1 ABSTRACT

Title

Post Authorization 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.

Keywords

Type 1 diabetes mellitus, implantable pump, Insuman Implantable 400 IU/mL, PASS, intraperitoneal.

Rationale and background

The importance of intensive insulin therapy in Type 1 diabetes has been established. Most patients with Type 1 diabetes mellitus use insulin subcutaneously, either as injections or as a continuous subcutaneous insulin infusion. However, intensive subcutaneous insulin therapy has several limitations such as difficulties achieving acceptable glycemic control, occurrence of severe hypoglycemic episodes (especially when combined with hypoglycemia unawareness), and/or subcutaneous insulin resistance.

Intraperitoneal (IP) insulin delivery by an insulin pump has been shown to be effective in patients with recurrent severe hypoglycemia or unreliable subcutaneous insulin absorption by bypassing the subcutaneous interstitial tissue and allowing preferential insulin absorption by the hepatic portal venous system, which is the physiological insulin pathway, and results in lower peripheral insulin levels and normalized glucagon. Continuous intraperitoneal insulin infusion (CIPII) has been available for more than 30 years and is used in only a few select types of patients, such as patients with a subcutaneous defect of insulin absorption, patients with recurrent severe hypoglycemia, or patients with poor glucose control despite having an optimal intensive subcutaneous insulin regimen.

Insuman Implantable 400 IU/mL is a specific Insuman formulation developed to replace Insuplant (a previous semi-synthetic insulin preparation that was granted marketing authorization 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, delivering insulin from a reservoir through a catheter into the peritoneal cavity.

In September 2013, a line extension of the already approved Insuman formulation was granted for Insuman Implantable 400 IU/mL by the European Commission based on the results of the Insuman development program. It included 2 studies (the pivotal phase 3 HUBIN-L-05335 and supported by the MIP 310 study).

The extension of application for Insuman Implantable 400 IU/mL was obtained for “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 hypoglycemia”. As part of additional pharmacovigilance activities included in the risk management plan (RMP), a PASS was proposed in order to further assess the frequency of the risks related to the use of Insuman Implantable 400 IU/mL in MIP, in routine clinical practice, especially focusing on long-term safety.

The Insuman IMplantable Observational Study (IIMOS) was a prospective study designed to provide important longitudinal data to add to the long-term safety profile of IP delivery of Insuman Implantable 400 IU/mL using the Medtronic MIP. This is the final report following early study termination, as agreed with European Union (EU) Pharmacovigilance Risk Assessment Committee (PRAC) on 27 January 2022 (EMEA/H/C/000201/MEA/041.5) due to poor feasibility of completing the originally planned study.

Research question and study objectives

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

- Severe hypoglycemia, hyperglycemia (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 were:

- 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 the IP region).
- To collect additional safety data by monitoring adverse events (AEs).

Intercurrent updates

Medtronic communicated its decision to discontinue the manufacturing and supply of the MIP in June 2017, and agreed to supply 125 final MIP units over a 2-year transition period for the phase out process). In the last years, due to the shortage in MIP components, less MIPs than planned initially were supplied. Consequently, the small number of patients enrolled, and the increasing number of patients explanted, compromised the feasibility of the study and limited the interpretation of the findings on long- term safety. Furthermore, no new safety concerns were identified in the yearly interim reports. Accordingly, Sanofi requested the early termination of the PASS. The request was endorsed by the PRAC on 27 January 2022 (assessment in procedure EMEA/H/C/000201/MEA/041.5). This final report covers the final analyses and includes all data collected up to 16 March 2022. The decreased sample size that was possible to enroll, and the shortened duration of patient level follow-up due to definitive MIP explantations, limits the interpretation of the results.

Study design

This was a post-approval, multinational, multicenter, observational, prospective cohort study for patients with Type 1 diabetes treated with Insuman Implantable 400 IU/mL who agreed to participate. The expected duration of this post-approval study was 10 years from entry of the first patient, and patients were to be followed until study end or definitive pump explantation, whichever came first.

Patient visits occurred according to routine clinical practice for the use of an implantable pump, which were at study entry, refill visits (approximately every 40 to 45 days), and at ad-hoc visits related to complications of the insulin treatment regimen or pump. Data were collected by site and entered in an electronic case report form (eCRF) (on an ongoing basis for AEs; at 3, and 6 months after study entry, and then every 6 months for other study related information). No visits or examinations, laboratory tests or procedures were mandated as part of this study.

Setting

- **Site and patient selection**: All physicians who were trained and who might prescribe Insuman Implantable 400 IU/mL at the certified sites in participating EU countries were eligible to enroll their patients into the study and were encouraged to do so. Medtronic MIP was launched in Belgium, France, Sweden, and the Netherlands. However, only France and Belgium sites agreed to participate in the study before Medtronic issued their decision to discontinue MIP production.
- **Participation:** Thirteen sites were initiated and enrolled patients: 12 sites in France and 1 site in Belgium. All certified sites in both countries participated in the study. All participating sites were university hospitals.
- **Duration:** The final analyses included all data collected from 27 April 2016 to 16 March 2022. Patients were followed from enrollment date until end of data collection, or until definitive pump explantation, whichever came first.
- **Data collection:** Data were 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 were entered into the eCRF at least every 6 months.
- **Safety data collection:** AEs and serious adverse events (SAEs) were reported on an ongoing basis. AEs were collected at each patient visit (approximately every 40 to 45 days), during ad-hoc visits, or phone calls. All AEs were followed until recovery or stabilization occurs, or until the end of the follow-up period, whichever came first. After the end of the study, the safety of the enrolled patients will continue to be monitored via routine pharmacovigilance activities which includes the collection of safety information through spontaneous reporting.
- **Impact of COVID-19 in the study:** The COVID-19 pandemic impacted healthcare during the study follow-up period. There were no significant delays in study data collection due to the pandemic, most patients returned to the sites to refill their pump. However, 4 patients discontinued the study because they were living in the United States

(US) (enrolled at a site in France) and due to the pandemic were not able to return to the study site to refill pump and continue to be followed-up in the study.

Participants and study size, including dropouts

- **Patients:** Approximately 400 patients who completed the non-comparative phase of the pivotal phase 3 HUBIN-L-05335 trial were considered as a potential source population for this PASS. Additionally, it was expected that up to 50 patients new to IP insulin may be available per year. However, following the decision of Medtronic to stop the production of the MIP, and the consequent availability constraints, the pumps produced were mainly used for replacement in patients who were already on a pump and very few newly implanted patients were expected. Therefore, the total projected sample was reduced to 260 patients. At study termination, 263 patients (14 new users and 249 long-term users) had been enrolled.
  - Patients identified and invited to participate: 265
  - Patients enrolled: 263
  - Patients discontinuing prematurely: 97

Variables and data sources

- **Data management, review, validation:** To ensure the quality and integrity of research, the present study was conducted in accordance with the Guidelines for Good Pharmacovigilance Practices (GVPs) and Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for Pharmacoepidemiology, the declaration of Helsinki and its amendments, and any applicable national guidelines.
- **Variables and evaluation criteria:** Analysis variables including safety concerns (important identified risks, important potential risks, and missing information) and all AEs and SAEs were reported. Main safety evaluation criteria (metabolic events [ie, severe hypoglycemia and hyperglycemia caused by insulin underdelivery due to pump jamming, pump dysfunction, or catheter occlusion], pump pocket infection, abnormal healing, and skin erosion) and secondary safety evaluation criteria (hypersensitivity reactions, focal hepatic steatosis, safety in pregnancy and lactation, deaths and other AEs) were sought from Investigators, medical records, death certificates, autopsy, and other sources as available and relevant to the events of interest.
- **Statistical considerations:** Statistics were performed according to the type of Insuman Implantable 400 IU/mL MIP user - patients with a duration from first pump implantation >6 months prior to study entry were classified as long-term users, and those with a duration from first pump implantation ≤6 months prior to study entry were considered new users.

  Categorical variables were summarized as counts and percentages (%) of patients in each category. Continuous variables were presented as the number of patients with data to be summarized (n), mean, standard deviation (SD), median, first and third quartiles (Q1 and Q3), minimum, maximum and number of patients with missing data.

- All AEs were described, with an additional focus on events of special interest, by presenting the number and percentage of patients reporting each of the important identified risks and important potential risks, and corresponding 95% confidence interval (CI), along with the event rate (number of events/ total exposure patient-time) and corresponding 95% CI.
- Kaplan Meier estimates of cumulative incidence, and corresponding 95% CI, were calculated based on the time to first occurrence of important identified risks, estimated as the length of time from the date of enrollment to the start date of the first occurrence of event during the study period.
- Cox regression analysis was performed to estimate hazard ratios (HRs) and corresponding 95% CI for the association of various patient or disease characteristics with time to first occurrence of important identified risks from date of enrollment.

Results

- **Overall participation status:** In total, 265 patients were identified as eligible and invited to participate.
  - Two patients refused to participate; thus, the total number of patients included in the analysis was 263, of which 14 (5.3%) were defined as new users (duration from first pump implantation to study entry of ≤6 months) and 249 (94.7%) were defined as long-term users (duration from first pump implantation to study entry >6 months).
    - Only 2 patients among the 14 new users (14.3%) had participated in the HUBIN-L-05335 trial, whereas 246 patients among the 249 long-term users (98.8%) had participated in the HUBIN-L-05335 trial.
    - One-hundred and forty (53.2%) of the 263 enrolled patients were still on a functional pump at the end of data collection, the remaining patients had the pump temporarily explanted or neutralized awaiting a therapeutic decision (n=26) or discontinued from the study prematurely (n=97).
- Ninety-seven patients discontinued the study prematurely, reasons for study discontinuation are listed below:
  - Twenty-three (8.7%) patients due to patient's or Investigator’s decision to stop CIPII and switch to another form of treatment.
  - Fifty-three (20.2%) patients following definitive pump explantation due to pump unavailability, in the context of the pump phase out process.
  - Eight (3.0%) patients due to an AE (or non-fatal SAE) during this study (in these cases, the patients were discontinued specifically due to the AE and not due to the phase-out process): This included 3 pump pocket infections, 1 skin erosion, 1 medical device implant site pain, 1 worsening of renal failure, and worsening of pancreas disorder leading to pancreas and renal transplant, 1 intestinal perforation, and 1 severe hypoglycemic coma with neurological sequelae.

  - Nine (3.4%) patients died during study follow-up: 3 due to myocardial infarction, 2 due to deaths of an unknown cause, 1 due to food choking, 1 due to coma of unknown cause, 1 due to brain stem hemorrhage, and 1 due to ovarian cancer.
  - Four (1.5%) patients discontinued due to "other" reason, because they were in the US (enrolled at one site in France), and due to the pandemic were not able to return to refill the pump.
- **Participation per period of the study:** The mean (SD) follow-up time was 4.7 (1.5) years (the observed follow-up was between 0.1 years and 5.9 years), with 262 (99.6%) patients reporting at least 1 follow-up visit at the time of early study termination.
- **Descriptive data at study entry:**
  - Most of the 263 enrolled patients were long-term users (n=249; 94.7%), with only a small group of new users (n=14; 5.3%).
  - At study entry**,** patients had a mean (SD) age of 56.5 (11.0) years, with 156 (59.3%) females and 107 (40.7%) males.
  - The mean (SD) body mass index (BMI) was 25.7 (4.3) kg/m^2.
  - The mean (SD) duration of Type 1 diabetes mellitus was 35.3 (12.0) years, and the mean (SD) time since initial IP treatment was 14.3 (8.3) years, with most patients (68.1%) recording brittle diabetes as the indication for IP treatment.
  - The mean (SD) serum glycosylated hemoglobin (HbA1c) was 7.7% (1.0).
  - The most frequent comorbidities at study entry were hyperlipidemia (65.0%), followed by hypertension (58.9%), cardiovascular disease (27.8%), peripheral vascular disease (19.8%), and depression (16.0%); 73.8% of patients reported to have at least 1 diabetes complication, especially neuropathy (40.7%), and nephropathy (24.0%).
  - All enrolled patients reported receiving at least 1 concomitant medication during the study.

Main results

All presented results and percentages include the full study population of 263 patients.

Important identified risks

A total of 451 AEs categorized as important identified risks (main safety evaluation) for the use of Insuman Implantable 400 IU/mL in Medtronic MIP were reported by 176 (66.9%) patients, including 108 events reported by 68 (25.9%) patients that were considered serious.

Severe hypoglycemia

A total of 115 severe hypoglycemia events were reported by 53 (20.2%) patients.

- Fifty-four severe hypoglycemia events reported by 29 (11.0%) patients were considered serious: 44 hypoglycemic unconsciousness events reported by 22 patients, 3 hypoglycemia events were considered medically important in 3 patients, and 7 events leading to hypoglycemic coma were reported in 7 patients.

- Thirty-nine severe hypoglycemia events reported by 19 (7.2%) patients were considered related to Insuman Implantable 400 IU/mL.
- Seven severe hypoglycemia events reported by 7 (2.7%) patients were considered related to Medtronic MIP: 2 due to catheter occlusion leading to increase in insulin doses, 1 due to pump jamming that lead to excessive bolus delivery, 1 due to pump jamming, and an excessive dose of subcutaneous insulin, 1 due to pump dysfunction, 1 due to communicator being out of order, and 1 following rinsing procedure with sodium hydroxide.
- Temporary pump explantation, definitive pump explantation, catheter rinsing, and catheter change were each required in 1 (0.4%) patient; temporary neutralization was required in 2 (0.8%, 95% CI: 0.1;2.7) patients.

Eight patients presented severe hypoglycemic events while not being on a functional pump and/or while Insuman Implantable 400 IU/mL was interrupted (4 patients with hypoglycemic unconsciousness events, 2 with severe hypoglycemia, and 2 with hypoglycemic coma). It was considered that these events were neither related to Insuman Implantable 400 IU/mL, nor Medtronic MIP.

Hyperglycemia caused by insulin underdelivery due to pump jamming, pump dysfunction, or catheter occlusion

A total of 308 hyperglycemia events caused by insulin underdelivery were reported by 142 (54.0%) patients (the most frequently reported important identified risk).

- The main causes of hyperglycemia were technical pump device dysfunction (159 events), complete catheter occlusion (103 events), other reasons (26 events), unknown reason (12 events), and pump jamming (8 events).
- Twenty-eight hyperglycemia events caused by insulin underdelivery reported by 23 (8.7%) patients were considered serious.
- Thirty-eight hyperglycemia events caused by insulin underdelivery reported by 29 patients were associated with hyperketonemia, and 2 led to diabetic ketoacidosis (DKA).
- One-hundred and forty-four hyperglycemia events caused by insulin underdelivery reported by 78 (29.7%) patients were also considered related to Insuman Implantable 400 IU/mL.
- One-hundred and seventy-six events reported by 102 (38.8%) patients led to catheter rinsing (the most common action taken with the pump device), 69 events in 55 (20.9%) patients led to catheter changes, and 63 events in 47 (17.9%) patients led to pump rinsing.
- Twenty-five hyperglycemia events in 23 (8.7%) patients led to temporary pump explantation due to insulin underdelivery, 17 events in 17 (6.5%) patients led to definitive pump explantation, and 11 events in 11 (4.2%) patients led to temporary neutralization (ie, pump stop at the time of study termination).

Pump pocket infection

A total of 23 pump pocket infections were reported by 22 (8.4%) patients.

- Twenty-one events reported by 21 (8.0%) patients were considered serious.
- None of the events were considered related to Insuman Implantable 400 IU/mL.
- Twenty events reported by 19 (7.2%) patients were considered related to Medtronic MIP.
- Ten (3.8%) patients had temporary pump explantation, while 12 (4.6%) patients had definitive pump explantation (pump pocket infection was the reason for patient discontinuation from the study due to definitive explantation for only 3 patients).

Skin erosion

A total of 5 skin erosions were reported by 4 (1.5%) patients.

- All 5 events were considered serious.
- None of the events were considered related with Insuman Implantable 400 IU/mL, while all events were considered related to Medtronic MIP.
- One (0.4%) patient had temporary pump explantation following 2 skin erosions, while 3 (1.1%) patients had definitive pump explantations following skin erosions (the skin erosion was the reason for discontinuation from the study of 1 patient, while the other 2 patients discontinued from the study due to lack of pump availability).

Abnormal healing

There were no reports of abnormal wound healing (at the surgical incision site after device implantation).

Event rates

The final event rates were aligned with what was reported in previous interim reports. The total exposure was 1306.4 patient-years (n=263 patients).

The event rates per 100 patient-years were:

- Severe hypoglycemia: 8.8 (95% CI: 7.2;10.4)
- Hyperglycemia due to insulin underdelivery: 23.6 (95% CI: 20.9;26.2)
- Pump pocket infection: 1.8 (95% CI: 1.0;2.5)
- Skin erosion: 0.4 (95% CI: 0.1;0.7)

Kaplan Meier estimate of the cumulative incidence over 5 years

The Kaplan Meier estimate of the cumulative incidence at 5 years after start of enrollment were:

- Severe hypoglycemia: 21.9% (95% CI: 17.1;27.8)
- Hyperglycemia caused by insulin underdelivery: 57.9% (95% CI: 51.6;64.3)
- Pump pocket infection: 8.3% (95% CI: 5.3;12.7)

- Skin erosion: 1.7% (95% CI: 0.6;4.5)

Recurrent event analysis

At 5 years after start of enrollment:

- The cumulative mean number of severe hypoglycemia events per long-term user was 0.51.
- The cumulative mean number of hyperglycemia events caused by insulin under delivery per long-term user was 1.62.

Cox proportional hazards model

Cox proportional hazards models were developed for severe hypoglycemia and hyperglycemia due to insulin underdelivery for long-term users only, as the low incidence of other important identified risks and the small number of new users would not allow for a meaningful interpretation of the results.

- **Severe hypoglycemia:** After adjusting for age, gender, and BMI, both hypoglycemic unawareness and concomitant use of other antidiabetic treatments were associated with the occurrence of severe hypoglycemia. Patients with hypoglycemic unawareness were 3.1 times more likely to experience severe hypoglycemia compared to patients without hypoglycemic unawareness over time (HR=3.05 [95% CI: 1.56;5.97], p=0.001). On the contrary, patients who used other antidiabetic treatments concomitantly were 69% less likely to experience severe hypoglycemia compared to patients who did not use such treatments over time (HR=0.31 [95% CI: 0.16;0.60], p<0.001).
- **Hyperglycemia caused by insulin underdelivery due to pump jamming, pump dysfunction, or catheter occlusion:** After adjusting for age, gender, and BMI, time since initial IP treatment at study entry was the only factor associated with the occurrence of hyperglycemia. Each 1 year increase in time since initial IP treatment at study entry was associated with a 3% decrease in the risk of hyperglycemia (HR=0.97 [95% CI: 0.944;0.995], p=0.022).

Important potential risks

- Only 1 event of hypersensitivity (one of the important potential risks) was reported, implant site dermatitis, and was considered related to the pump. It led to a surgical procedure to change MIP implant site.
- There were no reported AEs indicative of the important potential risks of focal hepatic steatosis or complications linked to phenol irritation, nor as potential clastogenic effect of phenol and insulin mitogenic compound.

Safety in pregnant and lactating women

- There were 7 pregnancies have been reported in 4 women (1 pregnancy was ongoing at study entry and 6 pregnancies occurred during the study, of which 1 resulted in a spontaneous abortion).
- Two women breastfed during study period (1 at study entry and 1 during the study).

- No new safety signals related to pregnancy and lactation were identified.

Other AEs

A total of 914 other AEs supporting the analysis of additional safety data (secondary safety evaluation) were reported by 226 (85.9%) patients, including 233 that were considered serious. No new long-term safety signals were identified.

- The following other AEs occurred in >10.0% of patients:
  - Infections and infestations were the most common system organ class (SOC), with 203 events reported by 102 (38.8%) patients
  - Metabolism and nutrition disorders with 83 events reported by 56 (21.3%) patients
  - Musculoskeletal and connective tissue disorders with 82 events reported by 56 (21.3%) patients
  - Injury, poisoning and procedural complications with 80 events reported by 55 (20.9%) patients
  - Gastrointestinal disorders with 64 events reported by 50 (19.0%) patients
  - General disorders and administration site conditions with 49 events reported by 44 (16.7%) patients
  - Nervous system disorders with 44 events reported by 38 (14.4%) patients
  - Eye disorders with 46 events reported by 35 (13.3%) patients
  - Cardiac disorders with 43 events reported by 35 (13.3%) patients
  - Vascular disorders with 34 events reported by 29 (11.0%) patients
  - Neoplasms benign, malignant and unspecified (incl cysts and polyps) with 32 events reported by 29 (11.0%) patients. Twenty of the events were malignant.
- A total of 233 SAEs were reported by 112 (42.6%) patients. Of these, 10 (3.8%) resulted in fatal outcomes: 3 myocardial infarction, 2 deaths of unknown cause, 1 ovarian cancer, 1 metastatic prostate cancer (for which the death occurred after withdrawal from the study), 1 brain stem hemorrhage, 1 coma, and 1 food choking. Only 3 events were considered related to Insuman Implantable 400 IU/mL: coma and death of unknown reason.
- Eighteen (6.8%) patients reported 21 AEs (including 6 SAEs) considered related to Insuman Implantable 400 IU/mL. The majority were from SOC Metabolism and nutrition disorders (13 AEs in 11 [4.2%] patients).
- Forty (15.2%) patients reported 49 AEs (including 23 SAEs) considered related to Medtronic MIP. The majority were from SOC General disorders and administration site conditions (25 AEs in 24 [9.1%] patients).
- Catheter rinsing in relation with other AEs was required in 8 patients for 9 events. Change of catheter in relation with other AEs was required in 8 patients for 8 events. Two patients

required pump rinsing for 2 events, and 4 patients required temporary neutralization for 4 events.

- Temporary pump explantation was required in 4 (1.5%) patients as action taken for 4 AEs: 2 implant site inflammation, 1 device related sepsis, and 1 increased insulin requirement.
- Definitive pump explantations were done in 11 (4.2%) patients as action taken for 12 AEs: 3 blood glucose fluctuation, 2 renal and pancreas transplant, 1 intestinal perforation, 1 endocrine pancreatic disorder and 1 renal failure [in the same patient], 1 implant site pain, 1 implant site erythema, 1 hyperglycemia not related to pump and 1 recurrent prostate cancer).

Pump explantations and insulin interruptions

- During the study, at least 1 temporary pump explantations occurred in 92 (35.0%) patients with a total of 105 temporary explantations overall, which were mainly related to end of pump life (52 [55.3%] out of 94 cases with reason available).
- Definitive pump explantations (excluding those among patients who died) were reported in 78 (29.7%) patients.
- Insuman Implantable 400 IU/mL was temporarily interrupted at least once in 73 (27.8%) patients for reasons other than an AE (mainly in relation with device dysfunctions). In addition, Insuman Implantable 400 IU/mL was temporarily interrupted in 66 (25.1%) patients due to AEs corresponding to the main safety evaluation, and in 20 (7.6%) patients due to AEs corresponding to the secondary safety evaluation.

COVID-19

- There were 11 confirmed COVID-19 infection in 10 patients (1 patient had 2 COVID-19 events: 1 stabilized, the other recovered at the time of early study termination, and the remaining 9 patients all recovered from COVID-19 without sequelae).
- There was 1 suspected COVID-19 infection and the patient was reported to have recovered with sequelae (bronchial surinfection).

Discussion

Limitations

Insuman Implantable 400 IU/mL in MIP was approved as last resort in the treatment of patients non-responsive to subcutaneous insulin, presenting with frequent, otherwise unexplained severe hyper- and/or hypoglycemia. The study population was a narrowly defined set of patients with Type 1 diabetes, who met the indication for use of CIPII because their diabetes was difficult to control.

Discontinuation of the Medtronic MIP led to reduced availability of pumps and implementation of a pump phase out process, which compromised the feasibility of completing the originally planned study. The total projected sample was reduced to 260 patients, which impacted the precision in reporting of the study objectives and reduced the ability to identify less common AEs. It is also to be noted that no new implantations were to be performed following MIP

discontinuation in 2017 and reimplantations were prioritized for patients who could benefit the most, namely the most severe patients who cannot be controlled with an alternative treatment. Due to the consequently low enrollment rate of new users, a comparison between long-term and new users was not possible.

In addition, pumps were not supplied on an ongoing basis as planned in the initial phase out process due to the manufacturing issues, leading to treatment interruptions and definitive pump explantation in patients who only needed a change of the device or who were supposed to be explanted only temporarily. This led to high rates of patient's discontinuation due to definitive pump explantation; and it should also be considered that during periods of temporary explantation, visits to the site may have been lower than when patients had to perform refill visits.

It was therefore agreed with the PRAC to terminate the study early, with a maximum observed follow-up of 5.9 years instead of the originally planned 10-years. Thus the information on long-term safety of Insuman Implantable 400 IU/mL needs to be interpreted in this context.

Most patients enrolled in the IIMOS study rolled over from the pivotal phase 3 HUBIN-L-05335 clinical trial. Patients who were withdrawn from the clinical trial due to an AE were unlikely to participate in IIMOS, which may have resulted in selection bias (creating a group of long-term users who might have higher tolerance to the drug). Therefore, the rates of AEs reported in long-term users within the IIMOS study may be lower than that reported in new users in the HUBIN-L-05335 trial.

Due to the observational nature of the study, no additional laboratory tests or procedures were performed as part of the study; resulting in high levels of missing laboratory data, as the tests would only be ordered in routine care when needed.

Cox proportional hazards models were developed for severe hypoglycemia and hyperglycemia due to insulin underdelivery in long-term users only. The number of new users (n=14) was too low to provide accurate estimates, to ensure convergence of the model, and to allow meaningful interpretation. In addition, the low occurrence of pump pocket infection (n=23), skin erosion (n=5), and absence of abnormal healing prevent the production of statistically relevant models. Finally, due to a large number of potential covariates to include in the models, a stepwise selection-based model approach was used despite its vulnerability to multiple testing, biased estimation of regression coefficients, overzealous precision, and residual confounding. Following PRAC recommendation after the 4th interim report, a full model (ie, all covariates included and no selection process) was planned for the final analysis. However, since the study was prematurely terminated and the final number of events was too low, this full model was not produced. With a full model, 1.8 events per variable for severe hypoglycemia and 6.1 events per variable for hyperglycemia would have been observed when 10 events per variable is considered as the lower limit criterion used in Cox regression analysis.

Interpretation

This is the final report of IIMOS, a post-approval, multinational, multicenter, observational, prospective cohort study to assess the safety of Insuman Implantable 400 IU/mL in MIP, in relation to important identified risks, important potential risks, missing information, and other

AEs. The observed event rates for important identified risks remains aligned with what has been observed in previous analyses.

The IIMOS study population (N=263) consisted mainly of patients from the HUBIN-L-05335 trial population (N=248, including 246 long-term users and 2 new users). There was a very limited number new users (N=14) enrolled, therefore, the ability to draw a robust interpretation on the real-world safety profile of Insuman Implantable 400 IU/mL in MIP is limited to long-term users (ie, patients with a duration >6 months from first pump implantation to study entry). The reduced sample size also prevented performing all planned analyses, so the results are limited to analyses that could produce reliable results. Moreover, as the study was terminated early, long-term safety is limited to 5-year follow-up instead of the originally planned 10 years.

Approximately two-thirds (66.9%) of the patients reported a total of 451 AEs categorized as important identified risks (main safety evaluation). The risks identified were consistent with the currently known safety profile of Insuman Implantable 400 IU/mL and were in accordance with the approved product label. Moreover, almost all of the events of important identified risks were resolved without sequelae, resolving or stabilized at the time of the time of study termination.

The total exposure was 1306.4 patient-years (n=263 patients) with a mean (SD) follow-up time of 4.7 (1.5) years. The event rates per 100 patient-years of important identified risks were: severe hypoglycemia 8.8 (95% CI: 7.2;10.4), hyperglycemia due to insulin underdelivery 23.6 (95% CI: 20.9;26.2), pump pocket infection 1.8 (95% CI: 1.0;2.5), and skin erosion 0.4 (95% CI: 0.1;0.7). These rates are aligned with what was reported in previous interim reports.

Although these rates are difficult to compare between studies due to methodological differences, a systematic review reported event rates of severe hypoglycemic events (ie, those requiring external assistance) during treatment with implantable insulin pumps in observational studies varying from 0 to 2.5 and 50 per 100 patient-years, in range with the event rate reported in this study; and event rates of pump pocket events (including infection, hematomas, skin erosion/ulcerations and migration of the pump) ranging from 2 to 8.5 per 100 patient-years, higher than reported in this study.

The overall study population was similar in terms of gender distribution, but somewhat older and with a longer duration of diabetes since diagnosis, than in previous studies of patients with implantable devices.

The cumulative mean number of severe hypoglycemia at 5 years after start of enrolment for long-term users was 0.51 which corresponds to approximately 127 events among 249 long-term users. However, at that timepoint, only 48 of the 249 (19.3%) long-term users had at least 1 severe hypoglycemia events. This suggests that recurrent severe hypoglycemia events are likely to occur.

The cumulative mean number of hyperglycemia events caused by insulin underdelivery at 5 years after start of enrolment per long-term user was 1.62 which corresponds to approximately 403 events among 249 long-term users. At that timepoint, 134 of the 249 (53.8%) long-term users had at least 1 hyperglycemia events caused by insulin underdelivery.

This also suggests that recurrent hyperglycemia events caused by insulin underdelivery are likely to occur.

In Cox multivariate models, after adjusting for age, gender and BMI, the risk of severe hypoglycemia increased by 3.1 times with hypoglycemic unawareness, which is consistent with what has been reported in the scientific literature. Conversely, the use of other antidiabetic treatments (mainly insulin) lowered the risk of severe hypoglycemia by 69%. This association is possibly due to underreporting of severe hypoglycemic episodes in patients during periods of temporary interruption of CIPII or may also reflect the fact that patients who were receiving concomitant subcutaneous insulin treatment had high levels of glycemia, thus were unlikely to develop hypoglycemia shortly after, or they may have monitored more closely to determine insulin dose, and therefore caught low levels earlier before it developed into hypoglycemia.

Length of exposure to IP treatment prior to study entry was associated with a decreased risk of hyperglycemia caused by insulin underdelivery. A 1 year increase in time since initial IP treatment at study entry decreased the risk of an event by 3%. While this result cannot support a clinically relevant conclusion, it could suggest that long-term users of IP treatment do not develop resistance to insulin with exposure.

Regarding characterization of important potential risks, missing information, and other safety signals (secondary safety evaluation), only 1 case of hypersensitivity (implant site dermatitis) considered related to Medtronic MIP was reported. No cases of focal hepatic steatosis or adverse outcomes from long-term exposure to phenol in the IP region were reported in the study. No safety signals were detected in relation to pregnancy or lactation.

Validity and Generalizability

To maximize patient enrollment and the generalizability of results to Insuman Implantable 400 IU/mL in a MIP target patient population, no exclusion criteria were established. To participate in IIMOS, patients were required to have a confirmed diagnosis of Type 1 diabetes and to be treated with Insuman Implantable 400 IU/mL in MIP at study entry and in accordance with the product approved label.

All patients included in the study were followed in routine practice at centers with experts in the use of the MIP and 94.3% of patients rolled over from the HUBIN-L-05335 clinical trial. They fulfilled the required indication for treatment with Insuman Implantable 400 IU/mL and the recommended conditions of use were followed. Therefore, the results from the study provide additional information on the Insuman Implantable 400 IU/mL safety profile. However, the inclusion of a majority of long-term users, with more experience with the drug and thus, possible better tolerance, may limit the generalizability of the results to patients with an exposure to Insuman Implantable 400 IU/mL of more than 6 months, as new users were not well represented in the study.

Conclusion

The study results were consistent with the currently known safety profile of Insuman Implantable 400 IU/mL and are in accordance with the approved product label. There were no

new safety signals identified, nor any new information that would change the current understanding or classification of the important identified risks, important potential risks, or missing information such as safety in pregnant and lactating women, and long-term safety. However, the reduced number of patients and the shorter follow-up period than originally planned, caused by the discontinuation of the MIP, limited the generalizability to long-term users (ie, patients had pump installed for more than 6 months prior to study entry), and the interpretation to a 5 year follow-up period. Nevertheless, the low observed event rate for long-term users is reassuring of a positive safety profile in this population.

Marketing Authorization Holder(s)

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Study Personnel

The Coordinating Investigator's and Company responsible medical officer's signed approvals of the report are provided in Annex 2, Study Report Approval (Principal or Coordinating Investigator Signature Form), (Sponsor Approval Form).

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The Company (Sanofi) was responsible for providing adequate resources to ensure the proper conduct of the study.

The Company was responsible for local submission(s) complying with data protection rules and any other local submission(s) required.

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