Axonal-Biostatem Group
Via Domitia business park
205, avenue des Gardians
34160 CASTRIES - FRANCE
: 33 (0) 4 67 04 87 54
: 33 (0) 4 67 04 87 71
e-mail : contact@biostatem.com

Sponsor

MEDTRUM France
88 T Avenue du Général Leclerc,
Boulogne Billancourt, France

STATISTICAL ANALYSIS PLAN

MedInPS

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

Study Type:	Randomized, open-label, multicenter, prospective clinical trial
Statistician :	Samuel GOURLAIN
Version no. :	1
Date:	03/05/2021
Version type :	SAP

LIST OF VERSIONS

Version	Parties involved	Date	Nature(*)	Rationale for the amendment
Draft 0.1	All	09/03/2021	C	Creation of the Statistical Analysis Plan
Final 1	All	03/05/2021	M	

(*) C: Creation, M: Modification, A: Addition, S: Deletion

SIGNATURE FORM

Auteur du Plan d'Analyse Statistique : Samuel GOURLAIN, Statisticien

Date :

Signature : Samuel Gourlain Signature numérique de Samuel Gourlain Date : 2021.05.17 10:55:16 +02'00'

Relecture et validation Axonal-Biostatem :

Fonction	Nom	Date / signature
Statisticien	Hugo LACOUR	Hugo Lacour Signature numérique de Hugo Lacour Date : 2021.05.17 11:33:58 +02'00'
Directeur de Projet	Jean-Pierre MEUNIER	17/05/2021

Relecture et validation Promoteur :

Fonction	Nom	Date / signature
Directeur Commercial	MARMOUNIER-WILHELM Melanie	11 mai 2021
Investigateur Principal	PENFORNIS Alfred	12 mai 2021 CENTRE HOSPITALIER SUD FRANCILIEN Pr Alfred PENFORNIS - Service d'Endocrinologie-Diabétologie N°T.PPS 10002476785 - FINESS 910002773 40, Av. Serge Dassault - 91106 CORBEIL-ESSONNES Cedex Tél. 01 61 69 30 86

TABLE OF CONTENTS

1 ABBREVIATIONS

ANSM	National Agency for the Safety of Medicines and Health Products
CRA	Clinical Research Associate
ATC	Anatomical, Therapeutic and Chemical Classification
CRO	Company Provider (*Contract Research Organization*)
eCRF	Electronic *Case Report* Form
UE	Undesirable Event
SAE	Serious Adverse Event
SD	Standard deviation
EVA	Visual Analog Scale
BMI	Body Mass Index
ITT	Intent to Treat
LPPR	List of Reimbursable Products and Services
NSN	Number of subjects needed
PDM	Personal Diabetes Manager
PP	Per Protocol
PT	Preferred Term
SNITEM	National Union of the Medical Technology Industry
SOC	Organ system class

The purpose of this document is to detail the statistical analyses that will be performed for the MedInPS study, based on the study protocol (Final Version 1.3, dated May 13, 2020). This document was drafted by the statistician, and reviewed and approved by the study sponsor prior to the baseline freeze.

2 RATIONALE FOR THE STUDY

The treatment of patients with type 1 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 which are metabolic emergencies (including coma): related either to hyperglycemia ± 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 effective 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 infusion. 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 administered. 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.

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 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 from 2019, the number of patients using an external insulin pump was estimated at 82,000.

Insulin pump administration has a different penetration rate depending on the type of diabetes and the age group (estimated penetration rate in adults: 16%, in children: 50%).

3 OBJECTIVES OF THE STUDY

3.1 MAIN OBJECTIVE

The primary endpoint is the estimate of HbA1c at 3 months 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 was calculated in each arm from measurements automatically recorded by a continuous glucose sensor that the patient was already using: the FreeStyle Libre.

3.2 SECONDARY OBJECTIVES

Secondary objectives were 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, out-of-target value, time in range, variability)
- Glycemic events (hypoglycemia and hyperglycemia - as defined by the ADA, coma, other complications)

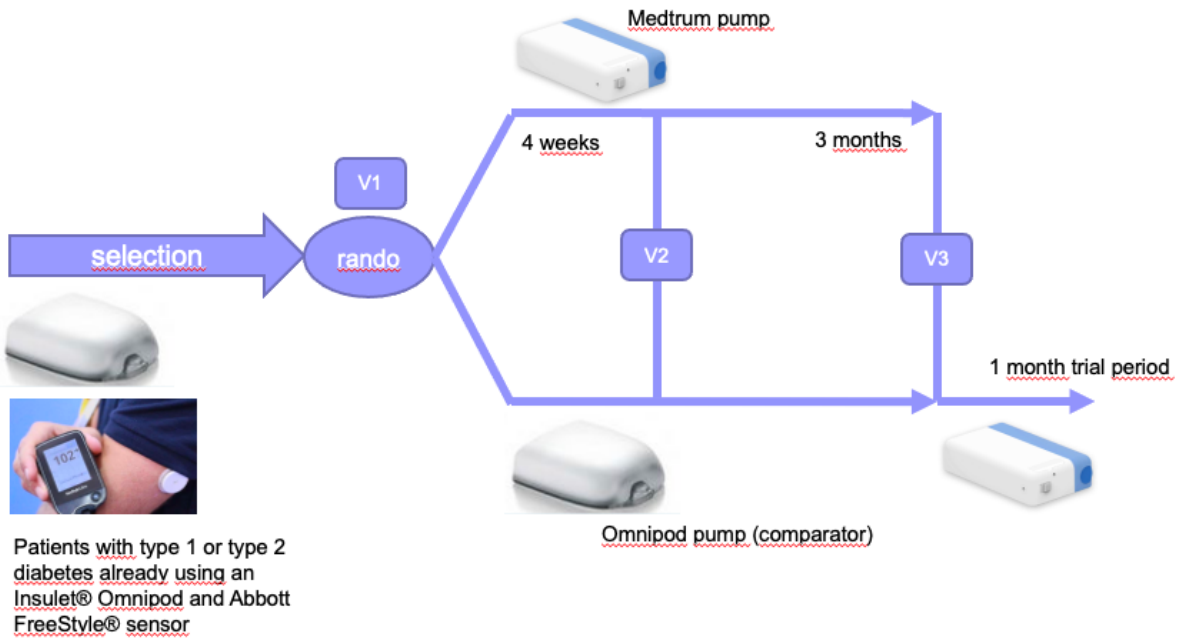
- Skin and general tolerance
- Technical incidents with the device
- Overall patient satisfaction, in the overall population and in each arm
- Insulin treatment compliance

4 METHODOLOGY

4.1 GENERAL SCHEME OF THE STUDY

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).

It was planned that 75 type 1 or 2 diabetic patients would 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 to be randomized into the Omnipod group (thus without changing their pump), it was proposed that these patients could use a Medtrum pump at the end of the study for 1 month. Thus, all patients in the study had the opportunity to use the new A7+ TouchCare® pump.

The expected duration of the study was: 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.

4.2 STUDY POPULATION

4.2.1 Patient selection

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

Each patient had to be informed by the investigator orally and in writing by means of the information leaflet informing them of the objectives and modalities of the study, of the collection and computer processing of their health data, of their right to withdraw from the study without having to justify themselves. The patient had the possibility to ask questions to the study staff of the investigating center. If a patient decided to participate, he/she had to sign the consent form approved by the Ethics Committee before any procedure related to the study.

A patient was included in the clinical study only after giving written informed consent and meeting all inclusion criteria and none of the non-inclusion criteria.

Because the patients in this study were not involved in emergency medical treatment, no consent was collected in this specific emergency setting.

4.2.2 Selection of centers

The study was carried out in France, 8 hospital centers specialized in diabetes were asked to participate in the study.

4.3 INCLUSION OF PATIENTS

4.3.1 Inclusion criteria

To be included in the study, all patients had to meet all the following inclusion criteria:

- 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 sensor (Abbott)
- A1c between ≥6.5% - ≤9.5%
- Treated with any type of rapid-acting insulin except FIASP (which can be substituted as needed) with up to 60 IU per day (no use of insulin supplements by pen injector allowed)
- Patient able to receive and understand study information, give written informed consent, and easily participate in the study

4.3.2 Non-inclusion criteria

Patients were not to participate in this clinical study if they met at least one of the following criteria:

- Patient already participating in another study
- Patient under the protection of the court or under guardianship or curatorship
- 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 and breastfeeding women
- Or any other criteria as determined by the investigator

4.4 EVALUATION CRITERIA

4.4.1 Primary endpoint

The primary endpoint is the estimation of HbA1c from the mean of glucose measurements over the last 10 weeks of follow-up.

Blood glucose levels were obtained from the measurements of 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 was asked to print the measurements from the software to facilitate monitoring of the reported data.

There will be no recalculation of the estimated HbA1c.

We have chosen to evaluate HbA1c obtained from a sensor measurement which is a good estimate of the average blood glucose level. The evolution of the classical HbA1c level is not informative on the time spent in hyper or hypoglycemia (whether or not the latter is symptomatic) because it does not reflect glycemic variability. In addition, the Nathan study highlights the reliability of estimating HbA1c over 14 days of continuous sensor measurements, as do the 2017 ADA Recommendations; more recently, the 2019 International Consensus on Time in Range recommendations reiterate the limitations of the HbA1c

criterion in the laboratory. The evolution of the monitoring of the effectiveness of insulin treatment is moving more and more towards average blood glucose and "Time in Range" (time spent in the target range/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.

4.4.2 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 of glucose measurements over each time period and over the entire study duration
  - Minimum and maximum values
  - Time in range expressed as a %.

  These values were automatically calculated by the FreeStyle Libre software and will be reported by the investigator.
- Glycemic events
  - Number of symptomatic and non-symptomatic hypoglycemic events during the evaluation period, broken down by severity level
  - Number of symptomatic and non-symptomatic hyperglycemia events over the evaluation period, broken down by severity level

  This information was derived from the Free Freestyle data and the data entered by the patient in the MDP.
  The definition of hypoglycemia and hyperglycemia is the ADA consensus definition:

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 were to 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, especially for pumps: pulling out, control problems, transmission difficulties, occlusion, leakage, 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
  - The delivered insulin doses were obtained from the pump data record. The total volume and the distribution between basal and bolus as well as the evolution of these doses during the study will be observed.
  - Although not allowed in the study, possible additional insulin injections with a pen were documented when appropriate.

4.4.3 Calculated/derived criteria

Source data	Bypass rule	Label	Format
Dates of inclusion	INC_D = (Date of last inclusion - date of first inclusion+1) / 30.44	Duration of inclusion (in months)	Digital
Inclusion and visit dates	STUDY_D = (Date of last patient follow-up - date of first inclusion+1) / 30.44	Duration of the study (in months)	Digital
Patient eligibility and randomization	ITT_D = -1 if the patient meets the inclusion and non-inclusion criteria and has used the pump device at least once -0 otherwise	Population ITT	0 = "No 1 = "Yes
ITT_D and major protocol deviation	PP_D = -1 if the patient belongs to the ITT population without major deviation from the protocol -0 otherwise	Population PP	0 = "No 1 = "Yes
Randomization	SAFT_D = -1 if the patient has used the pump device at least once -0 otherwise	Tolerance population	0 = "No 1 = "Yes
Pre-inclusion date and date of birth	AGE_D = (Pre-Entry Date - Date of Birth) / 365.25	Age (in years)	Digital
Date of pre-inclusion and date of discovery of diabetes	DIAB_D = (Pre-inclusion date - date of discovery of diabetes) / 365.25	Time since discovery of diabetes (in years)	Digital
Time since discovery of diabetes (in years)	DIAB_3CL = -0 if DIAB_D <5 -1 if DIAB_D = [5 ; 10[-2 if DIAB_D = >10	Time since discovery of diabetes (in classes)	0 = "Less than 5 years 1 = "Between 5 and 10 years

			2 = "More than 10 years
Number of years and months of treatment per pump	PUMP_D = Number of years * 12 + number of months	Time since starting pump therapy (in months)	Digital
Weight (kg) and height (cm)	BMI_D = (weight/height²)*10000	Body Mass Index (BMI)	Digital
IMC_D	IMC4CL_D = -0 if BMI_D<18.5 -1 if BMI_D = [18,5 ; 25[-2 if BMI_D = [25; 30[. -3 if BMI_D >= 30	BMI (in classes)	0 = "Less than 18.5 1 = " [18,5 ; 25[" 2 = " [25 ; 30[" 3 = "Greater than 30
Tolerance variables	AL_PBTOL_D = -1 if the patient reported during the follow-up an irritation/itching problem or a redness problem or another adverse event -0 otherwise	Patient with at least one tolerance problem	0 = "No 1 = "Yes
HbA1c value measured in the laboratory at D0 and 3M	EVOL_HBA1C_D = HbA1c at M3 - HbA1c at D0	Evolution of HbA1c between D0 and 3M	Digital
Estimated HbA1c (FSL) (%)	EVOL_eHbA1c = HbA1c estimate at V2 - HbA1c estimate at D0 (will also be calculated for V3 and V4)	Evolution of HbA1c estimation between D0 and V2,V3,V4	Digital
Average blood glucose at different follow-up times	EVOL_GLYC_V2 = Average blood glucose at V2 - Average blood glucose at D0 (will also be calculated for V3 and V4)	Evolution of the average blood glucose level between D0 and V2, V3, V4	Digital
Average daily basal dose at different follow-up times	EVOL_BASAL_V2 = Average daily basal dose at V2 - Average daily basal dose at D0 (will also be calculated for V3 and V4)	Evolution of the average daily basal dose between D0 and V2, V3, V4	Digital
Average daily bolus dose at different follow-up times	EVOL_BOLUS_V2 = Average daily bolus dose at V2 - Average daily bolus dose at D0 (will also be calculated for V3 and V4)	Evolution of the average daily bolus dose between D0 and V2, V3, V4	Digital

Number of Boluses/day at different follow-up times	EVOL_NB_BOLUS_V2 = Number of Boluses/day at V2 - Number of Boluses/day at D0 (will also be calculated for V3 and V4)	Evolution of the number of Bolus/day between D0 and V2, V3,V4	Digital
Time of wearing the FSL	PORT_70sup = -1 wear time greater than 70%. -0 otherwise	FSL wear time greater than 70%.	0 = "No 1 = "Yes

5 METHODOLOGY FOR STATISTICAL ANALYSIS

5.1 NUMBER OF SUBJECTS NEEDED (NSN)

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 corresponds to an estimated average HbA1c of 7.8% based on the experience of the three centers in the study's scientific committee, 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 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%.
On the basis of 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 was 60 patients (30 in each group).
Assuming that 20% of patients could not be analyzed (major discrepancies, missing data, lost to follow-up), the number of patients to be randomized was 75.
100 patients were finally included; to confirm our standard deviation hypothesis, a descriptive analysis of baseline HbA1c data for the entire population was performed in a blinded fashion at the end of the inclusion period. The standard deviation of the HbA1c estimate (FSL) was equal to 0.8.
With regard to the other assumptions of the protocol:

- Risk of first kind: 2.5%.
- Statistical power: 80%.
- Non-inferiority limit Δ : +0.4
- Assumed value of the difference between the two pumps: 0

The sample of patients needed for the study is estimated at 63 patients per group, for a total of **126 analyzable patients**.
As the study cannot include more than 100 patients, the statistical power of the study will be less than 80%.

5.2 GENERALITIES FOR STATISTICAL ANALYSIS

Depending on the nature of the criteria studied, the descriptive statistics will be as follows:
For categorical data: number of individuals, number of missing values, frequency and percentages of each of the variable's terms (excluding missing data in the denominator). Two-sided 95% confidence intervals will be provided when deemed appropriate. Percentage will be presented to one decimal place.
Statistical analysis of quantitative data: number of individuals, number of missing values, mean, standard deviation, median, quartiles, minimum and maximum. The data will be presented as follows: 1 decimal place more than the original variable for mean and standard deviation, 0 for median, quartiles, min and max.
Statistical analyses will be performed using SAS® software, version 9.4, SAS Institute, NC, Cary, USA.

5.3 MISSING DATA MANAGEMENT

All incomplete study dates will be charged as follows:

-The missing days will be replaced by 15
-The missing months will be replaced by the month of June (06)
-Thus, if the day and month are missing, the date considered will be: 15/06/YYYY

In case of calculation of duration resulting in negative values, these durations will be considered as missing.

5.4 MANAGEMENT OF EXTREME DATA ("OUTLIERS")

Before freezing the database, and prior to any statistical analysis, a review of the data will be performed to correct inconsistent and/or outlier data.
The agreements made will be validated by the sponsor and detailed in a data review report.

6 MODIFICATIONS TO THE ANALYSES PROVIDED FOR IN THE PROTOCOL

Not applicable

7 STATISTICAL ANALYSIS

7.1 STUDY POPULATION

7.1.1 Patient Status/General Study Data

Will be described:

- The number of participating centers in the study and the number of patients included per center
- The number of patients included
- The inclusion period (date of the first and last patient included)
- Duration of inclusion in months: (Date of last inclusion - date of first inclusion+1) / 30.44
- Study duration in months: (Date of last patient follow-up - date of first inclusion+1) / 30.44

An inclusion curve will also be presented.

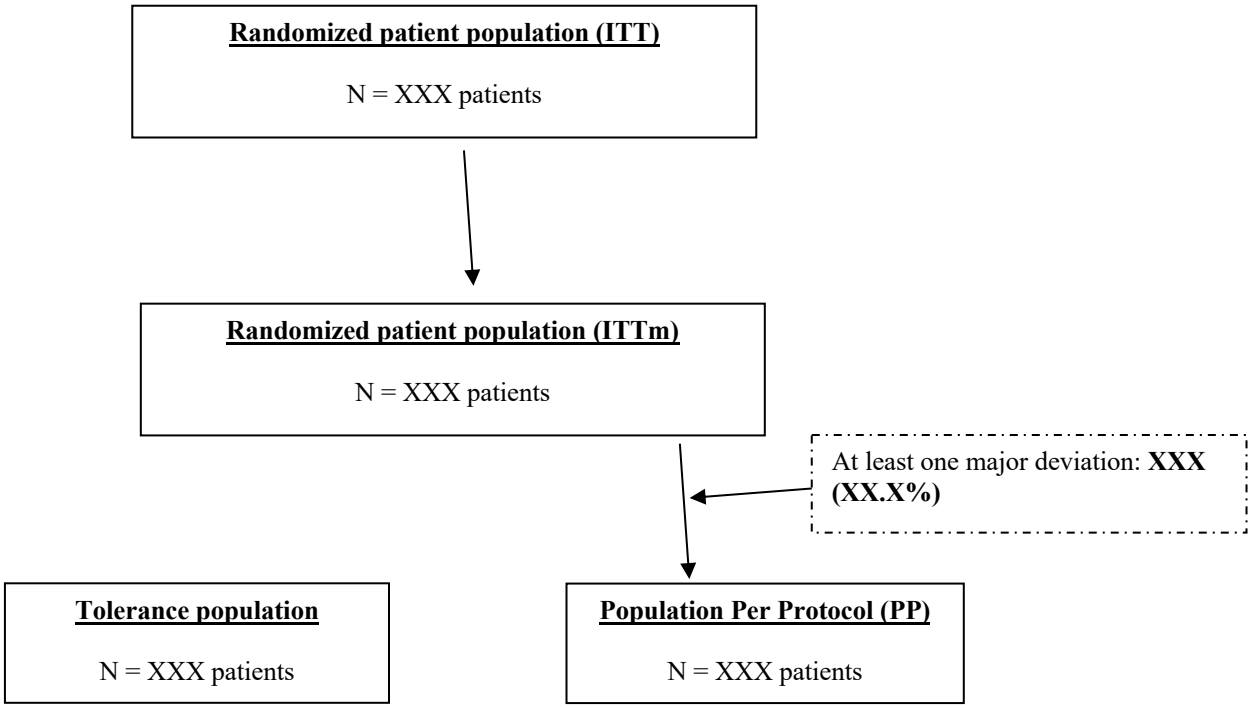
7.1.2 Deviations from the protocol

Protocol deviations will be summarized in tables for all included patients, specifying for each type of deviation the number of patients concerned.
The minor/major nature of deviations will be defined with the Sponsor and reported in the data review report.
In the event of a major protocol deviation, patients will be excluded from the Per Protocol analysis population.
The list of deviations from the protocol will be given.

7.1.3 Populations of analysis

Analysis populations will be presented with the number of patients in each treatment group.
Intent-to-treat (ITT) population: all included and randomized patients who used the pump device at least once.
Intent-to-treat (ITTm) population: ITT population with exclusion of the 4 patients discharged due to COVID-19.
Population Per Protocol (PP): ITT patients with no major protocol deviations.
Tolerance population: all patients who have used the pump device at least once.

The following flow-chart will be completed:



7.2 END OF STUDY

Will be described:

- Patient who completed the study according to the protocol
  - If not, reason:
    - Non-compliance with the criteria (screen failure)
    - Malfunction of a medical device that does not allow the study to continue
    - Patient's decision
    - Investigator's decision
    - Lost to view
    - Other
      - Other reasons will be given in a listing

7.3 PATIENT CHARACTERISTICS AT INCLUSION

Inclusion parameters will be described globally and according to their group allocated by randomization on the **ITT population and then on the ITTm population.**
Only demographic data will be described for **patients discharged with COVID-19**.
Demographics

- Age (years)
- Gender (female; male)
- Type of diabetes (type 1; type 2)
- Time since the discovery of diabetes
- Time since discovery of diabetes (<5 years; 5-10 years; >10 years)

- Type of diabetes treatment:
    - Time since starting pump therapy (months)

Associated oral treatment

- For patients with type 2 diabetes:
    - Associated oral treatment (yes; no)
    - The list of associated oral treatments will be given via a listing

Clinical examination

- Weight (kg)
- Size (cm)
- BMI calculated (kg/m²)
- BMI calculated in classes (Lean: <18.5 kg/m²; Normal: 18.5-<25 kg/m²; Overweight: 25-<30 kg/m²; Obese: >= 30 kg/m²)
- Heart rate (bpm)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

Biological data

- Last HbA1c measurement in the laboratory (%)

Sensor data

- Estimated HbA1c (FSL) (%)
- FSL Wear Time (%)
- FSL wear time > 70% (yes; no)
- Average blood glucose (FSL) (mg/dl)
- Blood glucose SD (FSL) (mg/dl)
- Coefficient of variation of glucose values (%)
- Number of hypoglycemia
- Time spent in hypoglycemia <70 mg/dl (%)
- of normoglycemic values > 70-180 mg/dl (%)
- Time spent above >180 mg/dl (%)

Pump data

- Name of insulin used (Novorapid; Humalog; Apidra; Other)
    - If other, details will be given in a listing
- Average total daily insulin dose:
    - Average Daily Basal Dose
    - Average daily bolus dose
    - Number of Boluses/day

7.4 ANALYSIS OF THE EVALUATION CRITERIA

7.4.1 Primary endpoint analysis

The primary endpoint is **the estimate of HbA1c** at 3 months based on the mean of continuous glucose measurements obtained during the last 10 weeks of follow-up.

HbA1c estimation will be described by treatment group and then by type of diabetes.

The non-inferiority analysis of the primary efficacy endpoint will be performed with an ANCOVA, with the medical device as an explanatory variable and an adjustment on the estimate of HbA1c at Baseline, on the PP population.

If the upper bound of the IC95% of the Omnipod-Medtrum estimated difference in means (LSmeans) exceeds the non-inferiority bound set at 0.4, non-inferiority will not be demonstrated.

If non-inferiority is demonstrated, a superiority analysis will be conducted. If the upper bound of the IC95% of the estimated difference in mean is less than -0.3, superiority will be demonstrated.

The MIXED procedure (SAS® 9.4) will be used.

Code:

```
proc mixed data=XX order=data;
where PP = 1;
class DM;
model ESTIM_HBA1c = ESTIM_HBA1c_BASELINE DM;
lsmeans DM / diff=control cl;
run;
```

A sensitivity analysis will be performed on the ITTm population with imputation of missing data by the mean or median according to the distribution of the primary endpoint.

A subgroup analysis will be performed on the population of patients with an LSP wear rate >70% at M3.

Exploratory analysis:

Univariate analyses will be conducted on age in 2 classes (below or above the median), sex, type of diabetes, center, and duration of diabetes in 3 classes (<5 years; between 5 and 10 years; >10 years). If the p-value <0.05, the variable will be included in the full model. Then a top-down stepwise strategy will be conducted to select the variables for the final model.

7.4.2 Secondary endpoint analyses

Analyses will be performed on the ITTm population.

Each variable will be described globally and by pump group.

The secondary endpoints are:

1. **HbA1c**

The evolution of HbA1c (measured in the laboratory) between D0 and 3M will be described, and a comparison between the groups will be made using a Student's t test or a Mann and Whitney test.

2. **Glucose level measurement**

The mean blood glucose level and its standard deviation (Blood Glucose Deviation SD) will be described over each period (between V1 and V2, then between V2 and v3, then between V3 and V4) and over the total duration of the study (mean, median, standard deviation, Q1-Q3, minimum and maximum). The coefficient of variation of glucose values will also be described.

The evolution of the average blood glucose level compared to baseline will be described at each visit.
FSL wear time (%) will be described.
The % of blood glucose values spent in target (time in range: [70; 180]), hypoglycemia (<70mg/dl), and hyperglycemia (>180 mg/dl) will be described over each time period in each pump group and in the total population.
For these criteria, comparisons between groups will be made using the Student or Mann-Whitney test.

3. Glycemic events

The number of hypoglycemic events will be described overall and in each period by severity level (according to ADA consensus definitions) overall and in each pump group.
Comparisons between groups will be made using Student or Mann-Whitney tests.
The % of time spent in hyperglycemia will be described overall and over each period and in each pump group. Comparisons between groups will be made using Student's t test or Mann and Whitney test.

4. Device tolerance

The analysis of this criterion is detailed in section 7.4 of this document.

5. Incidents with devices

The following criteria will be described for each period and by pump group (after reclassification):

- Pump occlusion (yes; no)
  - If yes, number of times
- Pump detachment (yes; no)
  - If yes, number of times
- Complete stop / breakage of the pump (yes; no)
  - If yes, number of times
- Other pump malfunction (yes; no)
  - All other possible malfunctions will be listed.

6. Patient satisfaction

The following criteria will be described for each period and by pump group:

- Responses to the Medtrum A7+ and Omnipod pump satisfaction questionnaires. Comparisons between pump groups of responses will be made using Student's t test or Mann and Whitney test if relevant or applicable.
- Answers to the specific questionnaire related to preference

7. Insulin treatment

The following criteria will be described for each period and per pump group, comparisons between groups will be made using Student's or Mann and Whitney test:

- Total dose administered daily (sum Basal + Bolus)
- Average Daily Basal Dose
- Average daily bolus dose
- Number of Boluses/day

The evolution of these criteria in relation to the baseline will be described at each stage.

Additional insulin injections with a pen during the study will be listed.

7.5 ANALYSIS OF TOLERANCE DURING THE STUDY

Analyses will be performed overall and by pump group 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).
The number of patients who had at least one tolerance problem will be described.
The following criteria will be described for each period and by pump group:

- Irritation/itching (yes; no)
    - If yes, maximum intensity (low; moderate; intense)
- Redness (yes; no)
    - If yes, maximum intensity (low; moderate; intense)
- Other adverse events (yes; no)
    - All other events related to tolerance will be given in a listing.

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

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

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

7.6 ANALYSES INTERMEDIATES

A descriptive analysis of baseline HbA1c data for the entire population was performed in a blinded fashion at the end of the inclusion period. This analysis is described in section 5.1 (NSN) of this document.

8 STATISTICAL TABLE TEMPLATES

The tables will be presented in the form :
Table xx: Description of quantitative variables

		Group A N=xxx	**Group B N=xxx**	**Total N=xxx**	**p-value**
Variable 1	N	x	x	x	
	Missing	x	x	x	
	Mean ± SD	xx.xx ± xx.xx	xx.xx ± xx.xx	xx.xx ± xx.xx	
	Median	xx.xx	xx.xx	xx.xx	
	Q1; Q3	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx	
	Min; Max.	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx	

		Group A N=xxx	Group B N=xxx	Total N=xxx	p-value
Variable 2	N	x	x	x	
	Missing	x	x	x	
	Mean ± SD	xx.xx ± xx.xx	xx.xx ± xx.xx	xx.xx ± xx.xx	
	Median	xx.xx	xx.xx	xx.xx	
	Q1; Q3	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx	
	Min; Max.	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx	

The 95% Confidence Intervals can be presented in the tables.

Table xx: Description of categorical variables

		Group A N=xxx	Group B N=xxx	Total N=xxx	p-value
Variable 3	N	x	x	x	X
	Missing	x	x	x	X
	Modality 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Modality 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Variable 4	N	x	x	x	X
	Missing	x	x	x	X
	Modality 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Modality 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Modality 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

The 95% Confidence Intervals can be presented in the tables.

Table xx: Description of IS by SOC and PT

SOC and PT	Total (N=xxx)		
	EI (1)	n (2)	% (3)
TOTAL	xx	xx	xx.x
SOC 1	xx	xx	xx.x
SOC 1 - PT 1	xx	xx	xx.x
SOC 1 - PT 2	xx	xx	xx.x
....	xx	xx	xx.x
SOC 2	xx	xx	xx.x
SOC 2 - PT 1	xx	xx	xx.x
SOC 2 - PT 2	xx	xx	xx.x
....	xx	xx	xx.x

(1) Number of EIs
(2) Number of patients with at least one AE
(3) % of patients with at least one AE

9 BIBLIOGRAPHY

1. CNEDiMTS opinion of May 30, 2017. External, portable, programmable insulin pumps.

2. Hanaire H, Lassmann-Vague V, Jeandidier N, et al. Treatment of diabetes mellitus using an external insulin pump: the state of the art. Diabetes Metab 2008;34:401-23

3. LassmannVague V, Clavel S, Guerci B, Hanaire H, Leroy R, Loeuille GA, Mantovani I, Pinget M, Renard E, Tubiana-Rufi N; Société francophone du diabète (ex ALFEDIAM) Expert consensus: When to treat a diabetic patient using an external insulin pump. Expert consensus. Société Francophone du Diabète 2009. Diabetes Metab. 2010 Feb;36(1):79-85. Epub 2010 Jan 13.

4. Borot S, Benhamou PY, Atlan C, Bismuth E, Bonnemaison E, Catargi B, Charpentier G, Farret A, Filhol N, Franc S, Gouet D, Guerci B, Guilhem I, Guillot C, Jeandidier N, Joubert M, Melki V, Merlen E, Penfornis A, Picard S, Renard E, Reznik Y, Riveline JP, Rudoni S, Schaepelynck P, Sola-Gazagnes A, Tubiana-Rufi N, Verier-Mine O, Hanaire H; Société francophone du diabète (SFD), Société française d'endocrinologie (SFE); Evaluation in diabetes of active implants Group (EVADIAC). Practical implementation, education and interpretation guidelines for continuous glucose monitoring: A French position statement. Diabetes Metab. 2018 ;44 :61-72.

5. The Diabetes control and complications trial research group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.

6. Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2010;(1):CD005103.

7. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med. 2008;25(7):765-774.

8. Sämann A, Mühlhauser I, Bender R, Hunger-Dathe W, Kloos C, Müller UA. Flexible intensive insulin therapy in adults with type 1 diabetes and high risk for severe hypoglycemia and diabetic ketoacidosis. Diabetes Care. 2006;29(10):2196-2199.

9. Karges B, Schwandt A, Heidtmann R, et al. Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia and Glycemic Control diabetic ketoacidosis among children, adolescents, and young adults with type 1 diabetes. JAMA. 2017;318(14):1358-66.

10. American Diabetes Association. Diabetes care in the hospital, nursing home, and skilled nursing facility. Sec. 13. In Standards of Medical Care in Diabetes - 2015. Diabetes Care 2015;38(Suppl. 1): S80-S85.

11. Leiter LA, et al. Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. Can J Diabetes 2005; 29: 186-92.

12. Zisser H.C, Howard C, Bevier W, and Jovanovičx L. Siphon. Effects on continuous subcutaneous insulin infusion pump delivery performance. Journal of Diabetes Science and Technology, Vol. 4, 2010; 98-103.

13. Bally L, Thabit H, Kojzar H, Mader J.K, Qerilmi-Hyseni J, Hartnell S, Tauschmann M, Allen J.M, Wilinska M.E, Pieber T.R, Evans M.L, Hovorka R. Day-and-night glycaemic control with closed-loop insulin delivery versus conventional insulin pump therapy in free-living adults with well-controlled type 1 diabetes: an open-label, randomised, crossover study. Lancet Diabetes Endocrinol 2017; 5: 261-70

14. When to treat a diabetic patient using an external insulin pump. Expert consensus. Société francophone du diabète (ex ALFEDIAM) 2009

15. S.Borot, , S.Franc, J. Cristant, A.Penfornis, PY.Benhamou, B. Guerci, H. Hanaire, E. Renard, Y. Reznik, C. Simon, G. Charpentier- Accuracy of a New Patch Pump Based on a Microelectromechanical System (MEMS) Compared to Other Commercially Available Insulin Pumps: Results of the First In Vitro and In Vivo Studies. Journal of Diabetes Science and Technology 2014, Vol. 8(6) 1133 -1141

16. https://solidaritessante.gouv.fr/IMG/pdf/Rapport_d_activite_du_CEPS_en_2013_version_francaise_.pdf

17. Nathan D.M, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine R.J for the A1c-Derived Average Glucose (ADAG) Study Group. Translating the A1c Assay Into Estimated Average Glucose Values. Diabetes care, volume 31, number 8, august 2008.

18. Lebenthal Y, Lazar L, Benzaquen H, Shlomit S, Philipp M. Patient perceptions of using the OmniPOD system compared with conventional insulin pumps in young adults with type 1 diabetes. Diabetes Tech & Therap. 2012;14(5):11-7.

19. Lane WS, Weinrib SL, Rappaport JM, Przestrelski T. A prospective trial of U500 insulin delivered by OmniPOD in patients with type 2 diabetes mellitus and severe insulin resistance. Endocr Pract. 2010; 16: 778-784.

20. Peyrot M, Rubin R.R. Validity and Reliability of an Instrument for Assessing Health-Related Quality of Life and Treatment Preferences. Diabetes Care, Volume 28, number 1, January 2005.

21. Bromba M, Campbell F, and Levy B.L. The Insulin Treatment Satisfaction Questionnaire and Assessment of Satisfaction with a Latest-generation Insulin Pump. Eur Endocrinol. 2015 Aug; 11(2): 67-69.

22. Bohannon N, Bergenstal R, Cuddihy R, Kruger D, List S, Massaro E, Molitch M, Raskin P, Remtema H, Strowig S, Whitehouse F, Brunelle R.L, Dreon D and Tan M. Comparison of a Novel Insulin Bolus-Patch with Pen/Syringe Injection to Deliver Mealtime Insulin for Efficacy, Preference, and Quality of Life in Adults with Diabetes: A Randomized, Crossover, Multicenter Study. Diabetes Technology & Therapeutics, Volume 13, Number 10, 2011.

23. Anderson RT, Skovlund SE, Marrero D, et al. Development and validation of the Insulin Treatment Satisfaction Questionnaire, Clin Ther, 2004;26:565-78.

24. Barnard K, Bromba M, de Lange M, et al, High reported treatment satisfaction in people with type I diabetes switching to latest generation insulin pump regardless of previous therapy, J Diabetes Sci Technol, 2015;9:231-6

25. Agiostratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman K.N, Kowalski A.J, Madden P, McElwee-Malloy M, Peters A, Raman S, Reifschneider K, Rubin K and Weinzimer S.A. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes care, volume 40, December 2017, 1622-1630.

26. Battelino T, Danne T, Bergenstal R , Amiel S, Beck R, Biester T, Bosi E, Buckingham B, Cefalu W, Close K, Cobelli C, Dassau E,DeVries JH, Donaghue K, Dovc K,1 Doyle F, Garg S, Grunberger G, Helle Sr, Heinemann L, B. Hirsch, Hovorka R, Jia W, Kordonouri O,

KovatchevB, Kowalski A, Laffel L, Levine B, Mayorov A, Mathieu C, Murphy H.R, Nimri R, Nørgaard K, Parkin CG, Renard E, Rodbard D, Saboo B , Schatz D, Stoner K,Urakami T,Weinzimer S, Phillip M: Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range-Diabetes Care Publish Ahead of Print, published online June 8, 2019
27. Guidance for Industry Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. FDA U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), December 2008.
28. LOB OPEN DATA- 2019

10 LEVEL OF VALIDATION OF ANALYSES

This chapter documents the validation of statistical analysis programs. The level of validation is defined with reference to the "Statistical Analysis Programming" procedure.
3 validation levels are defined:

- *Basic* = At each program execution, the programmer will make sure that his programming is valid. First, the code should be checked to make sure that it matches the expected analyses. Secondly, no error messages should appear in the "log/Journal" window. If this is not the case, the error should be corrected. Warnings and notes such as uninitialized variables, automatic replacement of missing data, data outside the graph area, ... should also be checked. Third, the output of the results should be checked to make sure that the submitted program is what it is supposed to do and that there are no errors in the presentation of the results.

- *NC (non-critical)* = The tables, listings and figures compiled in a single document will be verified by a qualified person other than the program developer with the study's observation book and statistical analysis plan as a support. Spot checks (number of participants, average, minimum, maximum, frequency, number of missing data) will be performed. Comparisons with other data (e.g. comparison of a figure with the source table) will be made.

- *CR (critical)* = A double programming and a comparison of the results will have to be carried out by a qualified person other than the developer of the program. In the event that the checks show discrepancies, the cause will be investigated and the programming will have to be redone if it turns out that the error came from the first programming.

Analyses with a "Basic + CR" level of programming validation	**Reference of the Statistical Analysis Plan**
- Populations	Section 7.1.3 " Populations of analysis "
- Main objective	Section 7.4.1 " Primary endpoint analysis "

The other analyses and programs have a default validation level of "Basic + NC".