3.4.2 Insulet Omnipod® Patch Pump (comparator device)

This medical device consists of a small pump that is glued directly to the skin and insulin is delivered into the subcutaneous tissue through a cannula that penetrates the skin when the pump is primed. Insulin is injected directly into the pump's built-in reservoir (no separate reservoir).
The pump must be removed when it is empty, at most every 3 days, and disposed of, a new one being put in place for the continuation of the treatment. It is therefore a single-use pump.

The pump has a Personal *Diabetes Manager (*PDM) with a non-touch screen. The PDM controls the pump and delivers insulin continuously (wireless radio frequency transmission). It allows you to record data for the previous 90 days.

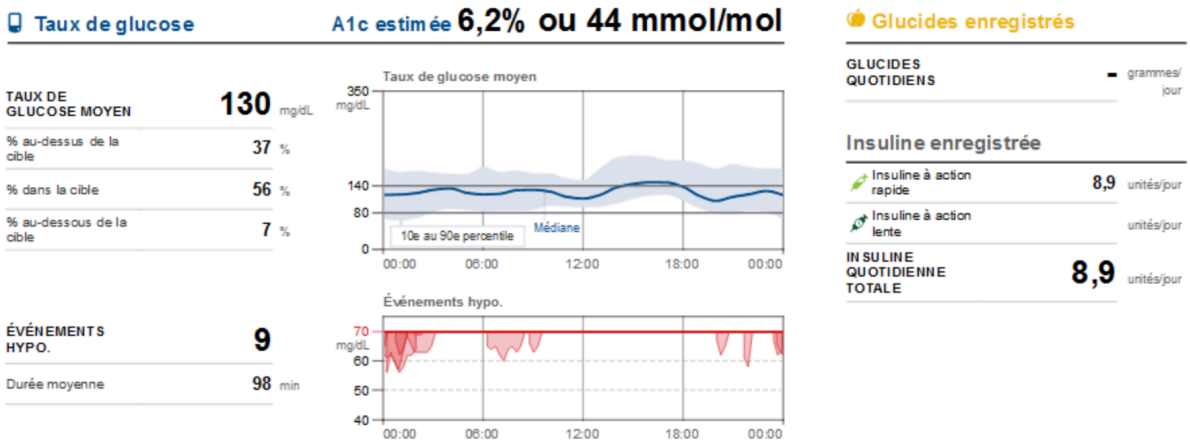
3.4.3 Centralization of information sources and identification keys

The clinical database of the study will be managed exclusively by the provider in charge of the study logistics (Axonal-Biostatem). This database will not contain any directly nominative data.
The provider provides the centers with an electronic observation book (e-CRF) accessible via the Internet. Each user is identified by a personal and unique login/password.

The identifiers for each patient according to the different data sources are as follows:

- **Pump-ID:** number of the pump kit given to the patient. This ID will be entered into the clinical database in the format | __| __| __| .
- **ID-eCRF**: unique patient identifier for the study in the clinical database (eCRF) on the format center no. - patient no. in the format | __| -| __| __| .

The centers will also use applications accessible via the Internet, made available by the manufacturers to visualize and exploit the data recorded and transmitted by the various devices used (pump, blood glucose meter).
For example, the data is returned to the physician in the form of graphs, tables and calculated average values. Physicians will thus be able to have, for each patient, the average blood glucose levels over the defined periods, the estimated A1C, the % of time in range, etc.



These applications are used routinely in the centers. Only the application provided by Medtrum for its pump data will require specific training for the centers.
Investigators will need to report these calculated variables in the eCRF to populate the clinical database of the study.

4 OBJECTIVES OF THE STUDY

4.1 MAIN OBJECTIVE

The primary endpoint was estimated HbA1c based on mean blood glucose measurements over the past 10 weeks for each pump use.

The patient's average blood glucose over the past 10 weeks will be calculated in each arm from measurements automatically recorded by a FreeStyleLibre sensor, which the patient is already using.

4.2 SECONDARY OBJECTIVES

The secondary objectives are to describe the following information:

- HbA1c values measured at the medical and biological laboratory at the beginning and end of the study
- Glucose measurements (minimum, maximum, mean/median, standard deviation, off-target value, time in range[Time in Range] , variability)
- Glycemic events (hypoglycemia and hyperglycemia - as defined by the ADA[25] , coma, other complications)
- Skin and general tolerance
- Technical incidents with the device
- Overall patient satisfaction, on the overall population, in each arm and comparison between the two arms
- Insulin treatment compliance

5 PATIENT SELECTION

The investigating centers will propose participation in the study for each patient potentially eligible for the study according to the inclusion and non-inclusion criteria.

Each patient must be informed orally and in writing by the investigator by means of the information leaflet informing them of the objectives and methods of the study, of the collection and computer processing of their health data, and of their right to withdraw from the study without having to justify themselves. The patient will have the opportunity to ask questions to the study personnel of the investigating center. If a patient decides to

participate, he or she must knowingly sign the consent form approved by the Ethics Committee before any study-related procedure.

A patient will only be included in the clinical study after he or she has given written informed consent and met all inclusion criteria and none of the non-inclusion criteria.

As the patients in this study are not involved in emergency medical treatment, no consent will be collected in this specific emergency setting.

6 STUDY POPULATION

6.1 INCLUSION CRITERIA

To be included in the study, all patients must meet all of the following inclusion criteria:

1. Patient with type 1 or type 2 diabetes, 18 years of age and older
2. Patient already equipped with an Omnipod® insulin patch pump (Insulet) and a FreeStyleLibre sensor (Abbott).
3. A1C between ≥6.5% - ≤ 9.5
4. Treated with any type of rapid-acting insulin except FIASP (which can be substituted as needed) with 60 IU maximum per day (no use of insulin supplements by pen injector allowed).
5. Patient able to receive and understand study information, give written informed consent, and readily participate in the study.

6.2 NON-INCLUSION CRITERIA

Patients will not participate in this clinical study if they **meet at least one of the following criteria**:

1. Patient already participating in another study
2. Patient under the protection of the court or under guardianship or curatorship
3. Type 2 diabetic patient requiring a daily dose of insulin greater than 60 IU per day
4. Patients unable to continue using an insulin pump for reasons such as: severe psychiatric disorders, rapid progression of ischemic or proliferative retinopathy prior to laser treatment, exposure to magnetic fields)
5. Patient allergic to nickel or adhesive
6. Patient not affiliated to a social security system
7. Pregnant and breastfeeding women
8. Or any other criteria as determined by the investigator.

6.3 PROHIBITED TREATMENTS

Investigators are free to manage their patients with diabetes as usual, but any treatment should be documented during the study, as well as any changes in treatment during the study. Therefore, there are no prohibited treatments during the study.

6.4 CRITERIA FOR PREMATURE PATIENT DISCHARGE FROM THE STUDY

Patients may be prematurely withdrawn from the study in the following situations:

- Inclusion found not to be in compliance with the protocol

- Patient decision: the patient is free at any time to withdraw from the study without prejudice to the quality of subsequent care
- Malfunction of a medical device that does not allow the study to continue or does not allow data to be collected reliably
- Any clinical reason given by the investigator
- Patient lost to follow-up.

If a patient withdraws prematurely from the study due to a specific stopping criterion, the reason and date of withdrawal should be reported in the case report book.
Any adverse events should be reported and documented according to the detailed instructions in Chapter 13.

6.5 REPLACEMENTS

Patients who leave the study will not be replaced.
If dropouts significantly affect the number of patients in the study, the Scientific Committee will be asked to make any useful decision, such as additional inclusions.

7 SCHEDULE OF VISITS AND STUDY PROCEDURES

7.1 SCHEDULE OF VISITS

For this study, the following visits or contacts will be made for each patient by the investigators:

- Visit 1 (D0): Inclusion visit with collection of informed consent and randomization of the type of pump to be used.
- Visit 2 (V2) 4 weeks later : Follow-up visit after 4 weeks of pump use
- Visit 3 (V3) 12 weeks after inclusion: End of study visit and measurement of the primary endpoint
- An additional month for patients in the Omnipod group to use the Medtrum pump (considered to facilitate participation in the study for patients who would be randomized to the comparator group)

7.2 EVALUATION SCHEDULE

The evaluation schedule is presented below in ***Table 2***.

	screening	inclusion	1M	3M	1M additional
					Omnipod patients only
seeking patients already using Insulet + FreeStyle Libre	X				
ensure availability of HbA1c <1M and blood glucose results	X				
informing the patient		X			
signature consent		X			
verification of inclusion and exclusion criteria		X			
randomisation of pump type		X			
socio-demographic data		X			
history of the disease		X			
HbA1c values and A1c estimates at inclusion		X			
major blood glucose events last month and last 6 months		X			
supply of MEDTRUM equipment		X			X
verification of the correct use of devices		X	X	X	
possible incidents with the devices			X	X	X
adverse events			X	X	X
collection and reporting of blood glucose data and events		X	X	X	X
collection and reporting of pump data			X	X	X
pump and PDM satisfaction questionnaire		P	P	P	P
P = questionnaire filled in by the patient					

Table 2 Evaluation Schedule

7.3 VISIT 1: INCLUSION VISIT WITH INFORMED CONSENT

No study-specific procedures should be performed until informed consent has been obtained from the patient.

Study procedures at Visit 1 include the following assessments:

- Provide verbal information about the study procedures and objectives as well as those presented in the package insert, and ensure that the patient has the opportunity to ask questions
- Obtaining the signature of the informed consent
- Collect the following data using the eCRF:
- Socio-demographic data
- Age of diabetes, type, age of insulin therapy
- HbA1C at the time of insulin pump prescription
- Current model of pump used by the patient
- Patient satisfaction with the current pump
- Type of insulin used
- Last HbA1C value less than one month old
- Available glucose measurements (average of glucose measurements, estimated HbA1c, time in range)
- Number of major glycemic events in the past month (as defined by the ADA) and in the past 6 months
- Randomization of the patient in the pump group "Omnipod" or "Medtrum

7.4 VISIT 2 (4 WEEKS): FOLLOW-UP VISIT AFTER 4 WEEKS OF PUMP USE.

- Collect tolerance data and possible adverse events, and report them as required from the eCRF
- Verify the conditions of use of the devices by the patient

- Collect time-stamped records of glucose values (as well as HbA1c estimated from average glucose measurements) and glycemic events, hypoglycemia and hyperglycemia, and insulin doses administered, from software provided by manufacturers
- Collect technical incidents with the device (catheter occlusion, alarms, pump detachment, pain, allergy, etc.)
- Patient satisfaction with their insulin delivery system
- Confirm or schedule the date of the V3 visit after 3 months of use
- Record all relevant data in the eCRF.

7.5 VISIT 3 (12 WEEKS): END OF STUDY VISIT

- Collect tolerance data and possible adverse events, and report them as required from the eCRF
- Verify the conditions of use of the devices by the patient
- Collect time-stamped records of glucose values (as well as HbA1c estimated from average glucose measurements) and glycemic events, hypoglycemia and hyperglycemia, insulin doses administered
- Collect technical incidents with the device (catheter occlusion, alarms, pump detachment, pain, allergy, etc.)
- Collect patient satisfaction and preference for either pump used (for Medtrum patients only)
- Recovering Medtrum materials
- Record all relevant data in the eCRF
- Offer the patient, if he is in the "Omnipod" group, to use a Medtrum pump for one month and make an appointment in one month for an end-of-study and material recovery visit

7.6 VISIT 4 (4 WEEKS AFTER THE END OF THE STUDY): AFTER 1 MONTH OF USE OF THE MEDTRUM PUMP (ONLY PATIENTS RANDOMIZED IN THE OMNIPOD GROUP)

- Collect tolerance data and possible adverse events, and report them as required from the eCRF
- Collect time-stamped records of glucose values (as well as HbA1c estimated from average glucose measurements) and glycemic events, hypoglycemia and hyperglycemia, insulin doses administered
- Collect technical incidents with the device (catheter occlusion, alarms, pump detachment, pain, allergy, etc.)
- Gather patient satisfaction and preference for either pump used
- Recovering Medtrum materials
- Record all relevant data in the eCRF

8 QUESTIONNAIRES PATIENT

Patients will be advised to complete the questionnaires in a quiet area, and not to be disturbed while completing them. The patient will be advised to plan the time needed to complete the questionnaires for each visit. The patient will be able to complete the self-administered questionnaires during the consultation or immediately afterwards with the help of the health care team if necessary.

The questionnaires to be completed contemporaneously with the visits are as follows:

- Satisfaction questionnaire on the use of each insulin pump (at all visits)

There is no standardized and validated questionnaire in French to assess satisfaction with the use of an insulin pump. A specific questionnaire was therefore developed for the needs of this study.

The investigators will explain to patients the importance of completing the self-questionnaires, as per the protocol instructions.

9 DATA COLLECTION AND QUALITY CONTROL

9.1 INFORMATION SYSTEM

An online solution for managing the clinical observations of the study (eCRF) is available to the investigators of the study (Ennov Clinical).

The clinical data is hosted in a professional data center in France with backup and protection guarantees that comply with clinical research recommendations. The administration of the solution is managed by Axonal-Biostatem and Ennov.

A web platform (cloud) is managed by MEDTRUM to allow the collection of data from the pump. This platform is managed by MEDTRUM, and an application allows investigators to visualize the data and make extractions from a website (cloud).

A web-based (cloud) platform is used to collect data from each patient's FreeStyle Libre blood glucose meter. This platform is managed by Abbott and an application allows investigators to view the data and make extractions.

A web platform (cloud) Diasend® from Glooko is used to collect data from the Omnipod® pump. This platform is managed by Glooko and an application allows investigators to visualize data and make extractions.

No identifiable patient data will be collected in the eCRF, only the investigators will know the identity of the patients. Neither the sponsor nor the service provider will have access to the applications that allow access to patient data.

The processes implemented will comply with the European General Data Protection Regulation (GDPR). The exercise of investigators' and patients' rights can be done at dataprotection@MEDTRUM.fr.

9.2 DATA ENTRY

9.2.1 Entered by the investigator

The patient's clinical data will be collected by the physician in an eCRF accessible via the Internet. Access to the eCRF will be individual by login and password, and the finalization of the data collection will require an electronic signature of the investigator.

The procedures for entering information into the eCRF will be explained to the physician during the study set-up visit. The physician should complete the eCRF as soon as possible after the information is collected, preferably on the same day as the visit.

Physicians will be identified in the application by a center number.

All patient data will be identified by a unique study-specific number in the eCRF database. Patients will also be identified in the eCRF by their initials (1st letter of first name and 1st letter of last name). Investigators are allowed to hold a correspondence list with patient's name data, but this information should not be included in the eCRF and should not be communicated to anyone, especially not to the Sponsor or the CRO provider.

9.2.2 Patient input

Data from the patient satisfaction questionnaires (self-questionnaires) will be collected on paper and entered by the investigating center into the eCRF.

9.3 DATA QUALITY CONTROL

Quality control of the database will be carried out throughout the conduct of the study in order to allow the final database to be frozen within a short time frame.

Correction requests will be generated automatically by the system. The CRO provider staff will be able to manually generate specific correction requests from the eCRF if necessary.

The study logistics center (Axonal-Biostatem) will ensure regular communication with investigators to request a response to unresolved eCRF correction requests.

The investigating physicians will be consulted to obtain their agreement for any correction of their data. The final data must be checked and approved by the investigator with his/her electronic signature.

9.4 FINAL FREEZE OF THE DATABASE

After the database has been declared "clean" for analysis (i.e., the most complete and accurate), the database will be frozen and saved before statistical analyses are launched, a freeze certificate will be documented.

Any changes to the database after this date can only be made by joint written agreement between the Study Sponsor and the statistician.

10 EVALUATION CRITERIA AND FOLLOW-UP

10.1 PRIMARY ENDPOINT

The primary end point was the estimation of HbA1c from the mean of glucose measurements over the last 10 weeks of follow-up.

Blood glucose levels will be obtained from the FreeStyle Libre continuous glucose sensor, extracted from the application provided by the manufacturer (already used in routine) and reported by the investigator in the eCRF. The investigator will be asked to print the measurements from the software to facilitate the monitoring of the reported data.

There will be no recalculation of the estimated HbA1c.

We chose to assess HbA1c from a sensor measurement that is a good estimate of mean blood glucose. The evolution of the classical HbA1c level is not informative on the time spent in hyper or hypoglycemia (whether or not the latter are symptomatic) and does not reflect glycemic variability. Moreover, if the study by Nathan[17] underlines the reliability of the estimation of HbA1c over 14 days of continuous measurements with a sensor, as well as the ADA Recommendations[25] in 2017, more recently those of the "International Consensus on Time in Range"[26] published in 2019 remind the limits of the HbA1c criterion in the laboratory. The evolution of the monitoring of the effectiveness of insulin treatment is increasingly oriented towards average glycemia and "Time in Range" (time spent within the target values).

We propose to evaluate, as a secondary endpoint, the evolution of HbA1c measured in the laboratory from a blood sample at the beginning and at the end of the study, as well as the Time in Range which is automatically calculated from the data of the FreeStyle Libre reader.

10.2 SECONDARY ENDPOINTS

The secondary endpoints were:

- **HbA1c:**
  - Value measured in the laboratory from a blood sample taken before the D0 visit and just before the 3-month visit

- **Glucose Level Measurements**
  - Average Glucose Measurements over each period and over the entire study duration
  - Minimum and maximum values
  - Time in range expressed as a % (see ADA and International Consensus on Time in Range recommendations[25,26])

  These values are automatically calculated by the FreeStyle Libre software and will be reported by the investigator.

- **Glycemic events**
  - Number of symptomatic and non-symptomatic hypoglycemic episodes during the evaluation period, broken down by severity level (see below)

- Number of symptomatic and non-symptomatic hyperglycemia events during the evaluation period, broken down by severity level (see below)

This information is derived from the FreeStyle Libre data and the data entered by the patient in the PDM.

The definition of hypoglycemia and hyperglycemia is the ADA consensus definition[25] :

Table 1—Summary of consensus definitions

Outcome	Definition
Hypoglycemia	Level 1: glucose <70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3.0 mmol/L) Level 2: glucose <54 mg/dL (3.0 mmol/L) Level 3: a severe event characterized by altered mental and/or physical status requiring assistance
Hyperglycemia	Level 1—elevated glucose: glucose >180 mg/dL (10 mmol/L) and glucose ≤250 mg/dL (13.9 mmol/L) Level 2—very elevated glucose: glucose >250 mg/dL (13.9 mmol/L)
Time in range	Percentage of readings in the range of 70–180 mg/dL (3.9–10.0 mmol/L) per unit of time

❖ **Device tolerance**

- Local skin tolerance at the pump site (adhesive hold) and at the FreeStyle Libre blood glucose sensor site (adhesive hold).
- Any local or systemic safety issues should be reported during the study, including the additional one-month phase at the end of the study for patients in the "Omnipod" group

❖ **Incidents with devices**

- Any type of incident involving the operation of the medical devices used, particularly for pumps: removal, control problems, transmission difficulties, obstructions, leaks, etc.

❖ **Patient satisfaction**

- Self-questionnaire evaluating satisfaction with the use of the device (pump+PDM)
- Final question regarding patient preference between the Medtrum device and the Insulet device

❖ **Insulin treatment**

- The insulin treatment used should be documented
- Delivered insulin doses will be derived from the pump's data logging
- Although not allowed in the study, possible additional insulin injections with a pen will be documented if applicable

10.3 OTHER CRITERIA

- Not applicable.

11 STATISTICAL ANALYSIS

11.1 JUSTIFICATION OF THE NECESSARY NUMBER OF PATIENTS

The objective of a non-inferiority study is to demonstrate that the mean difference between the 2 devices remains small and clinically insignificant.

The average blood glucose level achieved in real life with the Omnipod pump is 7.8% according to the experience of the three centers in the scientific committee of the study, which is consistent with the literature. We can assume that the average blood glucose level on the Medtrum pump is the same as on the Omnipod pump.

By setting the Δ threshold for non-inferiority at +0.4%, in accordance with FDA recommendations (Guidance for Industry Diabetes Mellitus (Developing Drugs and Therapeutic Biologics for Treatment and Prevention)), if the upper threshold of the IC95% difference between the 2 pumps (Medtrum-Omnipod) exceeds Δ (i.e., 0.4), non-inferiority will not be demonstrated.

Otherwise, the superiority of the Medtrum pump over the Omnipod pump can be tested, with a Δ' threshold set at -0.3%.

Based on these assumptions, based on the so-called "Less is better" design with α = 2.5%, β = 20%, and a standard deviation (SD) set at 0.55, the calculation of the necessary number of (analyzable) subjects is 60 patients (30 in each group).

Assuming that 20% of patients cannot be analyzed (major discrepancies, missing data, lost to follow-up), the number of patients to be randomized is 75. The number of centers to be recruited in 3 months maximum is 6.

To confirm our standard deviation hypothesis, a descriptive analysis of the baseline HbA1c data for the entire population will be performed blinded at the end of the inclusion period. If a large difference from our hypotheses is found, the sample size will be recalculated to maintain 80% statistical power for this study.

11.2 STATISTICAL ANALYSIS

11.2.1 General statistical methods

Data processing and statistical analysis will be carried out by the service provider, Axonal-Biostatem.

The statistical analyses will be described in a Statistical Analysis Plan (SAP) validated by the Sponsor and the Scientific Committee, prior to the freeze-in.

Statistical analyses will be performed after baseline freezing of the data with SAS® software (SAS Institute, NC, Cary, USA), version 9.4 or later.

Demographic data analyses will be performed in the ITT. Safety analyses will be performed in the Tolerance population. Non-inferiority analyses will be performed in the Per Protocol population and validated in the ITT population.

For quantitative variables, the usual statistics (n, missing n, mean, standard deviation (SD), median, first and third quartiles (Q1 and Q3), minimum and maximum) will be presented.

IC95% may be presented if relevant (especially for the primary endpoint).

For categorical variables, the usual statistics (n, missing n, frequency and percentage) of each modality will be provided.

Descriptive statistics will be provided in aggregate.

The type 1 error,α, is set at 5% for all analyses.

11.2.2 Study populations

To meet the study objectives, 2 populations will be defined:

- ITT: all included patients who used the pump device at least once. Patients will be analyzed according to their group allocated by randomization.
- Per Protocol: ITT patients with no major protocol deviations.
- Tolerance population: all patients who have used the pump device at least once.

11.2.3 Descriptive Analysis

All variables collected will be described and/or listed as individual data.

Efficacy and safety variables will be analyzed according to the sections below (11.2.4 and 11.2.5). Socio-demographic, clinical, medical history and treatment characteristics will be described according to the methodology presented in section 11.2.1.

11.2.4 Analysis of the effectiveness / performance of the device

Analysis of primary efficacy endpoint:

The non-inferiority analysis of the primary efficacy endpoint will be performed with an ANOVA, with the DM as an explanatory variable, on the *per protocol* population and then on the *intention-to-treat* population. If the upper bound of the IC95% of the Omnipod-Medtrum estimated difference in means (LSmeans) exceeds the non-inferiority bound, it will be rejected.

Non-inferiority bounds are defined in this protocol and will be used in the statistical analysis plan.

If non-inferiority is demonstrated, a superiority analysis will be conducted.

Secondary efficacy endpoint analyses:

The secondary efficacy endpoints will be analyzed for the variables listed below.

Each variable will be described globally and by pump group.

In case of non-inferiority analysis, the same methodology as for the primary endpoint will be used.

In case of comparison of quantitative variables, parametric (T-test) or non-parametric (Mann-Whitney) tests of comparison of means will be used. In case of comparison of qualitative variables, CHI^2 or Fisher exact tests will be used.

In case of tests on changes within each group, paired data tests will be used (paired data T-test or Wilcoxon signed ranks test, depending on the distribution of the data).

- **HbA1c:**
  - Evolution of the value measured in the laboratory from a blood sample taken before the D0 visit and just before the 3-month visit
  - Description in the total population, in each group and comparison between groups.

- **Glucose measurements**
  - Average of glucose measurements over each period and over the entire study duration
  - Description of the minimum and maximum values over the total duration of the study
  - Description of the % of Time in Range (see ADA and International Consensus on Time in Range recommendations[25,26])
  - Description in the total population, in each group and comparison between groups.

- **Glycemic events**
  - Description of the number of symptomatic and non-symptomatic hypoglycemic events during the evaluation period, broken down by severity level (see ADA consensus definitions[25])
  - Description of the number of symptomatic and non-symptomatic hyperglycemia events during the evaluation period, broken down by severity level (see ADA consensus definitions[25])
  - Description in the total population, in each group and comparison between groups.
  -
- **Device tolerance**
  - Description of local skin tolerance at the pump site and at the FreeStyle Libre blood glucose sensor site).
  - Description of any local or systemic safety issues reported during the study, including the additional one-month phase at the end of the study for patients in the "Omnipod" arm
  - Description in the total population, in each group and comparison between groups of the number of patients who had at least one tolerance problem.

- **Incidents with devices**
  - Description of any type of incident involving the operation of the medical devices used, particularly for pumps: pulling out, control problems, transmission difficulties, obstructions, leaks, etc.
  - Description in each group, in the overall population and comparison between groups

- **Patient satisfaction**
  - Description of the responses to the self-questionnaire assessing satisfaction with the use of the device (pump+PDM), in each group and in the total population
  - Comparison of responses between groups
  - Description of responses to the final question regarding patient preference between the Medtrum device and the Omnipod device: in each group and in the total population

- **Insulin treatment**
  - Description of insulin doses delivered
  - Description of any additional insulin injections with a pen during the study
  - Description in the total population, in each group and comparison between groups

11.2.5 Tolerance analyses:

The analyses will be performed on the tolerance population.

Prior to any analysis all DM-related incidents and DM-related tolerance will be coded by the MedDRA regulatory medical dictionary (version 20.0 or later).

A summary table (number and percentage of patients with an AE and number of events) by organ system class (OSG) and preferred term (PT) will be presented for the following categories of events by dissociating DM-related incidents and tolerance:

- According to the link (device AND procedure),
- Depending on the link (device OR procedure),
- Depending on the severity,
- Depending on the actions taken (de-pairing).

A listing of individual data will be provided describing all the information collected via the eCRF concerning the IS (including duration, resolution, severity criteria, linkage, severity etc.)

11.2.6 Intermediate analysis

No interim analysis is planned.

On the other hand, a descriptive analysis of the baseline HbA1c data for the whole population will be performed in a blinded fashion at the end of the inclusion period, in order to confirm or not the standard deviation hypothesis planned for the non-inferiority analysis. As this analysis is purely descriptive no α-risk adjustment is planned.

11.2.7 Subgroup analyses , exploratory analyses

They will eventually be described in the final statistical analysis plan.

12 QUALITY CONTROL

Monitoring

This study will be followed at all stages of its realization by CRAs of the service provider company (AXONAL-BIOSTATEM) mandated by the Developer.

This clinical study will be conducted according to the good practices of the ISO 14155 standard and if applicable according to the ICH-GCP E6(R2) recommendations.

The contractor's ARCs will be responsible for the set-up, monitoring and closing of the centers.

At the time of study implementation, the CRA will provide training on the content of the protocol and the eCRF to participating physicians. Training of the centers on the use of the medical device will be conducted by an authorized representative of the Sponsor.

At the Sponsor's request, site visits may also be conducted on a regular basis according to a set schedule. During these visits, the investigator will allow the CRA direct access to the various study documents: observation booklet, informed consent, investigator's binder and source documents, in a confidential manner. During these visits, the CRA will check the patient information and consent forms, will be able to compare the data recorded in the eCRFs with the source data (missing data, outliers), and will ensure that the study is conducted in compliance with the protocol and Good Clinical Practices (GCP).

The CRA will also verify, at each visit, that all adverse events (AEs) and in particular serious adverse events (SAEs) that may have been observed during the study are reported within the specified time frame.

At the end of the study a close-out visit will be conducted, and the CRA will arrange for the return of used/unused medical devices to the Sponsor.

Audits /Inspections

At the Sponsor's request, audits may be conducted to verify the quality of the data, their authenticity and compliance with the procedures outlined in the protocol. Where appropriate, these audits will be conducted during the course of the study and/or at the end of the study by auditors independent of the team responsible for the implementation and monitoring of the study.

In addition, representatives of the French health authorities, as well as those of the Comité de Protection des Personnes, may inspect the investigating centers at any time. If the investigator is aware of such an audit, he/she should immediately inform the sponsor.

The investigator should ensure that he/she is available on the day of the audit/inspection and that the auditors have free access to all source documents.

13 SIDE EFFECTS, VIGILANCE

The responsibilities of each stakeholder in terms of vigilance will be detailed in a document (Safety management Plan) validated by the sponsor.

The CRO (Axonal-Biostatem) will be in charge of collecting incidents related to the DM and tolerance incidents related to the DM to the study's vigilance correspondent (VIGIPHARM).

The Sponsor will be responsible for requesting additional information from the investigators, writing narratives, submitting reports of DM-related incidents and DM-related safety incidents to the investigators and the CPP, and reconciling data from the vigilance database and the clinical database.

The Sponsor will ensure that DM incidents and DM tolerance incidents are identified, that a database for reporting DM incidents and DM tolerance incidents is maintained, that DM incidents and DM tolerance incidents are reported to the appropriate authorities, and that vigilance reports are prepared.

13.1 DEFINITIONS

An adverse event (AE) is any undesirable medical event, unintended illness or injury, or adverse clinical sign (including abnormality, laboratory finding) in subjects, users, or others, whether or not related to the investigational medical treatment. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. For users or other individuals, this definition is limited to events related to the investigational medical device.

Adverse Device Effect (ADE): An adverse event related to the use of the medical device under investigation. This definition includes any adverse event resulting from inadequacies or inappropriateness in the instructions for use, deployment, implantation, installation and operation, or malfunction of the medical device under investigation. It includes any event resulting from an error in use or intentional misuse of the medical device under investigation

Serious Adverse Device Effect (SADE)

Is an adverse effect of the device resulting in one of the characteristic consequences of a serious adverse event described below

A Serious Adverse Event (SAE) is any AE that:

- Leads to death or
- Leads to serious deterioration of the subject's health condition, which has resulted in
    - endangerment of life, illness or injury or,
    - a permanent impairment of a body structure or function or,
    - hospitalization or prolongation of a hospitalization or,
    - medical or surgical intervention to prevent life-threatening disease, injury or permanent impairment of a body structure or function
- Causes fetal distress, fetal death, birth defect or congenital malformation.

Note: a planned hospitalization for a pre-existing condition, or a procedure required by the protocol, with no severity on the deterioration of the health condition, is not considered a serious adverse event.

Medical and scientific judgment should be used to decide whether other IS should also be considered serious, such as medically relevant events that may not be immediately life-

threatening, contribute to death, or result in hospitalization, but which may pose a potential danger to the patient or require intervention to prevent one of the consequences listed in the definition above

Unexpected adverse reaction: any adverse reaction whose nature, severity or course is not consistent with the information about the products, procedures and methods used in the research

Suspected Adverse Reactions: All AEs for which the investigator or sponsor believes that a causal relationship with the investigational component can reasonably be considered are considered suspected adverse reactions.

Suspected Serious Unexpected Adverse Reactions (SUSARs): A suspected serious unexpected adverse reaction is any noxious and undesired response to an investigational product, regardless of dose:

- That results in death, endangers the life of the person who is the subject of the research, requires hospitalization or prolongation of hospitalization, causes significant or permanent disability or incapacity, or results in a congenital anomaly or malformation;
- Whose nature, severity, frequency or course is inconsistent with information about the products, procedures and methods used in the research;
- For which the investigator or sponsor believes that a causal relationship with the investigational medical device can reasonably be expected.

New information: Any new information that may lead to a reassessment of the risk-benefit ratio of the research or the product under investigation, to changes in the use of the product, in the conduct of the research, or in the documentation of the research, or to the suspension or discontinuation or modification of the protocol of the research or similar research.

Intensity: The intensity of adverse events is assessed by the investigator using the following classification:

- Mild Grade 1: adverse event usually transient and without impact on normal activities;
- Moderate Grade 2: adverse event sufficiently troublesome to affect normal activities;
- Severe Grade 3: An adverse event that significantly alters the patient's normal course of activities, or is disabling or life-threatening.

Device failure

- Deficiency of the medical device related to its identity, quality, durability, reliability, safety or performance

Note: Device defects include malfunctions, operating errors, and improper labeling.

Any defects in the medical device related to its identity, quality, durability, reliability, safety, or performance should be documented throughout the clinical trial and properly managed by the sponsor.

Medical device defects that did not result in an adverse event, but could have resulted in a medical event

(a) if none of the appropriate steps had been taken,

(b) if the intervention had not been made, or

c) if the circumstances had been less fortunate,

should be reported as part of the study

Accountability: The investigator and Sponsor assess both the relationship of the adverse event (AE) to the device under investigation and the relationship of the AE to a protocol intervention

13.2 INVESTIGATOR'S RESPONSIBILITIES

13.2.1 Notification of adverse events (AEs)

Patients will be encouraged to report any DM-related incidents and DM-related tolerance incidents to the investigator.

At each assessment, the investigator will interview the patient to determine if any adverse events have occurred.

The physician will report in the eCRF all DM-related incidents and DM-related tolerance incidents observed or spontaneously reported by the patient throughout the study (as soon as the patient's signed consent to participate in the study is obtained).

AEs not related to the DM or not related to the procedure for implanting the DM will not be reported in the eCRF. However, physicians must report any adverse reaction suspected to be due to a drug or product by mail to the regional pharmacovigilance center (CRPV) on which they depend or on the website http://solidarites-sante.gouv.fr/soins-et-maladies/signalement-sante-gouv-fr.

DM-related incidents and DM-related tolerance incidents will be documented in detail in the observation book (eCRF). The following information should be filled in:

- Date and time of AR onset,
- Duration of AE (indicating the total duration of the AE or symptom or determining this duration from the start and end dates and times of the evolution),
- Intensity of AE (mild, moderate, severe),
- The causal relationship of the AR to the DM AND/OR to the procedure related to the DM,
- Any action taken with respect to the product under investigation and to address this AR,
- Evolution of the AR (e.g. complete resolution, persistence...),

The investigator should assess the intensity, severity and causality of all adverse events.

These should be followed up until the event is resolved.

Determination of duration:

If the total duration of the AR or symptom is not directly indicated, it will be calculated from its onset and end dates.

Intensity Assessment :

The investigator will specify the intensity of the AE according to the following classification: mild, moderate, severe taking into account the possible degrees of intensity of the event according to the following definitions:

Slight	▪ Causes mild or transient discomfort, not requiring intervention or treatment. ▪ Does not limit or interfere with daily activities.
Moderate	▪ Causes enough discomfort to limit or interfere with daily activities. ▪ May require treatment.
Severe	▪ Causes significant symptoms that prevent normal daily activities. ▪ May require an invasive procedure.

Accountability / causal relationship with the study product and research:

The sponsor will rule on the causality of the event that occurred.

Related	Any clinical or biological event with a chronological and semiological relationship compatible with the occurrence of the AR.
Unbound	The AR is clearly related to other causes, such as the patient's clinical condition or concomitant therapy.

Appraisal of AR development:

The investigator will also inform the Sponsor of any new follow-up information.

The investigator will specify the course of the AR according to the following classification:

- Favorable evolution/healing,
- In the process of recovery,
- Persistence of AR,
- Resolution / healing with residual effects (to be specified),
- Death,
- Unknown evolution.

At the end of the study, a list of incidents related to the DM and non-serious incidents of tolerance related to the DM will be published.

13.2.2 Reporting of Serious Adverse Events (SAE)

The investigator is responsible for notifying the sponsor via Axonal-Biostatem **without delay from the** day he/she becomes aware of all serious events related to the DM occurring during the research.

In the event of an SAE, the investigator must complete the specific form for SAEs provided by the Sponsor. Any SAE related to the DM must nevertheless also be reported on the eCRF pages intended for the collection of vigilance.

As soon as the investigator is aware of the occurrence of an ADR related to the DM, he/she must **immediately** notify **the Sponsor, or its representatives, and the CRO in charge of the study logistics** (Axonal-Biostatem) by e-mail within **24 hours of becoming aware of the event**, by sending the completed ADR form to :

Vigilance correspondent :

Responsible for the vigilance service :

CAROLINE NAVARRE

VIGIPHARM

265 Maurice Béjart Street

34 080 Montpellier

Tel: + 33 467 107 252- Fax: +33 (0)4-67-10-72-53

medtrum@vigipharm.fr

This SAE form must be completed and submitted for all SAEs, regardless of a possible causal relationship. This form is also available in the eCRF.

The investigator is asked to document in detail in the SAE report the course of the AE, as well as any treatment administered and any relevant data. The investigator will be asked to comment on the causality of the event in relation to the research on the SAE form.

The investigator should follow the SAE until it is resolved and inform the Sponsor of any new follow-up information and the progress of the SAE (follow-up report).

In the case of death, the investigator is requested to send the Sponsor any available additional information (e.g. autopsy report, medical report).

The CRO will immediately inform the study's vigilance correspondent (VIGIPHARM) by sending them the SAE form and ensuring that it is correctly transmitted.

13.2.3 Pregnancy Notification

The investigator must also notify the CRO vigilance correspondent (Axonal-Biostatem) of any case of pregnancy.

The CRO will immediately inform the study's vigilance correspondent (VIGIPHARM) by sending them the form for declaring grossness, and ensuring that it is correctly transmitted.

In case of notification of pregnancy, a follow-up of the AR will be done until 3 months after the birth of the child. Furthermore, if the birth is scheduled after the basic freeze, the information received will be processed afterwards.

13.2.4 Notification of overdose

The investigator must also notify the CRO vigilance correspondent (Axonal-Biostatem) of any case of drug overdose.

13.2.5 Notification of New Facts

Any development that may be sufficient to consider changes in the use of the medical device being tested, in the conduct of the research, or in the research documentation, or that may lead to a reassessment of the benefits and risks of the research, should be reported to the sponsor **without delay** by the investigator.

13.2.6 Notification of vigilance incidents

All vigilance incidents must be reported by the investigator after having been informed by e-mail to the Sponsor, or to its representatives and to the CRO in charge of the study logistics (Axonal-Biostatem), by sending the duly completed vigilance form.

Vigilance correspondent :

Responsible for the vigilance service :

CAROLINE NAVARRE

VIGIPHARM

265 Maurice Béjart Street

34 080 Montpellier

Tel: + 33 467 107 252- Fax: +33 (0)4-67-10-72-53

medtrum@vigipharm.fr

Notification without delay

Notification of incidents or risks of serious incidents involving a medical device that have resulted or may result in the death or serious deterioration of the state of health of a patient must be made without delay:

- Death of the patient or threat to life,
- Permanent or significant disability or incapacity,
- Need for hospitalization or prolongation of hospitalization,
- Any circumstance requiring medical or surgical intervention
- Occurrence of a congenital anomaly or malformation.

Other incidents

All of the following other incidents should also be reported by the investigator:

- Any malfunction or alteration in the characteristics or performance of the medical device,
- Any harmful and unintended reaction that occurs when the medical device is used for its intended purpose,
- Any harmful and unintended reaction resulting from the use of a medical device not in accordance with the manufacturer's instructions.

13.3 SPONSOR'S RESPONSIBILITIES

The Sponsor is responsible for the ongoing evaluation of the safety of the research and for reporting vigilance information to the appropriate regulatory authorities.

The sponsor will transmit to all concerned investigators via Axonal-Biostatem information that may affect the safety of the persons involved in the research, including any relevant

information regarding suspected ADRs related to the DM or any significant safety-related event.

13.4 SUPERVISORY COMMITTEE

All incidents involving the medical device will be collected during the study and evaluated by a Monitoring Committee.

This Supervisory Committee will consist of 3 independent members.

Each member will be required to sign an attestation of no potential pecuniary conflict of interest related to the study results, and should not be known to have a "strong opinion" on the relative merits of the interventions tested in the study.

This Committee will meet at the request of the Scientific Committee, the Sponsor or the investigators.

He will be responsible for:

- Conduct regular reviews of the safety and performance elements of the study to ensure the safety of participants and that the benefit/risk ratio remains favorable for continuation of the trial
- Monitor medical or scientific information made public that may have an impact on the study in progress and the safety of participants
- Carry out the adjudication of the SAEs to decide on the imputability or not of the medical device and/or the procedure of use
- Write recommendations on continuation, modification or discontinuation of the study to the Scientific Committee and the Sponsor, based on the criteria below.

A study termination is considered if:

- The data show a statistically significant increase in the risk of adverse events making the benefit/risk ratio unacceptable,
- A serious and unexpected risk is detected,
- The state of the art makes the studied technology obsolete.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 REGULATORY FRAMEWORK OF THE STUDY

This study will be conducted in compliance with the ethical principles of the Declaration of Helsinki revised in 2013, of the ICH-GCP E6(R2) Good Clinical Practices, the ISO 14155 standard, the European Regulation on medical devices 2017/745 and the French legislation on clinical studies .

According to the current French legislation, this study is considered as a type II research involving the human being (RIPH) (interventional study with minimal risks and constraints concerning a CE marked medical device not marketed in France).

14.2 SUBMISSION OF THE PROTOCOL AND STUDY CONTRACT

The study will start only after a favorable opinion of the Committee of Protection of the Persons drawn and will be sent for information to the ANSM.

14.2.1 Declaration to the Competent Regulatory Authorities

The study was registered in the French database and in the European database of studies under the ID-RCB: 2019-A02566-51.

This protocol was sent for information to the French National Agency for the Safety of Medicines and Health Products (ANSM).

Any amendment (corresponding to substantial modifications) will be sent for information to the Competent Authority before its implementation.

Any amendments to the protocol should be sent in writing to all investigators and signed and dated by the sponsor and investigators.

14.2.2 Declaration to the Ethics Committee

The protocol has been submitted in France to the Comité de Protection des Personnes (CPP) SUD-EST VI.

Neither the investigator nor the sponsor may modify this protocol without prior written agreement between the two parties. Any modification considered significant by the investigator or the person in charge of the study must be approved by the CPP before its implementation.

14.2.3 Protection of personal data

The study will be carried out in compliance with the European General Data Protection Regulation (RGPD) and with the French legislation (CNIL).

14.2.4 Declaration to the Orders Professional

The study will be in compliance with the obligations of the profession, and will respect the obligations of transparency of links of interest.

Patient and physician data will be collected in accordance with Chapter IX of Law 78-17 of January 6, 1978, as amended by Law 2004-801 of August 6, 2004 (known as the "Loi Informatique et Libertés") and Article 16 of Law 2018-493 of June 20, 2018 on the protection of personal data.

This protocol of Research Involving the Human Person will be carried out in accordance with the methodology of reference MR-001 of the CNIL of July 21, 2016 (Commission Nationale Informatique et Libertés).

A compliance file to MR-001 was created in order to document the applicable framework of the study. The Sponsor has taken the necessary steps with the CNIL and has committed to respecting the reference methodologies.

14.3 PATIENT INFORMATION AND CONSENT

Patients from whom personal data are collected will be individually informed by the investigating physicians before the beginning of the study (i.e. before any examination that may be necessary to select them for the study) of the objectives of the study, the methods, the nature of the information collected, the purpose of the data processing, the potential benefits and risks related to their participation, and the right to access and rectify the data with the physician.

This information is clearly and legibly stated on an information and consent form. The investigator will provide the patient with a copy of the information and informed consent form. Each patient will be given the opportunity to ask any questions they may have and will be informed of their right to withdraw their consent at any time during the study without having to provide a reason and without any consequences for future care.

Following this informative discussion, the investigator will ask the patient to date and sign the consent form. The patient can only be included in the study by the investigator after having obtained his or her informed, voluntary and written consent.

Any changes to the patient information and consent form must be submitted to the PPC for approval prior to use.

A copy of the dated and signed consent form should be given to the patient. The investigator should retain the original signed and dated consent form in the study file. The investigator will indicate on each case report form that he/she has informed the patient of the study and has obtained his/her voluntary written consent.

14.4 PRIVACY

All study materials provided by the Sponsor to the Investigator and his or her designated personnel are subject to a duty of confidentiality. Under no circumstances should their contents be disclosed to any third party not directly involved in the study, without the prior written permission of the Sponsor.

The investigator must ensure that patient anonymity is maintained. A unique identification code will be associated with each patient and used in all communications.

14.5 STOP THE STUDY

At the discretion of the Principal Investigator of this study, the study may be terminated at any time for medical reasons. In addition, the Sponsor reserves the right to stop the study at any time if it cannot be conducted in accordance with the protocol.

In the event of premature termination or suspension of the study, the study sponsor will promptly inform the investigator and the authorities. All study materials should be returned, destroyed or retained as directed by the sponsor.

14.6 ARCHIVING

Study documents must be archived by the participating center in a dedicated, access-controlled area for a period of 15 years, to ensure the confidentiality and protection of personal data collected during the study. The standard archiving procedures of the investigating center will be applied.

14.7 INSURANCE AND FINANCING

The Sponsor agrees to maintain a civil insurance policy for the duration of the study, in accordance with the legislation governing studies in humans.

In the event of damage or injury to subjects attributable to study treatment or participation in the study, as required by law and the GCP, MEDTRUM has purchased an insurance policy No. 0100534514058 190120 from HDI GLOBAL SE (Appendix 1).

This insurance policy covers the liability of the sponsor, the investigator and any other person involved in the study in accordance with the law.

As the claim for compensation may follow other routes than the one provided by the law of 20.12.1988, it is recommended that investigators have a civil liability insurance policy for their research activities.

The study is fully funded by MEDTRUM.

15 DOCUMENTATION AND USE OF STUDY RESULTS

All information related to this study and not yet published is confidential and remains the sole property of the Sponsor. The physician agrees to use this information only for the conduct of the study and for no other purpose except with the prior written consent of the Sponsor, except for possible communications to representatives of the relevant health authorities.

A report of the study will be written at the end of the study and will be submitted to the Scientific Committee for review and approval.

All study data and results are the sole property of the Sponsor.

Communications at scientific meetings and publications in peer-reviewed scientific journals will be made under the cover of the Scientific Committee which will validate their form and content in agreement with the Sponsor.

16 SCHEDULE OF THE STUDY

The projected schedule for the study is as follows:

- Regulatory submissions: October 2019
- Obtaining regulatory approvals: December 2019
- Implementation of the study: January to October 2020
- Patient Inclusion: January 2020 to November 2020
- End of follow-up of the last patient: March 2021
- Database freeze: June 2021
- Full study report with follow-up: December 2021

However, the total duration of the study or the recruitment period may vary depending on regulatory deadlines and recruitment capacities.

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18 APPENDICES

18.1 STUDY INSURANCE

HDI Global SE
Tour Opus 12 – Défense 9
77 Esplanade du Général de Gaulle
92914 PARIS LA DEFENSE CEDEX
478 913 882 RCS Nanterre
N° SIRET : 478 913 882 000 54

ATTESTATION D'ASSURANCE
RESPONSABILITE CIVILE PROMOTEUR DE RECHERCHES IMPLIQUANT LA PERSONNE HUMAINE

CONTRAT N°

Nous, soussignés **HDI GLOBAL SE** - Direction pour la France - TOUR OPUS 12, 77, Esplanade de la Défense 92914 PARIS LA DEFENSE agissant en qualité d'assureur, attestons par la présente que :

a souscrit un contrat de Responsabilité Promoteur de recherche impliquant la personne humaine sous le numéro ci-dessus référencé.
Ce contrat est conforme aux dispositions légales et réglementaires Françaises sur les recherches impliquant la personne humaine et notamment aux dispositions de la loi 88.1138 du 20/12/1988, modifiée par les textes subséquents notamment la Loi n°2012-300 du 5 Mars 2012 et son décret d'application n°2016-1537 du 16 Novembre 2016, pour la recherche dénommée ci-après :

Nom du promoteur :

Numéro d'enregistrement :
(EUDRACT ou n° fourni par l'ANSM)

Titre de la recherche :

Nombre de patients :

Début et fin prévisionnels :

La garantie est conforme à l'obligation d'assurance instituée par les textes de la loi précitée, article L 1121-10 du Code de la Santé Publique et articles R 1121-4 à R 1121-9 à la charge du promoteur, tant pour sa responsabilité que pour celle des intervenants.

La présente attestation est valable pour la durée de la recherche concernée et sa présentation vaut présomption de garantie à la charge de l'assureur.

Fait , le

Le Courtier
BIOMEDIC INSURE

L'Assureur
HDI GLOBAL SE

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