NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY (PASS) AMENDED PROTOCOL 2

COMPOUND: Recombinant Human Insulin (HR1799)

(Tradename: Insuman Implantable 400 IU/mL)

Post Authorisation Safety Study (PASS): an European observational cohort of patients with type 1 diabetes treated via intraperitoneal route with Insuman Implantable 400 IU/mL in Medtronic MiniMed implantable pump

STUDY NUMBER: HUBIN-C-06380

STUDY NAME: Insuman Implantable Observational Study

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CLINICAL STUDY DIRECTOR: Valérie PILORGET, MD

The Study is conducted by IQVIA (formerly Quintiles Switzerland SARL), Route de Pallatex 29, 1162 St Prex, Switzerland, herein after referred also as the "MAH REPRESENTATIVE".

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PASS Information

Title	Post Authorisation Safety Study (PASS): an European observational cohort of patients with type 1 diabetes treated via intraperitoneal route with Insuman Implantable 400 IU/mL in Medtronic MiniMed implantable pump
Protocol version identifier	1.0
Date of last version of protocol	14-March-2014
EU PAS register number	ENCEPP/SDPP/10872
Active substance	insulin human ATC code: A10AB01
Medicinal product	Insuman Implantable 400 IU/mL
Product reference	EU/1/97/030/202EU/1/97/030/203
Procedure number	EMEA/H/C/000201/MEA/047.5
Marketing authorisation holder(s)	Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany
Joint PASS	No
Research question and objectives	To increase knowledge on the safety profile of Insuman Implantable 400 IU/ml delivered by an implantable pump into the intraperitoneal cavity and to monitor the safe use in real life setting.
Country(-ies) of study	All European countries in which the Medtronic MiniMed Implantable Pump system (MIP) is used, i.e. France, Belgium, Netherlands, and Sweden.
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Marketing authorization holder(s)

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2 LIST OF ABBREVIATIONS

AE	Adverse event
BG	Blood Glucose
CIPII	Continuous intraperitoneal insulin infusion
CI	Confidence interval
CRF	Case Report Form
CRO	Contract Research Organization
DKA	Diabetic ketoacidosis
e-CRF	electronic Case Report Form
EDC	Electronic Data dcapture
EMA	European Medicines Agency
EU	European Union
FPI	First Patient In
GPP	Good pharmacoepidemiology practice
GVP	Good pharmacovigilance practice
HbA1c	Serum Glycosylated Hemoglobin
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IP	Intraperitoneal
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LPI	Last Patient In
LPO	Last Patient Out
MAH	Marketing Authorisation Holder(s)
MedDRA	Medical Dictionary for Regulatory Activities
MIP	MiniMed Implantable Pump
PASS	Post Approval Safety Study
PTs	Preferred terms
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCII	Continuous Subcutaneous Insulin Infusion
SC	Subcutaneous Injection
SMQ	Standardised MedDRA Queries

3 RESPONSIBLE PARTIES

The Scientific Committee will be responsible for coordinating the conduct of this multinational PASS. The Scientific Committee will assess the progress of the study at both global and site levels and is given full authority for presentation/publication of the results. The detailed responsibilities of the Scientific Committee, its relationship with the other actors responsible for the management and conduct of the registry, its membership, and the purpose and timing of its meetings are described in the Scientific Committee Charter and Study Guidebook.

4 ABSTRACT

Full Study Title: Post Authorisation Safety Study (PASS): an European observational cohort of patients with type 1 diabetes treated via intraperitoneal (IP) route with Insuman Implantable 400 IU/mL in Medtronic MiniMed implantable pump.

Background and Rationale:

The importance of intensive insulin therapy in type 1 diabetes has been established. Most of the patients with Type 1 Diabetes Mellitus use insulin subcutaneously, either as injections or as continuous subcutaneous insulin infusion (SCII). However, intensive subcutaneous insulin therapy has several limitations such as difficulties to reach acceptable glycaemic control, occurrence of severe hypoglycaemic episodes (especially when combined with hypoglycaemia unawareness), and/or subcutaneous insulin resistance.

Intra peritoneal insulin delivery by an insulin pump can be used by passing the subcutaneous interstitial tissue in preferential insulin absorption by the hepatic portal venous system and results in lower peripheral insulin levels. Continuous IP insulin infusion (CIPII) has been available for more than 30 years but is used in few selected patients such as patients with subcutaneous defect of insulin absorption, patients with recurrent severe hypoglycaemia, or patients with poor glucose control. Insuman implantable is a specific Insuman formulation (400 IU/ml) developed to replace insuplant (a previous semi-synthetic insulin preparation that was granted Marketing Authorisation in France in 1998) for use exclusively with the Medtronic MiniMed implantable pump (MIP) for CIPII. The pump is implanted between the subcutaneous abdominal tissue and the abdominal muscle and delivers insulin from a reservoir through a catheter into the peritoneal cavity.

A line extension of the already approved Insuman formulations was granted for Insuman implantable by the European Commission in September 2013 with the following indication: “treatment of adult patients with type 1 diabetes mellitus that cannot be controlled with subcutaneous insulin therapy (including pump), presenting with frequent, otherwise unexplained severe hyper- and/or hypoglycaemia”. Among pharmacovigilance activities proposed in the risk management plan (RMP), a non-interventional, prospective cohort study was designed to further assess frequency of the risks related to the use of Insuman in the implantable pump in routine clinical practice, especially long term safety.

This observational prospective study will provide important longitudinal data to add to the long term safety profile of IP delivery of Insuman Implantable 400 IU/mL using an implantable pump.

Research Question and Objectives:

The primary objective of the study is to better characterize some of the important identified risks related to the use of Insuman Implantable 400 IU/mL that are listed below:

- Severe hypoglycaemia, hyperglycaemia (caused by insulin underdelivery due to pump jamming, pump dysfunction or catheter occlusion).), pump pocket infection, abnormal healing (at the surgical incision site after device implantation), and skin erosion.

The secondary objectives of the study are:

- To better characterize other important potential risks related to the use of Insuman Implantable 400 IU/mL: hypersensitivity reactions to Insuman Implantable 400 IU/mL, hypersensitivity reactions to pump material and focal hepatic steatosis,
- To gain additional data about missing information: Safety in pregnant and lactating women and long term safety (including effect of long term exposure to phenol in IP region),
- To collect additional safety data (Adverse Events).

Study Design:

This is a multinational, multicenter, observational, prospective cohort study for patients with type I diabetes who are treated with Insuman Implantable 400 IU/mL. The duration of the study is ten years from entry of first patient.

No visits or examinations, laboratory tests or procedures are mandated as part of this study. Visits will occur according to routine clinical practice for use of an implantable pump which is at refill visits (approximately every 40 to 45 days) and at *ad hoc* visits related to complications of the insulin treatment regimen or pump. Data will be collected by site and entered in an electronic case report form (e-CRF) (on an ongoing basis for adverse events; at three, and six months after study entry and then every six months for other study related information).

Population:

Inclusion Criteria:

- Patients with type 1 diabetes using Insuman Implantable in a Medtronic MiniMed implantable pump and treated in accordance with the Insuman Implantable Summary of Product Characteristics.
- Signed written informed consent.

Exclusion Criteria: None

Expected number of countries: European countries based upon availability of Insuman implantable in the next decade.

Expected number of patients: Based on the number of patients already included at the time of the amendment n° 2, approximately 260 implanted patients will be followed in the study.

Variables

Data collection at study entry will include the following:

- Patient demography: date of birth, sex, weight, and height,
- Insulin use history,
- Medical history related to use of the implantable pump (including occurrence of diabetic ketotacidosis (DKA), hyperglycaemia and severe hypoglycaemia in the year prior to entry into the study or since pump implantation for patients recently implanted),
- Comorbidities, and history of diabetes complications,
- Concomitant medications, at entry visit,
- Most recent Urine microalbumine/creatinine ratio available and laboratory normal range, with sampling date (No laboratory test is to be drawn in patients for the purpose of the study),
- Most recent Serum glycosylated hemoglobin (HbA1c) and normal laboratory range with sampling date.

Patient data collected during the follow-up

After each contact with the patients (refill visits occur approximately every 40 to 45 days, *ad hoc* visits or phone calls), the investigator will report adverse events (in an expedited manner), including:

- severe hypoglycaemia,
- hyperglycaemia caused by insulin under-delivery (due to pump jamming, pump dysfunction or catheter occlusion),
- pump pocket infection,
- abnormal healing,
- skin erosion,
- hypersensitivity reaction to Insuman or pump material,
- focal hepatic steatosis,
- other adverse events (AEs), including diabetic complications,
- pregnancy/lactation.

In addition, at three and six months after study entry, then every six months (corresponding approximately to the period for four refill visits) all the following variables and relevant information since the last visit/data collection:

- Reason for visits (planned and if not planned; metabolic or device problem since the last collection),
- Concomitant medications, related to comorbidities, complications and diabetes treatment,
- Most recent urine microalbumin/creatinine ratio available every six months,

- Most recent HbA1c available every six months,
- Check of AE reporting.

In case of study discontinuation, the following data will be collected:

- Date of discontinuation,
- Reason for study discontinuation (eg, voluntary withdrawal, definitive pump explantation, death, lost to follow-up).

All AEs will be followed until resolution or until the end of the follow-up period, whichever comes first.

Data Sources

Investigators at each site will collect and provide pre-specified data on study participants at baseline and during follow-up visits. Data elements provided by investigators and staff will be collected from information routinely recorded in the medical record, or will be prospectively recorded for the purposes of the study. No visits or examinations, laboratory tests or procedures are mandated as part of this study.

Information required to validate Serious Adverse Events (SAEs) will be requested from investigators and medical facilities as needed by the medical monitors, which may include confirmation of diagnoses or conditions and relatedness of AEs by the treating investigators, medical records including laboratory test results and imaging procedure results, and death certificates.

Study Size

This is a descriptive study that is not testing a hypothesis. As such, a formal sample size calculation is not performed. It is planned to recruit all patients who are willing to participate, from all trained investigators in certified centers in all participating European countries, and without a minimum designated for any country or region. The projected study size will be approximately 260 patients. No new patient or a very limited number of newly implanted patients is expected.

Data Analysis

Eligible patients will be those who have signed an informed consent form (ICF) and have received at least one dose of Insuman Implantable 400 IU/mL

- Primary analysis

  Since the primary objective is to monitor the important identified risks, the analysis will be descriptive and the multiplicity control will not be considered.

  For the important identified risks including severe hypoglycaemia, hyperglycaemia due to underdelivery of insulin, pump pocket infections, skin erosion, and abnormal healing, the time to first event will be depicted by the Kaplan-Meier plot. The cumulative event rate and its 95% confidence interval (CI) will be presented yearly.

  The cumulative risk over the entire study and the instantaneous risk expressed as the hazard function over time will be presented graphically according to the time expressed in years and using a kernel smoothing method. A horizontal line will represent the incidence rate calculated, as number of patients with one or more events divided by the number of patients treated.

  For rare events, the rate per 100 patient-years with two-sided 95% CI will be provided.

- Other analysis

  For rare events, the rate per 100 patient-years will be provided using the same methodology as for primary analysis. For relatively common events with recurrence, recurrent event methods might be considered. A yearly summary of event rate will also be provided for selected AEs and SAEs.

Milestones

- Anticipated start of data collection (first subject enrolled):
- First patient in (FPI): Q1 2016
- Last patient out (LPO): Q1 2026 for last patient visit
- Interim reports on a yearly basis
- Data base lock: Q2 2026
- Final key results: Q2 2026
- Final study report: Q4 2026

5 AMENDMENTS AND UPDATES

Protocol amendment n°1 (17 December 2015):

Upon request of the PRAC, this amendment is issued in order:

- to specify that the patients included in the study will be treated in accordance to the insuman implantable Summary of Product Characteristics.

Consequently, the inclusion criteria is modified in the abstract and in Section 9.2.2.1 of the protocol.

In addition,

- The Sanofi Pharmacovigilance contact is updated.
- The IQVIA Pharmacovigilance contact is added.
- The EU PAS Register/ENCEPP registration number is specified.
- The milestones of the study are updated in the abstract and in Section 6 of the protocol.
- Minor update on data management process is done.

Protocol amendment n°2 (20 February 2018):

In June 2017, Medtronic, manufacturer and supplier of the MiniMed Implantable Pump (MIP), used with Insuman Implantable 400 IU/mL, has decided to start the phase-out process of the pump and will completely stop the manufacturing and the supply of MIP or MiniMed Implantable pumps by June 2019.

During the two-year transition period, Medtronic will produce a limited number of pumps, for replacement when needed in patients already implanted. Medtronic has committed to maintaining the supply of MIP accessories (eg, catheters and consumables needed for refill and rinse procedures), as well as Insuman Implantable until end of life of the last implanted pump.

This decision will have consequences on the study, mainly in terms of sample size, expected average followed-up duration by patient and possible limitations of the analyses performed.

The current amendment is issued to implement in the Study Protocol the appropriate changes, arising from the MIP phase-out, mainly in term of update of sample size.

In addition, the list of countries in which the Medtronic MiniMed pump is used and the contact name and details of the Marketing Authorisation Holder European Qualified Person responsible for PharmacoVigilance) are updated.

The planned study milestones are not modified, as of today: end of study (2026) being planned ten years after study entry of the first patient (that occurred in April 2016) and taking into account

that the estimated life duration of the pump is seven years (with an expected last Pump implantation in 2019). Milestones will be updated later, as needed.

Sample size reduction, updated corresponding precision expected for the evaluation variables (identified risks), and as a consequence, possible limitations of the statistical analyses performed will be described in the amended statistical analysis plan.

In addition, administrative changes were implemented: updates in the CRO name and contact (as of November 2017, Quintiles has changed its name to IQVIA) and change of procedure number.

6 MILESTONES

Milestone	Planned date
Start of data collection: FPI	Q1 2016
End of data collection: LPO	Q1 2026
Yearly Study progress report 1-9	Q3 2016 - Q3 2025
Registration in the EU PAS register	Q4 2015
Final report of study results	Q4 2026

7 BACKGROUND AND RATIONALE

7.1 BACKGROUND

The importance of intensive insulin therapy in type 1 diabetes has been established. Most of the patients with Type 1 Diabetes Mellitus use insulin subcutaneously, either as injections or as continuous subcutaneous insulin infusion (SCII). However, intensive subcutaneous injection (SC) insulin therapy has several limitations such as difficulties to reach acceptable glycaemic control, occurrence of severe hypoglycaemic episodes (especially when combined with hypoglycaemia unawareness), and/or subcutaneous insulin resistance.

Intraperitoneal (IP) insulin delivery by an insulin pump can be used by passing the subcutaneous interstitial tissue in preferential insulin absorption by the hepatic portal venous system and results in lower peripheral insulin levels. Continuous intraperitoneal insulin infusion (CIPII) has been available for more than 30 years but is used in few selected patients such as patients with subcutaneous defect of insulin absorption, patients with recurrent severe hypoglycaemia, or patients with poor glucose control.

Insuman Implantable is a specific Insuman formulation (400 IU/mL) developed to replace Insuplant (a previous semi-synthetic insulin preparation that was granted Marketing Authorisation in France in 1998) for use exclusively with the Medtronic MiniMed inplantable pump for CIPII. The pump is implanted between the subcutaneous abdominal tissue and the abdominal muscle and delivers insulin from a reservoir through a catheter into the peritoneal cavity (1), (2), (3), (4).

In September 2013, the extension of indication for Insuman implantable was granted by the European Commission based on the results of the Insuman development program. It included two studies (HUBIN_L_05335 and MIP 310) both of which demonstrated that the benefits of CIPII outweigh the risks in patients with diabetes mellitus type 1 who are unable to achieve glycaemic control using intensive SC insulin therapy. However, the previous studies (HUBIN_L_05335, the unique pivotal study, and MIP 310) were relatively small with limited patient population and of short duration follow-up period.

The risks of using Insuman Implantable are similar to those observed with insulin in general and Insuplant specifically, such as severe hypoglycaemia, antigenicity, hypersensitivity and hyperglycaemia which are also identified risks for Insuman with subcutaneous routes of administration. Since Insuman Implantable is given through an implanted pump, there are additional risks related to the placement of the pump that can results in adverse events (AE) of pump pocket infection, abnormal healing, and skin erosion. Device issues such as pump jamming, pump dysfunction and catheter occlusion may occur and may result in metabolic AEs such as hyperglycaemia.

7.2 RATIONALE

The extension of application for Insuman Implantable was obtained for “adult patients with type 1 diabetes mellitus that cannot be controlled with subcutaneous insulin (including pump) therapy, presenting with frequent, otherwise unexplained severe hyper- and/or hypoglycaemia.” The pharmacovigilance activities proposed in the risk management plan (RMP) included routine pharmacovigilance activities to monitor the safety of Insuman and additional pharmacovigilance activities in the form of a non-interventional, prospective cohort study to further assess frequency of the risk related of the use of insuman in the implantable pump in routine clinical practice, especially long term safety.

This observational prospective study will provide important longitudinal data to add to the long term safety profile of intraperitoneal (IP) delivery of Insuman Implantable 400 IU/mL using the Medtronic Minimed implantable pump.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective of the study is to better characterize some of the following important identified risks:

- Severe hypoglycaemia,
- Hyperglycaemia caused by insulin underdelivery due to pump jamming, pump dysfunction or catheter occlusion),
- Pump pocket infection,
- Abnormal healing (at the surgical incision site after device implantation),
- Skin erosion.

8.2 SECONDARY OBJECTIVES

The secondary objectives of the study are:

- To better characterize other important potential risks of Insuman Implantable 400 IU/mL: hypersensitivity reactions to Insuman Implantable 400 IU/mL, hypersensitivity reactions to pump material and focal hepatic steatosis,
- To gain more data about missing information: Safety in pregnant and lactating women and long term safety (including effect of long term exposure to phenol in IP region),
- To collect additional safety data with monitoring of adverse events.

9 RESEARCH METHODS

9.1 STUDY DESIGN

This is a post approval, multinational, multicenter, observational, prospective cohort study for patients with type 1 diabetes who agree to participate. All patients on Insuman Implantable 400 IU/mL in the MIP will be encouraged to participate in this registry for the duration of the study, which is 10 years from inclusion of the first patient.

This registry will include a cohort of adults with type 1 diabetes some of whom are those already treated with CIPII and included in HUBIN_L_05335 as well as patients with type 1 diabetes placed on implantable pump more recently. Both types of patients in this cohort will be treated under normal conditions of use. This registry plans to collect safety information on the status of each patient with type 1 diabetes treated with Insuman Implantable 400 IU/mL in a Medtronic MiniMed Implantable pump. The information collected will include disease characteristics including comorbidities, concomitant medications and late diabetes complications, some important safety risks (identified and potential), and missing information described in the RMP.

The design of the study will mirror real life clinical practice and management of these patients. The visits will be done according to routine clinical practice for intra-peritoneal insulin (i.e. study entry, ad hoc, and refill visits). Sites will record data for study endpoint assessments at each visit every 40 to 45 days into the clinical record which is the source document and complete the electronic case report form (e-CRF) at least every six months.

In order to evaluate the real-life conditions of use of Insuman Implantable 400 IU/mL in a Medtronic MiniMed Implantable pump, the choice of a non-interventional design is more appropriate than an experimental design. Moreover the characteristics of interest may not be available or with insufficient accuracy in patient’s electronic medical records; therefore a prospective mode of data collection for the purpose of the study objectives has been proposed.

9.2 SETTING

This registry will be multinational to ensure representativeness for this study be as exhaustive as possible due to limited number of patients treated with Insuman Implantable 400 IU/mL. The investigators and the patients will be strongly encouraged to participate.

The study population is a narrowly defined target population of patients with type 1 diabetes who meet the indication for use of CIPII because their diabetes is difficult to control. Specifically, Insuman Implantable is indicated for the treatment of adult patients with type 1 diabetes mellitus that cannot be controlled with subcutaneous insulin (including pump) therapy, presenting with frequent, otherwise unexplained severe hyper-and/or hypoglycaemia.

9.2.1 Duration of the study

Patients will be encouraged to participate in the registry and followed up to ten years after entry of the first patient or until definitive pump explantation whichever comes first.

9.2.2 Eligibility criteria

9.2.2.1 Inclusion criteria

- Patients with type 1 diabetes treated with Insuman Implantable 400 IU/mL in the MIP at study entry and treated in accordance with the Insuman Implantable Summary of Product Characteristics.
- Patient (or a legal representative) has provided written informed consent to participate in the study.

9.2.2.2 Exclusion criteria

- None

9.2.3 Analysis population(s)

Eligible patients will be patients for whom an informed consent form (ICF) has been signed and should have taken at least one dose of Insuman Implantable 400 IU/mL.

For this longitudinal study, analysis will be done on all eligible patients at baseline (baseline population), and then follow up data analysis will be performed yearly for the ten year duration of the study.

Information will be collected for all patients considered for the study on a tracking log and entered in the study database in order to describe the extent of potential selection bias. This information will be very minimal and non-identifiable since it will be collected outside the patient's consent; and may include: patient's age range, gender and reason for non-inclusion (patient consent not provided, or other reason).

9.2.4 Modalities of recruitment

9.2.4.1 Investigator selection

All physicians who are trained and who may prescribe Insuman Implantable 400 IU/mL at the certified sites in participating European Union (EU) countries are eligible for enrolling their patients into the Registry and will be encouraged to do so. Information on the PASS will be part of the training for certification. There is no selection quota or randomization for the investigators. All country specific regions are treated equally.

9.2.4.2 Patient selection

The registry will include all patients treated with Insuman Implantable 400 IU/mL using the MIP post launch who agree to participate.

The prescription of therapies is solely the responsibility of the patient's investigator.

All patients who agree to participate in the study will be consecutively enrolled. The patients are those for whom the investigator has decided to prescribe Insuman Implantable 400 IU/mL independent from participation in the registry.

The investigator should refer to the Summary of Product Characteristics, SmPC, and pump manuals for any information on treatment prescribed.

9.3 VARIABLES

Analysis variables include safety variables: important identified risks, important potential risks, and missing information and all AE/SAEs reported.

Main Safety Evaluation criteria (see Section 9.3.1), and other AEs and deaths will be sought from investigators, medical records, death certificates, autopsy, and other sources as available and relevant to the event of interest and will be used to classify metabolic endpoints and pump pocket infections, abnormal healing and skin erosion. All these events will be recorded in the e-CRF, according to the procedures, described in Section 11.

9.3.1 Main Safety Criteria Definitions and Measures

9.3.1.1 Metabolic events

1. Severe hypoglycaemia defined as "An event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration" (according to the EMA Guideline CPMP/EWP/1080/00 Rev.1, (5).

A severe hypoglycaemia may also fulfill criteria for SAE (hospitalization, coma, seizure).

2. Hyperglycaemia (caused by insulin under delivery due to pump jamming, pump dysfunction or catheter occlusion):
   - Any episode of hyperglycaemia with no apparent medical, dietary or insulin dosage reason will need investigation to identify the origin of the blood glucose (BG) increase. The origin of hyperglycaemia (pump jamming, pump dysfunction or catheter occlusion) will be recorded, as well as the corrective actions taken.
   - Can be associated with ketonemia > 0.5mmoL/L.

- Or with diabetic ketoacidosis (DKA). Diabetic ketoacidosis, defined as hyperglycaemia with symptoms such as polydipsia, polyphagia, polyuria, nausea, or vomiting; and presence of serum ketones, or moderate or large urinary ketones, will be confirmed with either arterial blood pH <7.25 or serum bicarbonate <15 meq/L; and treatment provided within a health-care facility. DKA is to be reported as an SAE.

9.3.1.2 Pump pocket infection

Surgical interventions for pump implantation or catheter replacement as well as repeated transcutaneous punctures of the pump-pocket for insulin refills and investigation procedures on the implanted system can lead to an infection at the implantation site. This may be treated with antibiotics alone or include pump explantation. When hospitalization is required for pump explantation as part of the treatment, SAE must be reported.

9.3.1.3 Abnormal healing

Patients may experience abnormal healing from the device implantation procedure without developing a pump pocket infection. When hospitalization is required for pump explantation as part of the treatment, SAE must be reported.

9.3.1.4 Skin Erosion

In extreme cases, an implanted device may erode through the skin, resulting in infection of the implant site and pump explantation. When hospitalization is required for pump explantation as part of the treatment, SAE must be reported.

9.3.2 Secondary Safety Criteria Definitions and Measures

9.3.2.1 Hypersensitivity reactions to Insuman Implantable 400 IU/ml or to pump material

Hypersensitivity reactions are all allergic or inflammatory systemic reactions occurring after drug exposure. This may occur in response to the insulin. It can be immediate (within few minutes) or delayed (usually within hours) reactions. The investigator will have to determine if the reaction occurred in response to Insuman Implantable or a pump component. The event is to be reported as an SAE if it meets seriousness criteria (see Section 11).

9.3.2.2 Focal Hepatic Steatosis

Focal hepatic steatosis may occur when the catheter is close to the liver capsule. Cases of focal hepatic steatosis may be associated with catheter obstruction, so cases of catheter obstruction will be reviewed by the investigator who will be requested to provide procedure records for this assessment.

9.3.2.3 Pregnancy and lactation

All cases of pregnancy will be reported. In addition to any AE/SAE related to maternal health during the pregnancy, information will be provided on the fetal outcomes. All cases of lactating women will also be reported. Narratives will be provided on all pregnancies.

9.3.2.4 Other Adverse events

All other AEs will be reported, in particular, complications linked to phenol irritation will be reported as well as potential clastogenic effect of phenol and insulin mitogenic compound.

9.4 DATA SOURCES

Data will be recorded from the patients' own diary and history reviewed by the investigator at the certified sites approximately every 40 to 45 days at the time of routinely scheduled insulin refill visits and/or at ad hoc visits related to complications as is the accepted real world clinical practice for CIPII. The data will be entered into the e-CRF at least every six months. AE and SAE reporting will be expedited on an ongoing basis (see Section 11).

Investigators will collect and provide pre-specified data on study participants at baseline. Data elements provided by investigators and staff will be collected from information routinely recorded in the medical record, or will be prospectively recorded for the purposes of the study. No visits or examinations, laboratory tests or procedures are part of this study.

Scheduled assessments for the study are presented in Section 9.6 Data Management.

9.5 STUDY SIZE

9.5.1 Determination of sample size

This is a descriptive study that is not testing a hypothesis and is including all patients who wish to participate. As such, a formal sample size calculation is not performed. The projected study sample size will be approximately 260 patients.

9.5.2 Sample size

It is planned to recruit all patients who are willing to participate, from all certified investigators in certified centers in all participating EU countries, and without a minimum required for any country or region.

9.6 DATA MANAGEMENT

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. All data required by the protocol will be entered via a secure web-based Electronic Data Capture (EDC) System designed for the study. Designated investigator staff will enter the

data required by the protocol into the EDC System of the study. Designated investigator staff will be given access to the EDC System after completion of the relevant training.

Sites will be given the option of completing the paper SAE and paper AE forms for expedited reporting in case they are temporarily unable to access to the EDC system (see Section 11.1.3.2). Paper AE/SAE forms will be shipped to the contract research organization (CRO) for expedited reporting to the MAH. As soon as the sites are again able to access the EDC system, the investigator or qualified designee, is responsible for entering the data temporarily reported on paper AE/SAE forms into the e-CRF.

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The e-CRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

High data quality standards will be maintained and processes and procedures used to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data.

9.6.1 Data collection schedule

The visits will be done according to routine clinical practice for CIPII, which includes routine visits approximately every 40 to 45 days and ad hoc visits for device interventions or BG control. The participating investigator will be asked to record all new patient data including patients new to the study but who may already be on CIPII at entry into the registry. After this initial data entry, sites will collect safety clinical data (AE/SAE) after each contact with the patient (routine scheduled visits every 40 to 45 days or at ad hoc visits). At three and six months after study entry, then every six months (corresponding approximately to the period for four refill visits), other patient data will be recorded in the e-CRF. AE/SAE will have expedited reporting. No post study follow up is required.

9.6.2 Data collected

9.6.2.1 Site/Investigators questionnaire

Date of completion of the most recent training/update of investigator and site certification will be collected.

9.6.2.2 Patient/Subject tracking log

A tracking log will be used for non enrolled patients. To comply with data privacy requirement, data collected on the patient tracking log will be fully anonymous (patients # [1,2,….], included: Yes/No, reason for non-inclusion).

9.6.2.3 Patient data

Data collection at the study entry (i.e. for new patients, the study entry visit should be performed as far as possible at the first clinical visit after pump implantation) will include the following:

- Patients training for pump use assessment,
- Date of signature of the ICF,
- Patient demography: date of birth, sex, weight, and height,
- Insulin history:
  - date of first insulin prescription (duration of type 1 diabetes),
  - indication for IP treatment,
  - initial date of IP treatment,
  - initial date of Insuman Implantable commercial treatment.
- Medical history:
  - Related to the pump use (including occurrence of DKA, hyperglycaemia and severe hypoglycaemia in the year prior to entry into registry or since pump implantation for new patients),
  - Comorbidities:
    a) hypertension,
    b) hyperlipidemia,
    c) cardiovascular diseases.
  - History of diabetes complications (if any):
    a) active proliferative retinopathy,
    b) nephropathy,
    c) neuropathy,
    d) hypoglycaemic unawareness.
- Concomitant medications will include all medications at this study entry visit.
- Most recent serum glycosylated hemoglobin (HbA1c) value available (and laboratory normal range), with sampling date (No laboratory test is to be drawn in patients for the purpose of the study and timing of test not related to entry into study).
- Most recent urine microalbumin/creatinine ratio available and laboratory normal range, with sampling date (No laboratory test is to be drawn in patients for the purpose of this study).

After each contact with the patients (refill visits -approximately every 40 to 45 days - ad hoc visits or phone calls)

- Collections of AEs (in expedited manner see safety Section 11), including:
- Severe hypoglycaemia,
- Hyperglycaemia caused by insulin under-delivery (due to pump jamming, pump dysfunction or catheter occlusion),
- Pump pocket infection,
- Abnormal healing,
- Skin erosion,
- Hypersensitivity reaction to Insuman or pump material,
- Focal hepatic steatosis,
- Other AEs, including diabetic complications,
- Pregnancy/lactation.

All AEs will be followed until recovery or stabilization or until the end of the follow-up period, whichever comes first.

In addition, at three and six months after study entry, then every six months corresponding approximately to the period for four refill visits, all the following variables and relevant information will be collected since the last visit in the e-CRF:

- Reason for visits (planned and if not planned; metabolic or device problem since the last data collection),
- Concomitant medications, related to comorbidities, complications and diabetes treatment,
- Most recent urine microalbumin/creatinine ratio available every six months,
- Most recent HbA1c available every six months,
- Review of proper collection of adverse events over the last six months period as described above,
- Date of last rinsing procedure,
- Corrective actions (including subcutaneous insulin injection) in case of pump jamming, pump dysfunction and/or catheter occlusion occurs.

In case of study discontinuation, the following data will be collected:

- Date of discontinuation
- Reason for Study discontinuation (e.g., voluntary withdrawal, definitive pump explantation, death, lost to follow-up)

9.6.3 Procedure for withdrawal of patients from study follow-up schedule

Participants may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. If a subject discontinues prior to completing the study follow-up period, any known reason for the discontinuation should be documented in the e-CRF. The participating investigators will make documented efforts (repeated phone calls, emails, contact to relatives, etc) to keep track of the patient, obtain information about the patient's health status and a reason for study withdrawal. Patients who continue on CIPII cannot be lost to follow up and must be followed at a certified center.

Pre-identified potential reasons for patient's withdrawal are: patient's withdrawal of consent, patient's or investigator's decision to stop CIPII and switch to another form of treatment, and death. If the patient is withdrawal from the study, following pump explantation in the context of the pump phase-out process, it will be clearly mentioned in the eCRF.

For patients who choose to stop CIPII, they are followed until any AE or SAE are recovered or stabilized. Once the pump has been discontinued and all AEs recovered or stabilized, no further information needs to be collected and the patient withdraws from the study.

9.6.4 Logistic aspects

9.6.4.1 Site documentation of pump performance

Sites document pump parameters such as refill accuracy and technical problems such as catheter obstructions and pump blockages are recorded in the patient's clinical record at the site on the standardized form provided by Medtronic. This is consistent with clinical practice for an implantable pump. When there is a device issue that correlates with any AE's including hypoglycaemia or hyperglycaemia, then that device issue is recorded in the e-CRF AE page or specific e-CRF pages designed to collect event of severe hypoglycaemia and hyperglycaemia.

9.6.4.2 Source Documents

In most cases, the source documents are contained in the subject's medical record and data collected on the e-CRFs must match the data in the medical records. In some cases, the case report forms (CRFs), or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site and clearly identify those data that will be recorded in the e-CRF, and for which the e-CRF will stand as the source document. All original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations. The site will be instructed to notify the Market Authorization Holder (MAH) representative before any destruction of medical records of study participants.

9.6.4.3 File Retention and Archiving

To enable evaluations and/or audits from regulatory authorities or Sanofi, the investigator agrees to keep records, including the identity of all participating subjects, all original signed ICFs, copies of all CRFs, SAE forms, source documents and adequate documentation of relevant

correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each site will receive a study site file at study initiation which contains all documents necessary for the conduct of the study and is updated throughout the study. This file must be available for review audits, or inspections and must be safely archived for at least 5 years after completing participation in the study. Documents to be archived include the subject enrolment log and the signed ICF. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify Sanofi.

9.7 DATA ANALYSIS

IQVIA will be accountable for the statistical analysis of the study data.

A complete overview of planned analyses and limitations due to sample size reduction will be available in the amended Statistical Analysis Plan (SAP).

Eligible patients will be those who have signed an Inform Consent Form (ICF) and have received at least one dose of Insuman Implantable 400 IU/mL. In this non-comparative cohort study, all data analyses will be purely descriptive and no statistical testing will be performed.

These descriptive analyses will be conducted on the entire study population and specific subpopulations of interest (eg, country).

Summary statistics (mean, standard deviation, median, interquartile range, minimum, and maximum values) will be presented for continuous variables and counts and, if relevant, percentages will be presented for categorical and binary variables.

9.7.1 Primary analysis

Since the primary objective is to monitor the important identified risks (see Section 9.3.1 for primary endpoints definitions, the analysis will be descriptive and the multiplicity control will not be considered.

- For the important identified risks including severe hypoglycaemia, hyperglycaemia due to underdelivery of insulin, pump pocket infections, skin erosion, and abnormal wound healing, the time to first event will be depicted by the Kaplan-Meier methodology. Globally, the total number assessed will be given and the number and percentage of events/censored will be calculated. For each time point (six-month and each year time-points), the number of patients at risk, the number of events and the probability (Kaplan Meier estimates) of an event and its 95% confidence interval (CI) will be given.
- Graphically, the cumulative risk over the entire study using life table approach, as well as the instantaneous risk expressed as the hazard function over time, will be presented according to the time expressed in years and using a kernel smoothing method.

Moreover, a horizontal line will represent the incidence rate calculated, as number of patients with one or more events divided by the number of patients treated.

- For rare events, the incidence rate using time to event approach will be considered: number of patients with the event, total patients years for the event, and incidence rate per 100 patient-years with its 95% CI will be calculated.

For the analyses purposes, all AEs will be recorded in the study safety database and classified according to Medical Dictionary for Regulatory Activities (MedDRA® version 16.1 or later) by system organ class and preferred terms (PTs).

9.7.2 Secondary analysis

For rare events, the rate per 100 patient-years will be provided considering the same approach than for the primary analysis. For relatively common events with recurrence, recurrent event methods might be considered. A yearly summary of event rate will also be provided for selected AEs and SAEs. See Section 9.3.2 for secondary endpoints definitions.

MedDRA PTs including bronchospasm, hypersensitivity, serum sickness, skin reaction, allergic oedema, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock, angioedema, circumoral oedema, eyelid oedema, face oedema, lip oedema, lip swelling, oedema mouth, periorbital oedema, tongue oedema, laryngeal oedema, laryngospasm, laryngo-tracheal oedema, pruritus allergic, pruritus generalised, rash pruritic, type I hypersensitivity, urticaria as well as hypersensitivity (standardised MedDRA Queries SMQ) will be used for identification of hypersensitivity reactions.

An analysis will be performed for detection of complications of long term exposure to phenol in IP region. AE/SAE will be described by MedDRA classification, with a special focus on the events classified in the MedDRA high level group terms: Gastrointestinal tract irritation (SMQ), Abdominal pain (SMQ), Abdominal pain upper (SMQ), Abdominal pain lower (SMQ), “Mesotheliomas” and “Hepatobiliary neoplasms malignant and unspecified”.

9.7.3 Yearly analyses

An analysis on the cumulative enrolled patients will be performed on a yearly basis along with a short statistical report at the time of Periodic Safety Update Report/Periodic Benefit-Risk Evaluation Report (Periodic Safety Update Reports//Periodic Benefit Risk Evaluation Report) updates.

9.7.4 Handling of Missing Data

Full details on handling of all missing data, which are common in observational studies, will be described separately in the SAP. The SAP will describe the methods for identifying where missing data methods should be applied, the techniques for identifying the type of missing information and the appropriate imputation methods to be used, if any, as per European Medicines Agency (EMA) 2010 guidance on missing data (6).

The proportion of missing data will be reported for each measured variable in the study.

9.8 QUALITY CONTROL

9.8.1 Data collection, validation and data quality control at MAH/MAH representative level

A study manual, including for-cause monitoring, as appropriate for the study design, will be developed and implemented.

Data will be collected using e-CRF.

The computerized handling of the data by the MAH/MAH representative after receipt of the data through e-CRFs may generate additional requests to which the participating Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be appended to the e-CRFs held by the Investigator and the MAH/MAH representative.

Data collection and validation procedures will be detailed in appropriate operational documents.

9.8.2 Data quality control at site level

Data quality control will be performed on active sites at site level (i.e., those that have enrolled at least one patient).

Quality Control will be performed by qualified designated personnel in each country.

The methodology of data Quality Control and appropriate consecutive corrective actions will be detailed in the study manual.

During the site initiation visit, the monitor will provide training on the conduct of the study to the investigator, co-investigator(s), and all site staff involved in the study. In order to ensure the integrity of the data, sites will be monitored. Site monitoring will be performed by IQVIA clinical research associates to examine compliance with the protocol and adherence to the enrolment process, data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. The monitor will perform source data verification by review of original subject records. The monitor will also validate expedited reporting of AE/SAE per local regulations.

The monitor will close out each site after the last subject’s final follow-up assessment is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures and frequency of monitoring visits will be described in a study manual. Monitor contact details for each participating site will be maintained in the Investigator Site File.

Representatives of the MAH quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site,

including the Investigator Site File, the completed e-CRFs and the subjects' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

In addition, high data quality standards will be maintained and processes via data management procedures, as previously described in Section 9.6.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Potential limitations of the study design and measures proposed to address them include the following:

Enrollment bias: Sites will be expected to consecutively enroll eligible subjects and to maintain tracking logs of all subjects meeting eligibility criteria, along with reasons for non-enrolment.

Healthy user bias/depletion of susceptibles: Long term users of Insuman + the pump (i.e. from the clinical trials) have generally shown tolerance to the treatment and may be at lower risk of some of the identified risks and other AEs than new users. This bias can be addressed by analyzing data separately for long term users and new users.

Inconsistent interpretation of e-CRFs by participating centers: All centers/sites will undergo standardized training and utilize standardized documentation for completing of CRFs at enrollment and for each follow-up assessment.

Follow-up bias: A low lost to follow-up rate of approximately 5% is expected, in part due to the ability of this observational study to follow up directly with subjects even if they do not return to the enrolling center. A very low rate will be envisioned as the patient will have to refill regularly the pump and therefore to come back to enrolling center. Maintaining a low rate of lost to follow-up will lower the risk of bias that could result, for example, if subjects with AEs were less likely to return to the study investigator for follow up.

Due to the Minimed Implantable pump phase out, the initial targeted recruitment (ie, initially 400 patients and up to 50 new patients per year) will not be achieved. The potential impact on the statistical analyses performed will be described in the amended SAP.

9.10 OTHER ASPECTS

9.10.1 Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (ie, substantial, significant) amendments will be approved by the relevant regulatory authorities and will usually require submission or notification to the relevant institutional review board/independent ethics committee (IRB/IEC) for approval or favorable opinion, if applicable. In such cases, the amendment will be implemented at the site only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed at each participating site and will be submitted to the relevant IRB/IEC or regulatory authorities where required by pertinent regulations. Any amendment that could have an impact on the subject's agreement to participate in the study requires the subject's informed consent prior to continued participation in the study.

Amendments and updates to the protocol will be documented in Section 5.

9.10.2 Study Governance and Committees

The study will be conducted in close collaboration with the Scientific Committee, comprised of qualified individuals with relevant experience and expertise. The Scientific committee will be governed by a Charter, detailing responsibilities and processes.

10 PROTECTION OF HUMAN SUBJECTS

To ensure the quality and integrity of research, this study will be conducted under the Guidelines for Good Pharmacovigilance Practices (GVPs) and Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, and any applicable national guidelines (7), (8), (9), (10).

10.1 RESPONSIBILITIES OF THE INVESTIGATOR /HEALTH CARE PROVIDERS

The Investigator/Health Care Provider will perform the study in accordance with this protocol, applicable local regulations and international guidelines.

It is the Investigator/Health Care Provider's responsibility to obtain written informed consent from patients prior to inclusion in the study, to fill in the CRF and to record all data pertinent to the investigation. She/he will ensure that the information reported in the CRF is precise and accurate.

Investigator/Health Care Provider, and under the Health Care Provider's responsibility, should fully inform the Patient of all pertinent aspects of the study including the written information. All patients should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the study, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

Prior to a patient's participation in the study, the Informed Consent Form should be signed and personally dated by the patient's parent(s) or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. Whenever possible, the consent will be signed by both parents/guardians. If only one parent or guardian signs the consent form, the participating Investigator/Health Care Provider must document the reason for only one parent or guardian's signature.

In addition, participants will sign the Consent Form as detailed below or will follow the Ethics Committee (IRB/IEC) approved standard practice for pediatric participants at each participating center (age of consent to be determined by the IRB's/IEC's or be consistent with the local requirements):

- Participants who can read the Consent Form will do so before writing their name on the form.
- Participants who cannot read will have the Consent Form read to them before writing their name on the form.

In relation with the population of patients exposed in the study i.e. pediatric/minor patients, the IRB/IEC should preferably ensure proper advice from specialist with pediatrics expertise (competent in the area of clinical, ethical and psychosocial problems in the field of pediatrics) according to national regulations. This should be documented.

The Informed Consent Form and the Information Sheet used by the Investigator/Health Care Provider for obtaining the Patient's Informed Consent must be reviewed and approved by the MAH/MAH representative prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval / favorable opinion.

10.2 RESPONSIBILITIES OF MAH/MAH REPRESENTATIVE

The MAH/MAH REPRESENTATIVE is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

The MAH/MAH REPRESENTATIVE is responsible for:

- Local submission(s) complying with data protection rules,
- Any other local submission(s).

10.3 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

10.3.1 Ethical principles

This study will be conducted in accordance with the principles laid by the 18th World Medical Assembly [Helsinki, 1964 (10)] and all subsequent amendments.

10.3.2 Laws and regulations

This study will be conducted in accordance with the guidelines for Good Epidemiology Practice (7), (8), (9), (10).

Each participating country should locally ensure all necessary regulatory submissions (e.g.: IRB/IEC) are performed in accordance with local regulations including local data protection regulations.

10.3.3 Data protection

The patient's personal data and Investigator's personal data which may be included in the MAH/MAH REPRESENTATIVE database shall be treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the Investigator and/or to the patients, the MAH/MAH REPRESENTATIVE shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.3.4 Insurance

Participating countries may contract insurance according to local specific requirements. The process for obtaining insurance will be detailed in the study manual for conduct of the study as it is delegated to a CRO, and the responsibilities regarding insurance will be mentioned in the contract.

10.3.5 Secrecy agreement

All material, information (oral or written) and unpublished documentation provided to the Investigator (or any action carried out by the MAH/MAH representative on their behalf), including the present protocol and the CRF, are exclusive property of the MAH/MAH representative.

These materials or information (both global and partial) cannot be given or disclosed by the Investigators or by any person of her/his group to unauthorized persons without the prior formal written consent of the MAH/MAH representative.

The Investigator shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

10.3.6 Record retention

The investigator shall arrange for the retention of study documentation until the end of the study. In addition the investigator will comply with specific local regulations/ recommendations with regards to patient record retention.

It is recommended that the Investigator retains the study documents at least five years (5) after the completion or discontinuation of the study, unless otherwise specified in the Investigator Agreement in line with additional standards and/or local laws.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

10.3.7 Discontinuation of the study

The MAH/MAH representative can decide at any time after agreement with EMA and for any reason to discontinue the study; the decision will be communicated in writing to the participating Investigator.

Similarly, should the Investigator decide to withdraw from the study, she/he will have to inform the MAH/MAH representative in writing.

If appropriate, according to local regulations, Ethic Committee(s) (IRB/IEC) and Competent Authorities should be informed.

10.3.8 MAH/MAH representative audits and inspections by competent authorities

The Investigator agrees to allow the MAH/MAH representative auditors/Competent Authorities inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. In case no ICF is signed, access to the source document is not allowed.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the competent authorities will be communicated by the Investigator to the MAH/MAH representative.

The Investigator shall take appropriate measures required by the MAH/MAH representative to take corrective actions for all problems found during the audit or inspections.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

All Adverse Events (AE) regardless of seriousness or relationship to Insuman Implantable, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for each patient are to be collected by the investigator and reported to the MAH/MAH representative within expedited time frame.

11.1 SAFETY INSTRUCTIONS

Specific instructions concerning safety management by the investigator during the trial are shown here to include management of abnormal laboratory values, reporting of outcome events as SAE or not.

All events will be managed and reported in compliance with all applicable regulations.

11.1.1 Definitions of Adverse Event (AE) and Serious Adverse Event (SAE)

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event.
- Suspected transmission of infectious agent ; is any suspected transmission of an infectious agent via a medicinal product (e.g., product contamination)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

11.1.2 Collection of Overdose and Pregnancy

An overdose of insulin can lead to severe and sometimes long-term and life-threatening hypoglycaemia. In these cases, the overdose has to be considered as SAE. Other symptomatic overdose has to be reported as adverse event.

All cases of pregnancies will have to be reported (see Section 9.3.2.3). In addition to any AE/SAE related to maternal health during the pregnancy, information will be provided on the fetal outcomes.

11.1.3 Obligations of the Investigator regarding safety reporting

11.1.3.1 Adverse Events collection

All AEs regardless of relationship to Insuman Implantable, spanning from the signature of the informed consent form until the end of the collection period as defined by the protocol for each patient, are to be recorded immediately (within 24 hours of awareness) for SAEs and within 30 days of awareness for non serious adverse events on the corresponding page(s) included in the e-CRF, as explained below:

11.1.3.2 Adverse event reporting to MAH/MAH REPRESENTATIVE

- **In case of Serious Adverse Events**

Since an e-CRF is used:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send the notification to the representative of MAH after approval of the Investigator within the e-CRF or automatically after a pre-set delay.
- SEND (preferably by fax or e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the MAH whose name, fax number and email address appear on the second page of this Protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Study are properly mentioned on any copy of source document provided to MAH/MAH REPRESENTATIVE. For laboratory results, include the laboratory normal ranges
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant Medication, patient status, etc.) should be sent (by fax or e-mail) to MAH/MAH REPRESENTATIVE within 24 hours of knowledge. In addition, any effort should be made to further document each Serious AE that is fatal or life threatening within the week (seven days) following initial notification.

A back-up plan is used (using paper flow) in case the e-CRF system does not work.

- **In case of non Serious Adverse Events**

  ENTER (within 30 days) the information related to the AE in the appropriate screens of the e-CRF; the system will automatically send the notification to MAH/MAH representative after approval of the investigator within the e-CRF or automatically after a pre-set delay.

11.2 SAFETY OBSERVATIONS

- The Investigator should take all appropriate measures to ensure the safety of the patients as per normal practice.
- In case of any Serious Adverse Event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study;
- In case of any Serious Adverse Event brought to the attention of the Investigator at any time after cessation of Insuman Implantable, and considered by him/her to be caused by Insuman Implantable with a reasonable possibility, this should be reported to the MAH/MAH representative.

11.3 OBLIGATIONS OF MAH/MAH REPRESENTATIVE

During the course of the study, the MAH/MAH REPRESENTATIVE will report safety data to health authorities according to Directive 2001/83/EC and in accordance with all applicable local and global regulations (e.g.: All serious ADR within 15 days from the date of receipt of the reports to the health Authorities; All non-serious ADR within 90 days from the date of receipt of the reports to the health Authorities for some European countries).

The MAH will report all safety observations made during the conduct of the study in the final study report.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorisation of the MAH/MAH REPRESENTATIVE conducting the study.

The Scientific Committee will have full access to the final data allowing for appropriate academic analysis and reporting of the study results.

12.2 PUBLICATIONS

The Scientific Committee/Study Chairman is responsible for presentations and/or publications. The study results must be submitted to the review of the Scientific Committee before publication.

All study investigators and Committee members give full authority to the Scientific Committee for primary presentation and/or primary publication of results. No other publication is allowed before the primary publication. Any subsequent presentation or publication by a study participant (including for substudies) must be approved by the Scientific Committee and make reference to the study and the primary publication.

The final decision to publish any manuscript/ abstract/ presentation will be made by the Scientific Committee after prior notice to the MAH/MAH REPRESENTATIVE allowing for its internal review and comments. All manuscript/ abstract/ presentation must be submitted to the internal review of the MAH/MAH REPRESENTATIVE at least forty-five (45) days. The MAH/MAH REPRESENTATIVE may request that the MAH/MAH REPRESENTATIVE's name and/or names of one or several of its employees appear or do not appear in such publication.

The MAH/MAH REPRESENTATIVE can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein.

A Publication Committee responsible for the overall publication plan can be set up upon needs. Its main mission will be:

- To define the overall publication plan including the primary publications reporting new scientific findings/data from the study
- To review and approve (or abstain) all other publications proposals and draft manuscripts regarding subsequent publications including local publications.

13 REFERENCES

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ANNEXES

Annex 1 List of stand-alone documents

None

Annex 2 ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 2)

Adopted by the ENCePP Steering Group on 14/01/2013

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	16
1.1.2 End of data collection[2]	☒	☐	☐	16
1.1.3 Study progress report(s)	☒	☐	☐	16
1.1.4 Interim progress report(s)	☒	☐	☐	16
1.1.5 Registration in the EU PAS register	☒	☐	☐	16
1.1.6 Final report of study results.	☒	☐	☐	16

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	19
2.1.2 The objective(s) of the study?	☒	☐	☐	21

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	22
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	22
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	24
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	26
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	23
4.2.2 Age and sex?	☒	☐	☐	28
4.2.3 Country of origin?	☒	☐	☐	26
4.2.4 Disease/indication?	☒	☐	☐	28

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.5 Co-morbidity?	☒	☐	☐	28
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	22

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	28
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	24
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	24

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	28
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	28

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	26
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	26
8.1.3 Covariates?	☒	☐	☐	26

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	26
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	26
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	26
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	32
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	26

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	26

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	31
10.2 Is the choice of statistical techniques described?	☒	☐	☐	31
10.3 Are descriptive analyses included?	☒	☐	☐	31
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	31
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	26
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	26
11.3 Are methods of quality assurance described?	☒	☐	☐	33
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	33
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	34

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	34
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	34
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	
12.3 Does the protocol address other limitations?	☒	☐	☐	34

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	37
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	37
13.3 Have data protection requirements been described?	☒	☐	☐	37

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	34

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	43
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	43

Comments:

Name of the main author of the protocol: Valérie Pilorget

Date: 14/03/2014

Signature: _____

HUBIN-C-06380 Amended protocol 1

ELECTRONIC SIGNATURES

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Le-Floch, Chantal	Regulatory Approval	22-Feb-2018 19:06 GMT+0100
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Mukherjee, Bhaswati	Clinical Approval	25-Feb-2018 17:09 GMT+0100