London, 25 July 2013
EMA/CHMP/424693/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Insuman

International non-proprietary name: INSULIN HUMAN

Procedure No. EMEA/H/C/000201/X/0091

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AC:	active control
ADA:	American Diabetes Association
ADAs:	anti-drug antibodies/anti-insulin antibodies
AE:	adverse event
AIA:	anti-insulin antibodies
AT:	as-treated
AUC:	area under the serum concentration time curve
AUC0-4h:	area under the serum concentration time curve calculated using the trapezoidal method from time zero to 4 h post dosing
BMI:	body mass index
CAPD:	continuous ambulatory peritoneal dialysis
CGM:	continuous glucose monitoring
CHMP:	Committee for Medicinal Products for Human Use
CI:	confidence interval
CIPII:	continuous intra-peritoneal insulin infusion
CIPII-EP:	continuous intra-peritoneal insulin infusion with an external pump
CIVII:	continuous intra-venous insulin infusion
Cmax:	maximum serum concentration observed
CSII:	continuous subcutaneous insulin infusion
CSR:	clinical study report
C_{trough}:	mean of three pre-dose serum concentrations measured 1 h, 0.5 h and immediately before dosing
CU:	compassionate use
DKA:	diabetic ketoacidosis
ELISA:	enzyme-linked immunosorbent assay
EPA:	Environmental Protection Agency
ESRD:	end stage renal disease
EVADIAC:	EVAluation dans le Diabète des Implants ACtifs
GCP:	Good Clinical Practice
HbA1c:	glycosylated haemoglobin
ICH:	International Conference on Harmonization

IM:	intramuscular
IP:	intra-peritoneal
IPC:	in-process control
ITT:	intent-to-treat
IU:	international unit
JP:	Japanese Pharmacopoeia
LBGI:	low blood glucose index
LNE/G-MED:	French notified body (for the European Directives covering medical devices)
MAGE:	mean amplitude of glycaemic excursions
MC:	multiple centre
MDI:	multiple daily injection
MedDRA:	Medical Dictionary for Regulatory Activities
MIP:	Medtronic MiniMed Implantable Pump
mITT:	modified intent-to-treat
N:	number of patients
NaOH:	Sodium hydroxide
OL:	open label
PG:	parallel group
Ph. Eur.:	European Pharmacopoeia
PP:	per-protocol
PPC:	personal pump communicator
R:	randomized
rDNA:	recombinant DNA
RfD:	reference dose
SAE:	serious adverse event
SB:	single blind
SC:	subcutaneous
SMBG:	self-monitored blood glucose
SmPC:	Summary of Product Characteristics
SMPG:	self-monitored plasma glucose
SOC:	system organ class
t1/2z:	terminal half-life
T1DM:	Type 1 Diabetes Mellitus

T2DM:	Type 2 Diabetes Mellitus
TEAE:	treatment emergent adverse event
tmax:	first time to reach maximum serum concentration observed
USP:	U.S. Pharmacopeial Convention

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sanofi-Aventis Deutschland GmbH submitted on 25 July 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Insuman Implantable, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Adult patients with type 1 diabetes mellitus who are candidates for intensive insulin therapy, when use of an implantable pump is medically appropriate.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application. The applicant indicated that insulin human was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Sanofi-Aventis Deutschland GmbH
Industriepark Höchst
Brüningstraße 50
D-65926 Frankfurt / Main
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Walter Janssens** Co-Rapporteur: **Pieter de Graeff**

- The application was received by the EMA on 25 July 2012.
- The procedure started on 15 August 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 November 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 3 November 2012
- During the meeting on 13 December 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 December 2012
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 March 2013
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 April 2013
- The PRAC Rapporteur RMP assessment report was adopted by PRAC on 16 May 2013
- During the CHMP meeting on 30 May 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 June 2013.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 19 July 2013
- During the meeting on 25 July 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Insuman Implantable on 25 July 2013.

2. Scientific discussion

2.1. Introduction

The purpose of this Extension Application is to register Insuman Implantable 400 IU/ml solution for (intraperitoneal) infusion. Insuman already has the following approved formulations which are solutions or suspensions for injection, with strengths of 40 or 100 IU/ml: Insuman Rapid, Comb 15, Comb 25, Comb 30, Comb 50, Basal and Infusat. These formulations are intended for subcutaneous use (the Rapid formulation may also be administered intravenously).

The Applicant aligned the remaining Insuman presentations with the latest QRD template, version 9, in this line extension procedure.

Insuman Implantable 400 IU/ml (solution for infusion in a vial) was developed to replace Insuplant 400 IU/ml (French national registration °1998, MAH Prostrakan Pharma).

Both Insuman Implantable and Insuplant have the same formulation. The only difference between these two drug products is the source of the human insulin used. The active substance in Insuman is

human insulin produced via recombinant DNA technology in *E. coli*, while the human insulin used in the manufacture of Insuplant is insulin derived from enzymatic modification of porcine insulin.

The manufacturing of this porcine-derived insulin was recently stopped. The recombinant human insulin Insuman Implantable 400 IU/mL was developed as a replacement therapy for Insuplant and is currently the only insulin available which can be used with the Medtronic MiniMed Implantable Pump (MIP) for continuous intra-peritoneal insulin infusion (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. Insuman Implantable 400 IU/ml is delivered by a continuous infusion at a basal rate with the remaining 40 – 60% as boluses divided between the three main meals. The reservoir is filled (and re-filled) with Insuman 400 IU/ml by trained healthcare personnel in hospital using aseptic procedures. Insuman Implantable 400 IU/mL has to be used under restricted medical prescription, in hospital only and in specialized units.

2.2. Quality aspects

2.2.1. Introduction

The extension of the Marketing Authorisation concerns a new route of administration (intraperitoneal use) associated with a new strength (400 IU/mL) and a new pharmaceutical form (solution for infusion). Insuman Implantable 400 UI/ml solution for infusion has been specifically formulated for use with a Medtronic MiniMed Implantable Pump (MIP). The implantable Medtronic MiniMed intraperitoneal insulin pump is a CE marked medical device, however there is a current procedure on going at the Notified Body (GMED) in order to update the CE mark (please refer to section 2.2.6).

2.2.2. Active Substance

Insulin human (HR1799) is manufactured from a fusion protein produced by an *Escherichia coli* strain that has been genetically modified with a corresponding recombinant plasmid. This fusion protein contains human proinsulin linked to an *E. coli* polypeptide. Insulin HR 1799 is delivered from this precursor by a multi-step procedure, including enzymatic cleavage, followed by rigorous purification.

Insulin HR 1799 (human insulin of rDNA origin) is a white to almost white powder practically insoluble in water, soluble in diluted mineral acids and sensitive to light.

No further data was provided regarding the active substance for this line extension application as the active substance has been approved for manufacturing finished product preparations for subcutaneous and intravenous use. The active substance used in this formulation is of the same quality as that used for the manufacture of the already approved Insuman, thus no new information or assessment is required.

2.2.3. Finished Medicinal Product

Insuman Implantable 400 UI/ml solution for infusion is a sterile neutral solution supplied in 10 ml single dose containers. The colourless type I glass vials are closed with a flanged cap made of aluminium with tear-off lid and inserted sealing disk made of chlorobutyl rubber. Details and specifications for the vial, stoppers and seals have been provided and are satisfactory.

The solution is only for use with the Medtronic implantable pump for intraperitoneal delivery. At each refill of the implanted pump, insulin human 400 IU/mL solution for infusion is transferred into the pump reservoir using the sterile refill syringe and needle provided. The refill is performed at hospital under aseptic conditions and the procedure is described in detail in the Pump Manual.

Pharmaceutical Development

The finished product is a neutral buffered solution (pH 7.5) of insulin HR1799, stabilized with polyethylene-polypropylene glycol (poloxamer 171). The neutral pH was chosen to have an optimum local tolerability of the preparation. The formulation contains phenol as an antimicrobial preservative and Trometamol as a buffering agent to stabilize the pH at 7.5.

The excipients were chosen taking into account compatibility with insulin, stability, local tolerance and manufacturing process.

All the excipients are described in the European Pharmacopoeia, except Poloxamer 171 which is a non-compendial excipient. Additional requirements for microbiological purity and bacterial endotoxins have been included. The specifications proposed for Poloxamer 171 are satisfactory and the methods can be considered as suitably validated.

Insulin human 400 IU/ml solution for infusion should not be mixed with other products. The solution can only be in contact with the buffer solution, (a placebo solution comprising the excipients minus insulin and zinc chloride) used as shipping fluid and rinsing buffer. Medtronic MiniMed Implantable pumps are shipped with shipping fluid inside the pump reservoir. During the first implant, the pump is emptied and rinsed with Insulin human 400 IU/ml solution for infusion and then filled for use. Any trace of shipping fluid / rinse buffer left in the pump will not be incompatible with Insuman Implantable.

The information provided on pharmaceutical development is considered satisfactory and the applicant adequately outlined the criticalities of the finished product.

Adventitious agents

No excipients of human or animal derived material are used in the manufacture of this medicinal product.

Manufacture of the product

The manufacturing process is based on conventional dissolving, mixing, pH-adjustment, filtration, filling and packaging techniques. Since the product is heat labile the sterility is ensured by sterile filtration and aseptic filling. Appropriate controls are in place.

The content of the vial is intended to be transferred aseptically to the reservoir of the implanted pump. Although the (re-)filling procedure of the pump is performed in hospital under aseptic conditions, phenol was added to the formulation as antimicrobial preservative in order to provide microbial protection in case of accidental contamination during transfer.

The preserving properties of the formulation are sufficiently supported by the preservative efficacy testing also covering an in-use period of 45 days.

Validation results have been provided for three consecutive production scale batches manufactured with three different active substance batches. Results of process controls and of final quality controls of three consecutive production scale batches were reviewed and assessed.

The manufacturing process is sufficiently described and the validation data demonstrate that the process is reproducible and capable, within its specified design parameters, of consistently producing a finished product of the required quality. The assay results obtained during manufacture and filling indicate that the solution is stable during preparation and filling.

Product specification

The control of finished product is ascertained by suitable specification tests and limits. The limits are well in line with pharmacopoeial requirements and have been appropriately justified. The analytical methods have been adequately validated and, where relevant, are compliant with Ph. Eur. requirements.

Batch analyses data from three consecutive production scale batches of insulin human solution for infusion have been provided. All batches met the acceptance criteria.

Stability of the product

The stability of the finished product was studied with three full scale batches stored for 24 months at long-term conditions (+5 ± 3°C), for 6 months at accelerated conditions (+25 ± 2°C/60% ± 5%RH) and for 8 weeks under stress conditions (+37 ± 2°C). A photostability study was also performed on one batch exposed for 1 day to artificial sunlight. Vials were stored in an inverted position.

Based on the data provided, the proposed shelf-life of 24 months for the finished product when stored at 2-8°C, protected from light is considered acceptable.

To support the prescribed use of Insuman in combination with the pump the following information has been provided:

- in-use *in vitro* stability study

- analysis of *in vivo* samples (analysis of solutions recovered from the pump reservoir before a refill)

The provided data shows that insulin solution is stable during the 45-day in-use period in the pump. The data also indicate that the NaOH rinse procedure is suitable to prevent pump blockage by fibril formation.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Information on composition, pharmaceutical development and manufacture has been presented in a satisfactory manner.

The manufacturing process is well described. It was demonstrated that the manufacturing process of Insulin Implantable is capable, within its specified design parameters, of consistently producing a finished product of required quality.

The in-process control (IPC) tests are described and deemed suitable for controlling and monitoring the manufacturing process.

Overall, the finished product is well controlled. The list of specification tests, their limits and justifications, the validation of the methods as well as the characterization of impurities are considered appropriate.

The provided information on the reference standards is satisfactory. The packaging materials are suitably described and comply with the relevant requirements. The shelf-life and storage conditions as proposed by the applicant are acceptable.

Insuman Implantable can only be used with the Medtronic implantable pump. The tests performed to demonstrate the suitability and compatibility of the pump with the Insuman implantable solution are adequately described.

To guarantee insulin solution stability and to prevent pump blockage, a refill cycle of 45 days is recommended together with a monitoring of the stroke volume. In addition, a sodium hydroxide rinse procedure should be performed every 6 months or when stroke delivery accuracy falls below the acceptance criterion. The sodium hydroxide rinse procedure performed under these conditions was demonstrated to be appropriate to prevent pump blockage by fibril formation.

The rinsing sodium hydroxide solution composition is provided. It is classified and registered as a medical device. The EC Certificate has been provided together with the EC Certificates of the pump.

The initial septum study/inlet valve assembly testing for absence of leakage was designed to demonstrate a 5-year of service with less frequent refill and rinse procedures than the currently proposed schedule.

To take into account the modified shortened refill (45 days) and rinse cycles (every 6 months) as well as the extended battery life (7 years), the applicant has started a study to demonstrate septum/inlet valve integrity and absence of leakage. The presented protocol ETP13-5469 is considered acceptable. The purpose of this protocol is to define the procedure and test conditions to verify the functional reliability of the MIP Inlet Assembly through the expected life conditions, including manufacturing and service life.

The CHMP recommends the applicant to provide results of the study and to modify the shelf-life of the pump if necessary.

The applicant submitted a change to the notified body (LNE/G-MED) to extend the use of Medtronic MiniMed Implantable Infusion Pump with rDNA human insulin and to align the physician manual with Insuman 400 IU/ml SmPC (refill cycle and rinsing procedure). Currently it is under evaluation by LNE/G-MED and their feedback is expected in September 2013. The applicant is recommended to provide the outcome from the evaluation carried out by LNE/G-MED to the CHMP.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

Based on the submitted data, the application for Insuman Implantable is recommended for approval based on quality grounds.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The CHMP recommends the applicant to provide results of the study to demonstrate septum/inlet valve integrity and absence of leakage (protocol ETP13-5469) and to modify the shelf-life of the pump if necessary.
2. The applicant is recommended to provide the outcome from the evaluation carried out by the notified body (LNE/G-MED) regarding the change to extent the use of the Medtronic MiniMed Implantable Infusion Pump with rDNA human insulin and to align the physician manual with Insuman 400 IU/ml SmPC (refill cycle and rinsing procedure) once available.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant provided the study reports of four non-clinical studies which were conducted in compliance with GLP regulations. In addition, the results of two non-GLP studies were submitted and described in the non-clinical overview and summaries.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In a rabbit study it was shown that formulations of recombinant human insulin (100 IU/mL) and semi-synthetic human insulin (100 IU/mL) had the same blood glucose lowering effect, following subcutaneous (SC) or intraperitoneal (IP) administration. However, the IP route of administration elicited only a pharmacodynamic response in half of the tested animals (6 out of 12) vs. most (11 out of 12) SC treated animals. The similar pharmacodynamic response of both tested insulins is in concordance with earlier studies where both insulins (100 IU/ml) were tested in different formulations after subcutaneous injection in rabbits and dogs. Since clinical efficacy data are available, no additional studies have been performed with Insuman Implantable 400 IU/mL; this was acceptable to the CHMP.

2.3.3. Pharmacokinetics

Based on the identity of the recombinant human insulin (HR1799) to the endogenous human hormone, no absorption, distribution, metabolism or excretion (ADME) studies were performed.

Drug interaction studies were not considered necessary or appropriate to be performed in animal experiments, since additional administration of other drugs may potentiate or attenuate the pharmacological effect of insulin on blood glucose concentrations, for which considerable and sufficient clinical experience is available.

The pharmacokinetics of Insuman Implantable 400 IU/mL in humans was investigated in the comparative phase of the clinical trial HUBIN_L_05335.

The above approach taken by the applicant was considered acceptable by the CHMP.

2.3.4. Toxicology

Single dose toxicity

In a single-dose study, rats were administered semi-synthetic human insulin in a formulation with 400 IU/mL and excipients identical to the Insuman Implantable 400 IU/mL formulation by IP injection at a volume of 10 mL/kg. This IP administration of 4000 IU/kg (including 27 mg/kg of phenol) did not cause any clinical symptoms, macroscopically visible changes or irritations in the abdominal cavity.

One additional single-dose toxicity study in rats was performed, where recombinant human insulin (100 IU/mL) was compared with semi-synthetic human insulin (100 IU/mL) following SC injection. For both insulins no signs of toxicity were observed.

There have been clinical findings of reversible hepatic subcapsular steatosis in diabetic patients treated with intraperitoneal insulin therapy. In view of this the applicant investigated this issue further in the non-clinical setting.

A published study in diabetic (Streptozotocin induced) rats (Ebel et al) that received Humulin (100U/ml) IP for 5 days via a pump and a catheter that had been fixed to the liver capsule demonstrated that focal steatosis occurred in livers from day 1 to day 5 after the start of treatment. Treatment was stopped at day 5 and complete reversibility was observed at day 10. This study confirmed the clinical findings and supported the hypothesis that high local insulin levels at the liver capsule may induce a focal hepatic steatosis.

A second study (Stéphanie Dal-Ros, Nathalie Jeandidier, Elodie Seyfritz, William Bietiger, Claude Péronet, François Moreau, Michel Pinget, and Séverine Sigrist, Impact of intraperitoneal insulin infusion on metabolism and hepatic oxidative stress in streptozotocin-Induced Diabetic-rats, 2013, Hepatology) was done with Insuplant in diabetic rats to compare the IP route of administration to the SC route. This study has shown that insulin administered by IP is mainly absorbed by the portal vein and is not associated with insulin resistance in the liver. Livers were examined after 1 and 4 weeks of treatment: there were no signs of macroscopic or physiopathologic modifications, and no signs for subcapsular focal steatosis. There were also no signs for local intolerance that might be due to phenol in the formulation of Insuman Insuplant.

No further toxicity studies were considered necessary since they would not eliminate the potential risk of focal hepatic steatosis in patients.

In addition, the company provided an overview of the toxicity of phenol. In particular, the potential of phenol to induce local irritation or promote carcinogenicity of the formulation was assessed on the basis of the provided data. The data focuses on the genotoxic and clastogenic effects of phenol only. The Applicant discusses several publications which show that IP administration of phenol resulted in no or only weak clastogenic effect. A calculation showing that exposure of the liver after IP administration will be low is also presented. The Applicant also presented data showing that if phenol does not have a direct genotoxic and carcinogenic effect, it can act as a promoter of such an effect. Phenol has for example been demonstrated to be a skin-tumor promoter. Human insulin is mitogenic and could be expected to promote growth of pre-existing tumours but not to initiate formation of tumours. Phenol is a promotor, so it also is not considered to initiate a tumour. So, theoretically, no carcinogenic effect is expected as a consequence of exposure to a combination of a promotor and a mitogen. The CHMP concluded that based on the available data there was no reason for concern.

Local Tolerance

A local tolerance study, comparing 100 IU/mL formulations of recombinant human insulin with semi-synthetic human insulin at a subcutaneous dose of 1 IU/kg revealed no local toxicity. This study, however is not relevant for the assessment of the local tolerability of Insuman Implantable. No local tolerance studies were conducted with Insuman Implantable 400 IU/mL. This was accepted by the CHMP.

2.3.5. Ecotoxicity/environmental risk assessment

A justification for not performing an environmental risk assessment was submitted in line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). The CHMP agreed that Insuman Implantable is exempted of ERA due to the nature of its active substance.

2.3.6. Discussion on non-clinical aspects

Insuman Implantable 400 IU/mL is a new formulation of recombinant human insulin. This formulation is to be used in Medtronic implantable pumps as a continuous infusion by the intraperitoneal route.

Insuman (human recombinant insulin for subcutaneous use) was already the subject of a nonclinical evaluation at the time of its initial authorisation and the local tolerance of this substance after SC injection is well known.

A few nonclinical studies have been performed on the new formulation. Results show a pharmacological activity similar to that of the semi-synthetic insulin and a good local tolerance in the rabbit when administered subcutaneously.

Two non-GLP non-clinical studies were submitted that studied the impact of insulin (either Humulin or Insuman Insuplant) administered IP along with phenol. Although of very short duration as compared to the clinical use, these studies are consistent with what has been observed in two clinical cases. Focal steatosis occurs very rapidly when the catheter is fixed to the hepatic capsule and that high concentrations of insulin (with phenol) reach the liver surface, always in the same region.

Insuman Implantable contains phenol as excipient. Phenol is clastogenic *in vivo* in micronucleus assays and potentially genotoxic. Its co-administration along with insulin, a mitogenic compound, might be an issue in case the catheter that delivers the product is stuck to or near the liver capsule and the two products are delivered long term and at high doses always near the same liver region. The long term risk was discussed by the Applicant, and the potential risks of the combination insulin/phenol in a situation where the catheter is not mobile were also discussed, leading to the conclusion that no carcinogenic effect is expected as a consequence of exposure to a combination of a promotor (phenol) and a mitogen (insulin).

2.3.7. Conclusion on the non-clinical aspects

The CHMP considers there are no outstanding non-clinical issues which preclude the granting of the marketing authorisation.

2.4. Clinical aspects

2.4.1. Introduction

The studies described in this study programme investigated CIPII (Continuous Intraperitoneal Insulin Infusion) with Insuman Implantable 400 IU/ml and/or Insuplant 400 IU/ml in patients with type 1 diabetes mellitus. There is one pivotal study, HUBIN _L _05335, comparing Insuman Implantable 400 IU/mL and Insuplant 400 IU/mL (both active treatments). There is one supportive study, MIP 310, which compares either Insuman Implantable or Insuplant to subcutaneous insulin delivered either with multiple daily injection or external subcutaneous pump. There are six additional supportive studies in type 1 diabetic patients using Insuplant 400 IU/ml (active treatment) with the MIP (Medtronic MiniMed implantable pump).

The comparative phase of HUBIN provides clinical experience in 168 patients, 84 randomized to Insuman Implantable and 84 in the Insuplant comparator arm. The study phase of MIP 310 provides experience in 50 patients with CIPII, exposed to both Insuman Implantable and Insuplant. In the uncontrolled MIP 310 study extension, the continuation and maintenance phases provided additional safety data in those patients on MIP. The six additional supportive studies provide clinical experience particularly for safety in approximately 600 type 1 diabetic patients with Insuplant 400 IU/ mL.

Publications describing the EVADIAC (EVAluation dans le Diabète des Implants ACtifs) group's clinical experience with the intra-peritoneal pump and other studies with Insuplant 400 IU/mL and the MIP are also discussed.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	**No. of study centres / locations**	**Design**	**Study Posology**	**Study Objective**	**Subjs by arm entered/ compl.**	**Duration**	**Gender M/F Median Age (range)**	**Diagnosis Incl. criteria**	**Primary Endpoint**
HUBIN_L_05335	12 France	R, SB, PG, MC, AC	Insuman Implantable 400 IU/mL via MIP 2007C or Insuplant 400 IU/mL via MIP 2007C	To compare Insuman Implantable 400 IU/mL with Insuplant 400 IU/mL with respect to efficacy, pump refill accuracy	84 Insuman CIPII 84 Insuplant CIPII 168/164	160 days	85/83 52.0 (26-80)	T1DM already treated with Insuplant via MIP 2007 HbA1c ≤ 9.0 % error at refill ≤ 20%	HbA1c Refill accuracy
	17 France, The Netherlands, Sweden, Belgium	OL, MC	Insuplant 400 IU/mL via MIP 2007C	Efficacy, safety, refill accuracy, device interventions	164	6 months			
	17 France, The Netherlands, Sweden, Belgium	OL, MC	Insuman Implantable 400 IU/mL via MIP 2007C	Efficacy, safety, refill accuracy, device interventions	412	ongoing			
310	6 USA	R, MC, OL, AC, PG	Insuplant 400 IU/mL via MIP 2007C, followed by	To compare CIPII via the MIP with intensive SC insulin	52 CIPII 52 SC 104/97	180 days	40/64 41.7 (18.2-65.5)	T1DM HbA1c ≥ 7.5 MDI or CSII for at least 3 months	HbA1c Severe hypoglycaemia
			Insuman Implantable 400 IU/mL via MIP 2007C	Non-inferiority of severe hypoglycaemia		180 days			
			vs Subcutaneous insulin			360 days			
302	14 USA, 4 France	MC, OL	Insuplant 400 IU/mL via MIP 2001	Safety, efficacy of Insuplant 400 IU/mL via MIP 2001	260/108	At least 18 months, up to 10 years	143/117 37.75 (19.6-64.9)	T1DM for at least 1 year	HbA1c
302H	3 France	MC, OL	Insuplant 400 IU/mL via MIP	Feasibility, reliability, safety of	15/11	6 months up to 10	6/9 36.65 (26.7-	T1DM for at least 1	HbA1c

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age (range)	Diagnosis Incl. criteria	Primary Endpoint
			2001	Insuplant 400 IU/mL via MIP 2001		years	59.7) Mean age 41.5	year	
CU	24EU	MC, OL, CU	Insuplant 400 IU/mL via MIP 2001	No formal objectives	252/252	3.5 years	N=123 60/63 N=136 Mean age 38.6 (18.4-61.3)	T1DM	HbA1c
303	29 EU	MC, OL	Insuplant 400 IU/mL via MIP 2001	Long term safety of Insuplant 400 IU/mL	345/345	18-24 months Up to 5 years	N=143 67/76 N=165 Mean age 39.2 (18.4-66.3)	T1DM Pat's from studies 302&CU	HbA1c Pump refill accuracy
303A	15 France	MC, OL	Insuplant 400 IU/mL via MIP 2007	Long-term safety of Insuplant 400 IU/mL	420/378	6 years & 4 months	N=383 168/215 N=384 46.0 (19.0-75.0)	T1DM, Pat's with MIP or were implanted during study	Serious adverse events, unanticipated adverse events
307	22 EU	MC, OL	Insuplant 400 IU/mL via MIP 2001	Changes in mean refill accuracy and time to non-surgical intervention following MIP with modified sideport catheter	110/107	9 months Up to 15 months	N=41 20/21 N=50 Mean age 40.9 (25.1-663.)	T1DM Pat's from studies 302&303	Pump refill accuracy
344VA	8 USA	MC, R	Insuplant 400 IU/mL via MIP 2001 vs SC insulin	Efficacy Insuplant 400 IU/mL vs SC insulin	CIPII=59, MDI=62 121/105	12 months	121/0 56.2 (47.9-64.4)	Male, T2DM, ≥ 1 sc insulin/day HbA1c ≥ 8%	HbA1c, blood glucose levels Quality of life

AC=active controlled, CU=compassionate use, MC=multicenter, OL=open label, PG=parallel group, R=randomised, SB=single blind

2.4.2. Pharmacokinetics

Insuman Implantable 400 IU/ml is an insulin with rapid onset and short duration of action. The pharmacokinetic properties of insulin depend primarily on its route of administration, followed by

physical activity, temperature and other variables. In subjects without diabetes, the serum half-life of insulin is four to six minutes when injected subcutaneously.

The intraperitoneal route of insulin infusion bypasses the subcutaneous interstitial milieu and causes a predominant diffusion of insulin through the hepatic portal venous system. In the HUBIN study pharmacokinetic assessments were performed in a subset of 24 patients (11 on Insuman and 13 on Insuplant) all administered IP (see below).

Absorption

By means of a sub-study in the study HUBIN_L_05335, the PK profile of Insuman Implantable 400 IU/mL following intra-peritoneal infusion has been investigated and compared with that of Insuplant 400 IU/mL following intra-peritoneal infusion. 24 patients were evaluated (Insuman:11 – Insuplant:13).

Following CIPII administration of 0.15 IU/kg Insuman Implantable 400 IU/mL or Insuplant 400 IU/mL, no statistically significant differences were observed for Tmax, Cmax and AUC0-4h at visit 5. For Insuman Implantable, Tmax was 0.54 hours, Cmax in serum was 210 ± 129 µIU/ml and AUC0-4h was 286 ± 122 µIU•h/ml. The similar Cmax and AUC0-4h indicate a similar exposure to both insulins.

Summary of PK parameters of Insuman Implantable 400 IU/ml and Insuplant U400 following intra-peritoneal infusion

Mean ± SD (Geometric Mean) [CV%]	0.15 IU/kg	
	Insuman Implantable Visit 5	Insuplant Visit 5
N	10	11
C_{max}	210 ± 129	148 ± 131
(µIU/mL)	(177) [61.6]	(104) [88.9]
t_{max}[a]	0.54	0.75
(h)	(0.00 - 1.00)	(0.50 - 1.00)
$t_{1/2z}$	2.73 ± 3.91	2.41 ± 1.60
(h)	(1.76) [143.1]	(2.07) [66.3]
AUC_{0-4h}	286 ± 122	245 ± 197
(µIU•h/mL)	(259) [42.8]	(184) [80.5]
$AUC_{Bolus,0-4h}$[b]	217 ± 88.4	106 ± 76.7
(µIU•h/mL)	(199) [40.7][c]	(84.4) [72.6]

[a] Median (Min - Max)

[b] Corrected AUC_{0-4h} due to bolus injection, calculated by subtraction of the contribution of the basal infusion ($4 \cdot C_{trough}$) from the measured AUC_{0-4h}: $AUC_{Bolus,0-4h} = AUC_{0-4h} - 4 \cdot C_{trough}$

[c] N=9, Subject 250002025 was not included in calculation of summary statistics because the $AUC_{Bolus,0-4h}$ value was negative

No statistically significant difference between the two insulins was observed for Cmax, Tmax, T1/2z and AUC0-4h

A statistically significant difference (p=0.0066) was observed for AUCBolus,0 4h (defined as AUC0-4h-4•Ctrough) with an intergroup ratio (Insuman Implantable / Insuplant) being 2.36 with CI 95 % [1. 3108 ; 4.2538]. The AUCBolus,0 4h of Insuman Implantable was 217 ± 88.4 µIU•h/ml.

The cause for this difference could not conclusively be elucidated. Even if potential causes are conceivable, the applicant cannot give a definite explanation for this observation.

Distribution

No study was performed. The intra-peritoneal route of insulin infusion bypasses the subcutaneous interstitial milieu and mimics the function of normal beta cells by a predominant diffusion of insulin through the hepatic portal venous system.

Elimination

Following CIPII administration of 0.15 IU/kg Insuman Implantable 400 IU/mL or Insuplant 400 IU/mL, no statistically significant difference was observed for t1/2z. After administration of Insuman Implantable 400 IU/mL, insulin was eliminated from serum with an apparent mean half-life of 2.7 hours.

Dose proportionality and time dependencies

Not applicable.

Special populations

- Impaired renal function

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

- Impaired hepatic function

In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

- Elderly

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

- Children

The safety and efficacy of Insuman Implantable (intraperitoneal use) have not been established in paediatric patients.

Pharmacokinetic interaction studies

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

The interactions properties of Insuman Implantable are documented based on earlier studies with other insulin formulations that apply to this submission. No specific drug-drug interaction study for this new route of administration is performed.

2.4.3. Pharmacodynamics

No pharmacodynamic studies have been performed with Insuman Implantable 400 IU/mL.

The Applicant has submitted a literature review of continuous intraperitoneal insulin infusion. CIPII is thought to offer a route of delivery more similar to the normal physiological route than current subcutaneous therapies.

The pharmacodynamic action of insulin is sufficiently known and the CHMP agreed that no further studies were required.

2.4.4. Discussion on clinical pharmacology

In the phase III study HUBIN_L_05335, except for AUCBolus,0-4h (intergroup ratio Insuman Implantable / Insuplant: 2.36 IC95 % [1.3108;4.2538]), no statistically significant between group difference in PK parameters was observed.

The HUBIN study does not compare PK between other routes of insulin administration and IP, but it does show comparability between Insuman and Insuplant (both through IP route). Mean insulin concentrations reached tended to be slightly higher for Insuman (AUC bolus), but on the other hand trough levels tended to be lower and there were no statistical differences in regard to the other pharmacokinetic nor pharmacodynamic parameters (hypo- and hyperglycaemia, glycaemic control) between Insuplant and Insuman. Therefore it was agreed that the differences between Insuman and Insuplant have no real clinical relevance. As IP insulin administration should be, and is in clinical practice, only used in a very small subset of patients and therefore recruitment potential of patients is very limited, the CHMP considers that the HUBIN trial is sufficient to assess differences in PK profile between Insuplant and Insuman Implantable IP administration. In addition the data are considered reassuring for comparability between both insulins. However, no direct comparison with other routes, such as subcutaneous, of insulin administration was made. As IP pumps are mainly used in a population were SC insulin administration has become problematic, one might wonder whether such a direct comparison would make sense. The fact that use of IP insulin should be restricted to patients with problematic SC treatment because of demonstrated absorption issues through SC administration of insulin is reflected in the SmPC. In conclusion, indirect comparison of SC (published data on PK from SC insulin administration) versus IP (HUBIN study, though limited) administration is now available and can suffice. It is considered by the CHMP that larger direct comparisons are probably not feasible nor clinically relevant when the patient population is clearly defined as a population in which SC treatment has been rendered impossible or highly problematic.

In the scientific literature, the intraperitoneal and subcutaneous insulin injections were compared, intraperitoneal insulin delivery resulting in earlier, higher and more acute peak insulin concentrations than achieved by subcutaneous injection. After IP administration, plasma insulin profiles mimic physiological events more closely.

The literature speaks well about the important reduction of severe hypoglycaemic events, which is the most impressive benefit of the clinical use of implanted insulin pump using IP insulin delivery, related to the good reproducibility of insulin absorption, the combined quicker time to peak and return to baseline, and the closer-to-physiological insulin levels after IP vs. SC bolus administration.

According to the literature and as discussed by the applicant in the dossier, using intraperitoneal insulin delivery is related to the increased production of anti-insulin antibodies in some patients. The applicant further discussed the effect of the increase in anti-insulin antibody levels on the PK parameters. As observed in the different articles, the apparition of insulin antibodies in insulin-treated patients is known for a long time but thanks to the use of semi-synthetic or recombinant human insulin, the prevalence has decreased. However, many patients still produce levels of insulin antibodies that may be clinically significant with respect to glycaemic control. Moreover, some data suggest that implantable insulin pumps induce a stronger immune response against insulin than conventional treatment. According to Lassmann-Vague et al. 1995, the increase in insulin immunogenicity did not induce significant metabolic consequences in the case of programmable insulin pumps. However, the consequences of high anti-insulin levels in type I diabetic patients are still controversial and not confirmed by all authors. In this context, the HUBIN study does not really add any new information in regard to this subject and all patients were pretreated with Insuplant, which makes impossible to assess the exact effect of Insuman Implantable.

This issue can therefore be considered as resolved from a pharmacokinetic perspective especially as sufficient information is stated in sections 4.4 and 4.8 of the SmPC, and the necessity for a potential dose-adjustment is adequately mentioned. With regards to immunogenicity the applicant presented safety data on the IP route of administration from study MIP310, including lack of clinically relevant immunogenicity for patients who were naive to IP therapy.

Time dependency was not possible to explore as the results obtained on visit 2 were not presented by the Applicant as the serum samples taken at visit 2 were analysed after the expiring date of the confirmed storage stability. It was not clear whether the measured concentrations reflect the true values. The Applicant was requested to provide extended storage and stability data if possible. These measurements are ongoing and will be provided as a legally binding post-authorisation measure in December 2013.

The Applicant provided a comparison of pharmacokinetic parameters determined on visit 2 with those determined approximately 4 months later on visit 5, which revealed no time dependency in the PK of human insulin following intraperitoneal administration of Insuman Implantable 400 IU/mL. Intra- and inter-patient variability data are provided. For Cmax and AUC0-4h, the intrapatient variability is similar following intraperitoneal administration of Insuman Implantable 400 IU/mL and Insuplant 400 IU/mL. For AUCBolus,0-4h, the intra-patient variability is markedly lower following administration of Insuman Implantable 400 IU/mL. Compared to intraperitoneal administration of Insuplant 400 IU/mL, the respective administration of Insuman Implantable 400 IU/mL resulted in lower inter-patient variability of Cmax, AUCBolus,0-4h and AUC0-4h.

In conclusion, the PK of human insulin following intraperitoneal administration of Insuman Implantable 400 IU/mL is not time dependent and results in a similar or even lower variability in its PK compared to intraperitoneal administration of Insuplant 400 IU/mL.

2.4.5. Conclusions on clinical pharmacology

The CHMP considers the there are no outstanding pharmacology issues which preclude the granting of the marketing authorisation.

The applicant committed to submit the results of the extended storage and stability measurements, as these data are not yet available.

2.5. Clinical efficacy

There are two studies that support the efficacy of Insuman Implantable and they are discussed below. The comparative phase of HUBIN is the pivotal study that compares Insuman Implantable and Insuplant, and MIP 310 that compares the use of CIPII and SC insulin. The additional studies with Insuplant are observational trials that add to the safety data base and knowledge on the use of intra-peritoneal insulin.

2.5.1. Main study (HUBIN_L_05335)

Methods

HUBIN was a phase 3, multicenter clinical trial that consisted of 3 phases:

1. The first phase is a **comparative**, randomized in parallel group, single blind (for patient) phase with **Insuman** Implantable 400 IU/mL or **Insuplant** 400 IU/mL as active comparator, during 4 refill cycles, carried out in French patients (randomized: 169, treated 168). One primary objective of the comparative phase of the pivotal HUBIN study was to demonstrate the non-inferiority of Insuman Implantable as the investigational drug compared to Insuplant on glycaemic control as evaluated by change in HbA1c from baseline. The co-primary objective of the comparative phase of HUBIN was the pump refill accuracy over 4 refill cycles, i.e. 160 ± 20 days in patients.
2. Running parallel with the comparative phase, there is a **non-comparative phase** with **Insuplant** 400 IU/mL (164 patients). The objectives of the Insuplant non-comparative phase was to assess efficacy measured as HbA1c and refill accuracy, safety and device interventions during the open-label treatment period with Insuplant (Insuplant noncomparative phase).

- At the end of the comparative phase, all patients included in the comparative phase and the Insuplant non-comparative phase were entered into a **non-comparative phase with Insuman** Implantable 400 IU/mL. In addition, starting in July 2011, 94 patients have been included directly in the Insuman Implantable 400 IU/mL non-comparative phase to ensure the continuity of their treatment up to the approval of the product. The objective was to assess efficacy, safety, refill accuracy evolution and device interventions during the open-label treatment period with Insuman.

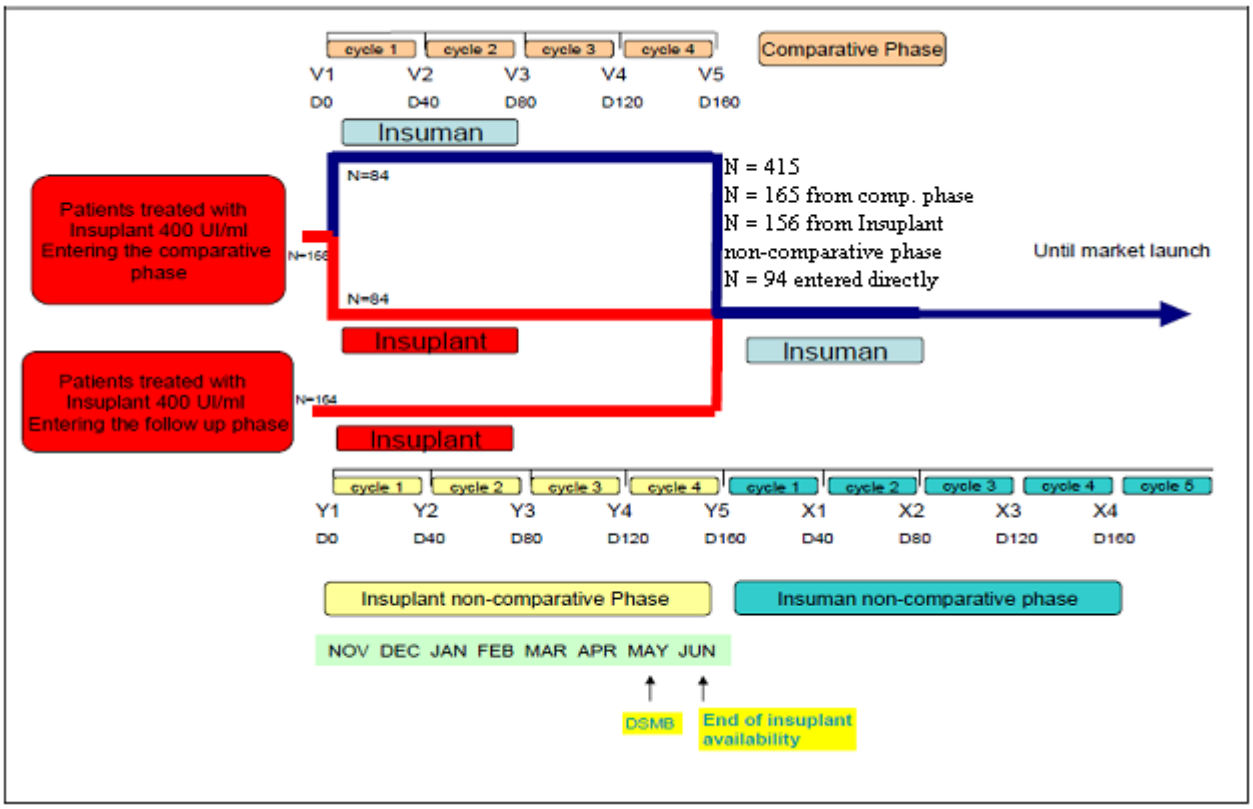


Figure 1 HUBIN trial design

Study Participants

The comparative phase of HUBIN was carried out in 168 patients with type 1 diabetics already treated with CIPII (Insuplant 400 IU/ml via a Medtronic MiniMed Implantable System 2007) most of whom met EVADIAC criteria for intra-peritoneal pump at time of implantation. Indication for pump implantation was due to "brittle diabetes" in 63.8% of the patients and was similar in both insulin treatment groups. Inclusion criteria were: HbA1c ≤9.0% and a percentage of error at refill equal or below 20%. Patients older than 65 years of age were allowed.

Treatments

In the comparative phase of HUBIN, patients were randomized to either Insuman Implantable 400 IU/mL or Insuplant 400IU/mL in the MIP 2007 pump model.

The starting dose regimen (basal rates and boluses) of treatment at inclusion visit was expected to be the same as the one administered to the patient prior to entering the trial.

Before patient's selection in the comparative phase, systematic 10 min-NaOH rinse procedure with catheter flush via sideport had to be performed before administration of randomized insulin. Pump refill had to be performed every 40 ± 5 days during the comparative phase. In case of pump system failure, patients were instructed to use subcutaneous insulin to control their diabetes.

When refill accuracy was equal to or below 85% during the study, NaOH rinse procedure with catheter flush via sideport had to be performed.

When a catheter blockage or encapsulation was diagnosed or suspected, laparoscopy was required to confirm the diagnosis and resolve catheter obstruction if confirmed.

Objectives

One primary objective of the comparative phase of the pivotal HUBIN study was to demonstrate the non-inferiority of Insuman Implantable 400 IU/mL as the investigational drug compared to Insuplant 400 IU/mL on glycaemic control as evaluated by change in HbA1c from baseline. The co-primary objective of the comparative phase of HUBIN was the pump refill accuracy over 4 refill cycles, i.e., 160 days in patients.

Outcomes/endpoints

Co-primary efficacy parameters (measured at baseline and each refill cycle):

- Refill accuracy after 4 refill cycles: percentage difference between the theoretical refill volume calculated by the personal pump communicator (PPC) using programmed values and the actual refill volume used by weight measurement:

  (theoretical – actual)/theoretical x 100 %

- HbA1c change from baseline after 4 refill cycles

Secondary efficacy parameters:

- Actual and theoretical daily insulin doses between two refills.
- Insulin basal rate and boluses of the 24 hours preceding each visit.
- Frequency of use of subcutaneous insulin, and total amount of subcutaneous insulin used. ("rescue insulin")

Key safety endpoints:

Other assessments: Device interventions

- Number of extra-refill.
- Number of rinsing procedures.
- Number of pump blockages as defined as no insulin delivery despite the 4-hour NaOH rinsing procedure.
- Number of other device interventions: pump, catheter, PPC, refill kit and mini-med needle interventions.

Sample size

In the comparative phase of HUBIN, a total of 46 patients were required (or 23 per treatment group) to attain at least 95% power for the refill accuracy, the co-primary criterion, to establish the non-inferiority comparison at the 5% level assuming that the standard deviation is 5%, with a non-inferiority limit set at 5%. For the other co-primary criterion, change from baseline in HbA1c, a total of 160 patients were required (or 80 per treatment group) to attain at least 80% power to establish at the 5% level the non-inferiority, assuming that the standard deviation of change from baseline in HbA1c is 1%, with a non-inferiority limit set at 0.4%. An assumed zero true difference between the two randomized treatments was considered for both criteria. So, a total of 160 patients were included and randomized in this study in order to reach an acceptable global power to establish the non-inferiority for both co-primary criteria.

Randomisation

For the comparative phase, the randomization list was produced and kept by the sponsor biostatistician. To randomize a patient, the Investigator had to call to an Interactive Voice Response System.

Blinding (masking)

The comparative phase of the HUBIN study was blinded for the patient only. In order to ensure the single blind, the preparation of syringes with the appropriate study medication at each refill was done by the investigator away from the patient before administration.

The blinding was not respected for 4 patients: 3 on Insuman and 1 on Insuplant.

Statistical methods

The hypothesis of non-inferiority of the Insuman Implantable 400 IU/mL compared to the Insuplant 400 IU/mL was tested by calculating the bilateral 95% CI of the difference between groups (Insuman Implantable 400 IU/mL and Insuplant 400 IU/mL) of the HbA1c change from baseline after 4 refill cycles. The non-inferiority of the Insuman Implantable 400 IU/mL compared to the Insuplant 400 IU/mL was established if the upper limit of the 95 % CI did not exceed the non-inferiority border, i.e., 0.4%.

Similarly for the other co-primary endpoint, the hypothesis of non-inferiority of the Insuman Implantable 400 IU/mL compared to the Insuplant 400 IU/mL was tested by calculating the bilateral 95% CI of the difference between groups (Insuman Implantable 400 IU/mL and Insuplant 400 IU/mL) of the refill accuracy after 4 refill cycles. The non-inferiority of the Insuman Implantable 400 IU/mL compared to the Insuplant 400 IU/mL was established if the upper limit of the 95 % CI did not exceed the non-inferiority border, i.e., 5%.

The non-inferiority analysis was performed in the per protocol (PP) and the modified intention to treat (mITT) populations. The two populations have equal importance and should lead to similar conclusion. Last observation Carried Forward method was applied for the main co-criteria for the patients who had missing values.

For refill accuracy after 4 refill cycles, a complementary analysis with maximum bias (missing values replaced by 0 in Insuplant group and by Q3 value in Insuman Implantable group) was also conducted in the mITT population to assess the effect of missing refill accuracy values.

Results

Participant flow

169 patients were included in the **comparative phase** between 16 November 2010 and 20 January 2011 by 15 centers. All included patients were randomized: 84 in the Insuman Implantable 400 IU/mL group and 85 in the Insuplant 400 IU/mL group.
Patients' disposition: 164 patients (82 patients of each group) completed the study. In the Insuman Implantable 400 IU/mL group, 2 patients (2.4 %) were withdrawn: one for adverse event (explantation before a planned pregnancy) and the other for pump blockage during the rinsing performed before investigational product initiation. In the Insuplant 400 IU/mL group, 3 patients (3.5 %) were withdrawn: one for adverse event (no healing of the skin after pump implantation), another for pump failure at first refill, and the third for deviation of inclusion criteria (error percentage superior to 20 %).

164 patients already treated with Insuplant 400 IU/mL via Medtronic MiniMed Implantable System 2007, were included in the **Insuplant non-comparative phase**, running in parallel with the comparative phase (first patient enrolled: 22 November 2010; last patient completed: 19 September 2011). Treatment and observation duration in the Insuplant non-comparative phase depended on the inclusion date. Patients enrolled later were followed for fewer cycles as all patients had to switch to Insuman during the same period. (6 cycles (0.6%), 5 cycles (12.8%), 4 cycles (50.6%), 3 cycles (70.1%), 2 cycles (81.7%) to 1 cycle (99.4%)).
Patients' disposition: 155 patients completed the study; 9 patients withdrew due to: adverse events (3, blocked catheter, catheter occlusion, pump explantation), death (1), lack of efficacy (1), pump explantation (1), pump failure (1), switch to external insulin pump (1) and pump battery low voltage (1).

417 patients enrolled in the **non-comparative phase with Insuman**. The first patient enrolled 17 November 2010. This means that **the patients treated with Insuman in the comparative phase of the HUBIN trial are included in the analysis of the Insuman non-comparative phase**. These involved patients already treated with Insuplant 400 IU/mL via Medtronic MiniMed Implantable System 2007 or Patients being re-implanted with a new pump (first fill with insulin) or patients being implanted with MiniMed Implantable Pump. Patients completed 16 to 0 cycles (16 cycles (0.2%), 15 cycles (1.0%), 14 cycles (4.8%), 13 cycles (11.5%), 12 cycles (19.2%), 11 cycles (22.1%), 10 cycles (26.1%), 9 cycles (46.8%), 8 cycles (78.7%), 7 cycles (89.7%), 6 cycles (93.0%), 5 cycles (94.5%), 4 cycles (96.4%), 3 cycles (97.4%), 2 cycles (98.3%), 1 cycles (98.8%), 0 cycles (100%)).

Patients' disposition: 404 patients (96.9%) continued at the cut-off date (30 June 2012); 13 patients withdrew due to: adverse events (10); wish to discontinue (2); anti-insulin antibody syndrome (medical history, 1). The adverse events leading to study drug withdrawal were: 7 patients (1.7 %) with adverse events in relation with the pump (device battery issue: 1 patient, device dislocation: 1 patient, drug delivery device removal: 1 patient, implant site inflammation: 1 patient, device related infection: 1 patient, implant site infection: 1 patient and skin erosion due to pump: 1 patient), 1 patient with hyperglycaemia, ketosis and cognitive disorders, 1 patient with hypoglycaemia and 1 patient with cerebrovascular accident. Out of the patients who experienced at least one serious treatment emergent adverse event, 2 patients died.

Baseline data

In general, patient populations in the Insuman Implantable and Insuplant groups were similar in terms of baseline characteristics including duration of diabetes, duration of CIPII and reason for treatment with CIPII.

Patients were 53±10.85 years old (**Table**). The distribution of the BMI classes is similar between the two groups; 17.9% of the Insuman Implantable group and 16.7% of the Insuplant group have a BMI >30 Kg/m².

Table 2: Demographic data in mITT population for HbA1c

Demography	Insuman N = 84	Insuplant N = 84	mITT population for HbA1c N = 168
Age (years)			
N	84	84	168
Mean ± Std dev	53.46 ± 11.64	53.35 ± 10.06	53.40 ± 10.85
Median	53.50	52.00	52.00
Min ; Max	26 ; 80	29 ; 73	26 ; 80
Q1 ; Q3	45.50 ; 62.00	46.00 ; 62.00	46.00 ; 62.00
Age in classes			
N	84	84	168
• < 40 years old	11 (13.1 %)	6 (7.1 %)	17 (10.1 %)
• [40 ; 50 [years old	23 (27.4 %)	26 (31.0 %)	49 (29.2 %)
• [50 ; 60 [years old	23 (27.4 %)	28 (33.3 %)	51 (30.4 %)
• ≥ 60 years old	27 (32.1 %)	24 (28.6 %)	51 (30.4 %)
[18 ; 65] years old	70 (83.3%)	71 (84.5%)	141 (83.9%)
[66 ; 75] years old	12 (14.3%)	13 (15.5%)	25 (14.9%)
> 75 years old	2 (2.4%)	0 (0%)	2 (1.2%)
Gender			
N	84	84	168
• Male	46 (54.8 %)	39 (46.4 %)	85 (50.6 %)
• Female	38 (45.2 %)	45 (53.6 %)	83 (49.4 %)
BMI (kg/m²)			
N	84	84	168
Mean ± Std dev	25.68 ± 3.56	25.47 ± 4.36	25.58 ± 3.97
Median	25.49	24.68	25.11
Min ; Max	19.4 ; 32.9	17.6 ; 38.9	17.6 ; 38.9
Q1 ; Q3	22.60 ; 28.40	22.84 ; 28.05	22.69 ; 28.11
BMI in classes			
N	84	84	168
• BMI < 18.5 KG/M²	0 (0.0 %)	2 (2.4 %)	2 (1.2 %)
• BMI [18.5 ; 25[KG/M²	36 (42.9 %)	44 (52.4 %)	80 (47.6 %)
• BMI [25 ; 30[KG/M²	33 (39.3 %)	24 (28.6 %)	57 (33.9 %)
• BMI ≥ 30 KG/M²	15 (17.9 %)	14 (16.7 %)	29 (17.3 %)

In the mITT population for HbA1c, the mean time from the diagnosis of type 1 diabetes was 32.4 years on average (median: 32.1 years) and the duration of treatment with CIPII was on average 11.7 years (median: 11.0 years). The current pump had been implanted for 2.4 years on average (median: 2.1 years) and current insulin (Insuplant) had been used for 8.9 years on average (median: 7.2 years). There was no clinically significant difference in the distribution of these criteria between the two treatment groups (Table **Table** 3). The data for the mITT population for HbA1c are shown. No differences were shown for diabetes history for other populations.

Table 3: Diabetic medical history in mITT population for HbA1c

Diabetic medical history	Insuman N = 84	Insuplant N = 84	mITT population for HbA1c N = 168
Time from the diagnosis of Type 1 diabetes (years)			
N	84	84	168
Mean ± Std dev	32.81 ± 10.14	31.94 ± 10.67	32.37 ± 10.39
Median	32.10	32.12	32.10
Min ; Max	15.0 ; 55.9	7.8 ; 63.5	7.8 ; 63.5
Time from the diagnosis of Type 1 diabetes in classes			
• < 20 years	9 (10.7 %)	10 (11.9 %)	19 (11.3 %)
• [20 ; 30 [years	25 (29.8 %)	27 (32.1 %)	52 (31.0 %)
• [30 ; 40 [years	27 (32.1 %)	29 (34.5 %)	56 (33.3 %)
• ≥ 40 years	23 (27.4 %)	18 (21.4 %)	41 (24.4 %)
Time from treatment start with CIPII (years)			
N	84	84	168
Mean ± Std dev	11.76 ± 6.99	11.66 ± 7.15	11.71 ± 7.05
Median	11.00	11.00	11.00
Min ; Max	0.5 ; 28.7	1.0 ; 21.2	0.5 ; 28.7
Time from treatment start with CIPII in classes			
• < 5 years	19 (22.6 %)	25 (29.8 %)	44 (26.2 %)
• [5 ; 10 [years	19 (22.6 %)	15 (17.9 %)	34 (20.2 %)
• [10 ; 15 [years	14 (16.7 %)	6 (7.1 %)	20 (11.9 %)
• ≥ 15 years	32 (38.1 %)	38 (45.2 %)	70 (41.7 %)
Time from implantation of the current pump (years) (*)			
N	84	84	168
Mean ± Std dev	2.28 ± 1.63	2.48 ± 1.87	2.38 ± 1.75
Median	1.99	2.45	2.06
Min ; Max	-0.0 ; 5.3	-0.0 ; 8.2	-0.0 ; 8.2
Time from implantation of the current pump in classes			
• < 1 year	20 (23.8 %)	27 (32.1 %)	47 (28.0 %)
• [1 ; 3 [years	40 (47.6 %)	23 (27.4 %)	63 (37.5 %)
• [3 ; 6 [years	24 (28.6 %)	33 (39.3 %)	57 (33.9 %)
• ≥ 6 years	0 (0.0 %)	1 (1.2 %)	1 (0.6 %)
Time from start of current insulin (Insuplant) (years)			
N	68	64	132
Mean ± Std dev	9.23 ± 6.12	8.49 ± 6.25	8.87 ± 6.17
Median	7.98	6.74	7.16
Min ; Max	0.5 ; 28.7	0.3 ; 21.2	0.3 ; 28.7
Time from start of current insulin (Insuplant) in classes			
• < 5 years	19 (27.9 %)	27 (42.2 %)	46 (34.8 %)
• [5 ; 10 [years	21 (30.9 %)	15 (23.4 %)	36 (27.3 %)
• [10 ; 15 [years	19 (27.9 %)	8 (12.5 %)	27 (20.5 %)
• ≥ 15 years	9 (13.2 %)	14 (21.9 %)	23 (17.4 %)

(*) The min of 'Time from implantation of the current pump (years)' equal to -0.0 concerns the patients implanted the day after the visit 1

Source: Statistical Report T09A

Numbers analysed

The included set was composed of all patients who signed their consent form. Analysis populations are presented below in Table 4.

Table 4: Summary of analysis populations

	Insuman N = 84	Insuplant N = 85	Included population N = 169
mITT population for refill accuracy	66 (78.6 %)	64 (75.3 %)	130 (76.9 %)
mITT population for HbA1c	84 (100.0 %)	84 (98.8 %)	168 (99.4 %)
PP population for refill accuracy	62 (73.8 %)	56 (65.9 %)	118 (69.8 %)
PP population for HbA1c	75 (89.3 %)	70 (82.4 %)	145 (85.8 %)
Safety population	84 (100.0 %)	84 (98.8 %)	168 (99.4 %)

The modified intention to treat (mITT) population includes patients who gave their informed consent, for whom there is confirmation of successful allocation of a randomization number through the study treatment allocation system, who were exposed to the study drug, i.e., who received at least one administration of the study drug and who had an evaluation for each primary outcome (mITT for HbA1c and mITT for refill accuracy).

No post-baseline refill value means no available post-baseline refill value (Insuman 1 patient and Insuplant 3 patients) or no valid post-baseline refill value (17 patients in each group). This is 20 % of the study population. Invalidation was deemed necessary because of inconsistencies of refill accuracy values at different visits for a same patient.

Experts checked refill accuracy values. All outliers were defined as invalided values.

The per protocol populations were defined as subsets of the mITT population without major protocol violations for each primary parameter. The main deviations observed were: "Duration of insulin injection >7 days" in 6.5% of the patients and "Time between refills not in the interval 40 ± 5 days" in 4.8% of the patients.

9.2% of the patients of the mITT population for refill accuracy presented at least one major deviation: 6.1% of the patients in Insuman Implantable 400 IU/mL group and 12.5% in Insuplant 400 IU/mL group. The rate of the deviation "Time between refills not in the interval 40 ± 5 days", was also higher in the Insuplant 400 IU/mL group (6.3%) than in the Insuman Implantable 400 IU/mL one (1.5%).

One patient of the Insuplant 400 IU/mL group who was not treated was excluded from Safety population.

Outcomes and estimation

In **the comparative phase of the HUBIN study**, conducted to show that recombinant insulin formulation (Insuman Implantable 400 UI/ml) could replace semi-synthetic insulin (Insuplant 400 UI/ml), analysis in the PP populations and in the mITT populations both concluded on the non-inferiority of the Insuman Implantable 400 IU/ml compared to the Insuplant 400 IU/ml for the two co-primary endpoints:

1. The **refill accuracy after 4 refill cycles** (95% CI of the intergroup difference [-5.81 ; -0.50] in PP population and [-5.21 ; -0.31] in mITT population for refill accuracy – non-inferiority limit: 5%).
2. The **HbA1c change from baseline after 4 refill cycles** (95% CI of the intergroup difference [-0.36 ; 0.11] in PP population and [-0.30 ; 0.16] in mITT population for HbA1c – noninferiority limit: 0.4%).

The non-inferiority of the Insuman Implantable 400 IU/ml compared to the Insuplant 400 IU/ml was also confirmed in the complementary analysis with maximum bias (missing values replaced by 0 in Insuplant group and by Q3 value in Insuman) for the parameter refill accuracy after 4 refill cycles (95% CI of the intergroup difference [-3.25 ; -0.61] in mITT population).

Analysis of secondary efficacy criteria has shown similar results in PP population and mITT population for HbA1c:

1. A slight decrease in actual and theoretical daily insulin doses in both treatment groups with no clinically significant difference between treatment groups nor between actual and theoretical doses.
2. No clinically significant difference between both treatment groups for the dose used during the last 24 hours at each visit.

There were similar rates of patients in the two treatment groups who received at least one other insulin injection "rescue insulin" during the study: 11/84 patients of the Insuman Implantable group versus 10/84 patients of the Insuplant group. Subcutaneous insulin was used most of the time during delivery system dysfunction (catheter occlusion, PPC issue): 9/11 patients for Insuman Implantable 400 IU/ml group and 7/10 patients for Insuplant 400 IU/ml group.

The baseline HbA1c value in the mITT population for HbA1c was 7.74±1.04% and the change from baseline varied between -0.06 and -0.25 % for the same population. In the Insuman arm this was 7.76±0.92 at baseline and the change from baseline varied between -0.08 and -0.31 %.

The refill accuracy in the mITT population for refill accuracy varied between -0.19 and 1.13 and between -0.31 and -1.71 for the Insuman arm.

No clinically significant difference was observed between the two treatment groups for the incidence of hypoglycaemia and hyperglycaemia.

In the **Insuplant non-comparative phase of the HUBIN study**, the results for the primary efficacy criteria were:

Table 5. Primary efficacy criteria in the Insuplant non-comparative phase of the Hubin trial

Refill accuracy error percentage		Analysis population N = 164
Change from baseline at V2		
	N	109
	Mean ± Std dev	2.67 ± 10.10
	Median (Min ; Max)	2.78 (-31.4 ; 41.27)
Change from baseline at V3		
	N	89
	Mean ± Std dev	2.29 ± 10.58
	Median (Min ; Max)	2.25 (-26.9 ; 36.98)
Change from baseline at V4		
	N	82
	Mean ± Std dev	1.08 ± 9.98
	Median (Min ; Max)	0.80 (-28.1 ; 35.05)
Change from baseline at V5		
	N	59
	Mean ± Std dev	1.24 ± 11.00
	Median (Min ; Max)	2.16 (-28.8 ; 27.63)
Change from baseline at V6		
	N	18
	Mean ± Std dev	3.77 ± 9.79
	Median (Min ; Max)	1.97 (-13.70 ; 27.20)

HbA1c (%)		Analysis population N = 164
Change from baseline at V2		
	N	76
	Mean ± Std dev	-0.01 ± 0.57
	Median (Min ; Max)	0.00 (-2.30 ; 1.80)
Change from baseline at V3		
	N	85
	Mean ± Std dev	-0.14 ± 0.71
	Median (Min ; Max)	-0.30 (-2.30 ; 1.90)
Change from baseline at V4		
	N	53
	Mean ± Std dev	-0.04 ± 1.04
	Median (Min ; Max)	-0.10 (-2.10 ; 3.80)
Change from baseline at V5		
	N	48
	Mean ± Std dev	-0.09 ± 0.99
	Median (Min ; Max)	-0.10 (-3.00 ; 2.80)
Change from baseline at V6		
	N	7
	Mean ± Std dev	0.70 ± 1.16
	Median (Min ; Max)	0.80 (-0.80 ; 2.30)

The change in the refill accuracy error percentage from baseline did not substantially change during the Insuplant non-comparative phase; the mean (± sd) changes from baseline varying between 1.08 ± 9.98 % (V4) and 2.67 ± 10.10 % (V2). Missing values for refill accuracy were mainly due to inconsistency in values, which was also the case in the comparative phase of the HUBIN trial.

HbA1c was stable during the study, the mean (± sd) HbA1c varying between 7.80 ± 1.25 % (V3) and 8.13 ± 1.32 % (V4), and the mean changes from baseline between -0.01 ± 0.57 % (V2) and -0.14 ± 0.71 % (V3). The missing rate of HbA1c values is mainly due to study design.

Analysis of secondary efficacy criteria has shown an actual daily insulin dose slightly smaller than theoretical dose at each visit, and a slight decrease in actual and theoretical daily insulin doses.

The interim analysis **all patients treated with Insuman in the HUBIN trial** were considered since their first fill with Insuman until the cut-off date for the interim analysis.

Refill accuracy error percentage did not substantially change during the study phase. The mean (± sd) changes from baseline varied between -0.59 ± 14.18 % (cycle 4 – 256 patients) and 6.12 ± 11.91 % (cycle 13 – 25 patients). Mean (± std) refill accuracy error percentage was -0.59 ± 8.50 % (median: -0.12 %) at first refill after pump implantation and 4.40 ± 9.86 % (median: 3.35 %) at baseline.

HbA1c was stable during the study phase, the mean (± sd) HbA1c varying between 7.74 % (C2 - 325 patients and C12 - 65 patients) and 8.02 % (C9 – 144 patients), and the mean changes from baseline between -0.19 % (C2 – 294 patients) and 0.06 % (C8 – 223 patients). Mean (± std) HbA1c value at baseline (for interim analysis) was 7.92 ± 1.28 % (median: 7.70 %).

Secondary efficacy criteria showed that actual and theoretical daily insulin doses of each cycle and the dose used during the last 24 hours did not significantly change from cycle 1 to 8. From cycle 9 to 14 the required dose was higher.

The basal and bolus doses (IU) of the last 24 h varied between 52.70 ± 27.73 and 55.91 ± 32.78 from cycle 1 to 8, in an ITT population above 300 patients. And from cycle 9 to 14, in an ITT population below 170 patients these values varied between 59.98 ± 37.95 and 67.02 ± 43.71.

The apparent shift in insulin dose when examining the whole population most likely represents heterogeneity of patients at different cycles in the population in the Insuman non-comparative phase. For the subpopulation of those 90 patients who all achieved cycle 10, there was actually a decrease in

insulin need from cycle 1 to cycle 10 and there was consistency between actual and theoretical doses of insulin.

As obese subjects need larger amounts of insulin, the Applicant performed an analysis of the reduction in HbA1c and AEs according to BMI category. Efficacy and safety were comparable for the different categories. No differences between weight classes were observed for refill accuracy.

163 patients (39.1 % of the ITT population) used subcutaneous insulin at least once during the study phase. Subcutaneous insulin was used most of the time during delivery system dysfunction (reason of 241 / 389 injections; i.e. 62% of the cases) or due to metabolic control issues.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 6. Summary of Efficacy for trial HUBIN_L_05335 Comparative phase

Title: Evaluation of Insuman Implantable 400 IU/ml in patients with Type 1 diabetes treated with the Medtronic MiniMed Implantable Pump System using Insuplant 400 IU/mL		
Study identifier	Study Number: HUBIN_L_05335 EudraCT Number: 2010 – 021373 -3 7	
Design	Phase III multicenter clinical trial with a French 6 month-comparative, parallel group and randomized phase coupled with a parallel European open label phase and followed by a European Insuman Implantable open label extension phase.	
	Duration of main phase (Comparative phase):	6 months
Hypothesis	Non-inferiority	
Treatments groups	Insuman Implantable 400 IU/mL group Insuplant 400 IU/mL group	Treatment: Insuman Implantable 400 IU/mL, Duration: 6 months, Number randomized: 84 Treatment: Insuplant 400 IU/mL, Duration: 6 months, Number randomized: 85
Endpoints and definitions	Co-Primary Endpoints: • Refill accuracy after 4-refill cycles (i.e. 160 ± 20 days). • Change from baseline in HbA1c after 4-refill cycles.	• For each insulin refill, the amount of insulin utilized since the last refill and the number of days separating the two refills was assessed. Refill accuracy was calculated as the percentage difference between the theoretical refill volume calculated by the PPC using programmed values and the actual refill volume used by weight measurement. • Blood samples for HbA1c measurements were collected at the randomization visit (baseline value = Day 1) and at each refill cycle.

	Secondary Endpoints: • Actual and theoretical daily insulin doses between two refills • Insulin basal rate and boluses of the 24 hours preceding each visit. • Frequency of use of subcutaneous insulin, and total amount of subcutaneous insulin used by time period.	• Actual and theoretical daily insulin doses were calculated at each refill from actual and theoretical amount used after conversion in International Units (IU), and reported to the time between the refill and the previous refill in days. • Insulin basal rate and boluses of the last 24 hours were recorded at each visit. • Rescue medication (i.e. any insulin supply that was not delivered via the pump) had to be documented: Frequency of use of subcutaneous insulin, and total amount of subcutaneous insulin used by time period (INN of the insulin, dose, duration and reason).
Database lock	Comparative phase: 16 December 2011	

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Modified Intent-to-treat: The modified Intent-To-Treat (mITT) population included patients who have given their informed consent, for whom there was confirmation of successful allocation of a randomization number through the study treatment allocation system, and who were exposed to the study drug (i.e. who received at least one administration of the study drug) and who had an evaluation for each primary outcome (mITT for HbA1c and mITT for refill accuracy). Per-protocol: The Per-Protocol (PP) populations were subsets of the mITT population without major protocol violations for each primary parameter. Time point: after 4-refill cycles (i.e. 160 ± 20 days)				
Descriptive statistics and estimate variability	Treatment population	PP population for refill accuracy		mITT population for refill accuracy	
		Insuman	Insuplant	Insuman	Insuplant
	Number of subjects	62	56	66	64
	Refill accuracy after 4 refill cycles (%) Mean ± Std dev Median (Min ; Max)	-0.08 ± 8.14 -1.46 (-16 ; 27)	3.07 ± 6.17 3.04 (-7 ; 22)	0.06 ± 8.00 -1.29 (-16 ; 27)	2.82 ± 5.91 2.91 (-7 ; 22)

Effect estimate per comparison	Co-Primary Endpoint: Refill accuracy	Comparison groups	Insuman and Insuplant	
			PP population	mITT population
		Intergroup difference ± Std error	-3.15 ± 1.34	-2.76 ± 1.24
		Confidence interval (CI) 95% of the intergroup difference	[-5.81 ; -0.50]	[-5.21 ; -0.31]
		P-value (ANOVA)	0.0205	0.0273

Descriptive statistics	Treatment population	PP population for HbA1c		mITT population for HbA1c	
		Insuman	Insuplant	Insuman	Insuplant

and estimate variability	Number of subjects	75	69	84	84
	HbA1c change from baseline after 4 refill cycles (%) Mean ± Std dev Median (Min ; Max)	 -0.25 ± 0.67 -0.30 (-1.90;1.80)	 -0.12 ± 0.74 -0.10 (-2.20;2.30)	 -0.27 ± 0.70 -0.30 (-1.90;1.80)	 -0.20 ± 0.79 -0.20 (-3.60;2.30)

Effect estimate per comparison	Co-Primary Endpoint: Change from baseline in HbA1c	Comparison groups	Insuman and Insuplant	
			PP population	mITT population
		Intergroup difference ± Std error	-0.13 ± 0.12	-0.07 ± 0.12
		Confidence interval (CI) 95% of the intergroup difference	[-0.36 ; 0.11]	[-0.30 ; 0.16]
		P-value (ANOVA)	0.2808	0.5430

Notes	169 patients were included in the comparative phase between 16 November 2010 and 20 January 2011 by 15 centres. 164 patients (82 patients of each group) completed the study. In the Insuman Implantable 400 IU/mL group, 2 patients (2.4 %) were withdrawn: one for adverse event (explantation before pregnancy planned, as specified in the protocol) and the other for pump blockage during the rinsing performed before investigational product initiation. In the Insuplant 400 IU/mL group, 3 patients (3.5 %) were withdrawn: one for adverse event (no healing of the skin after pump implantation), another for pump failure at first refill, and the third for deviation of inclusion criteria (error percentage superior to 20 %). Analyses in PP populations and in mITT populations concluded both to the non-inferiority of the Insuman Implantable 400 IU/ml compared to the Insuplant 400 IU/ml for: • Refill accuracy after 4 refill cycles as the upper limit of the 95% CI did not exceed the non-inferiority limit (5%). • HbA1c change from baseline after 4 refill cycles as the upper limit of the 95% CI did not exceed the non-inferiority limit (0.4%). Although not pre-specified, non inferiority is confirmed even with a more stringent non inferiority limit of 0.3% Analysis of secondary efficacy criteria has shown similar results in PP population and mITT population for HbA1c: • a slight decrease in actual and theoretical daily insulin doses between baseline and visit V5 in both treatment groups, and no clinically significant difference between treatment groups nor between actual and theoretical doses. • no clinically significant difference between both treatment groups for the dose used during the last 24 hours at each visit.
Analysis description	**Co-primary Endpoints** The hypothesis of non-inferiority of the Insuman Implantable 400 IU/mL compared to the Insuplant 400 IU/mL was tested by calculating the bilateral 95% CI of the difference between groups (Insuman Implantable 400 IU/mL - Insuplant 400 IU/mL) of the refill accuracy after 4 refill cycles. The non-inferiority of the Insuman Implantable 400 IU/mL compared to the Insuplant 400 IU/mL was established if the upper limit of the 95 % CI did not exceed the non-inferiority border, i.e. 5%. The hypothesis of non-inferiority of the Insuman Implantable 400 IU/mL compared to the Insuplant 400 IU/mL was tested by calculating the bilateral

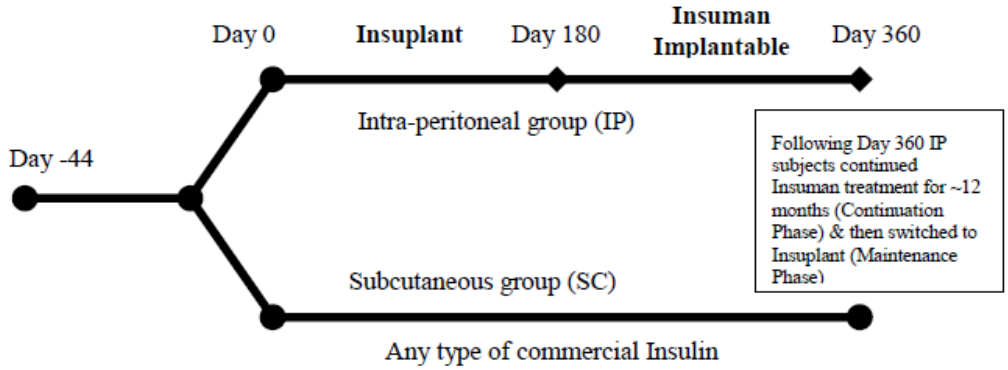
	95% CI of the difference between groups (Insuman Implantable 400 IU/mL - Insuplant 400 IU/mL) of the HbA1c change from baseline after 4 refill cycles. The non-inferiority of the Insuman Implantable 400 IU/mL compared to the Insuplant 400 IU/mL was established if the upper limit of the 95 % CI did not exceed the non-inferiority border, i.e. 0.4%. **Secondary Endpoints** Descriptive statistics by treatment group and overall were provided for the secondary endpoints.

Clinical studies in special populations

No specific studies have been performed in special populations.

Supportive study MIP 310 and other supportive studies

Figure 2. Schedule – Study Phase, Continuation and Maintenance Phases of Study MIP 310



Study 310 was a randomised, active-control, parallel group, phase III study in T1DM subjects. The study was designed to demonstrate non-inferiority of IP administration of insulin using the MIP 2007 model compared with intensive SC administration of insulin. The CIPII group received two insulin formulations during the 360 day Study Phase: Insuplant 400 IU/ml for the first 180 days and Insuman Implantable 400 IU/ml for the second 180 days. The SC group received pre-existing insulin injected subcutaneously (by injection or infusion via external pump), at doses specified by the patient, for 360 days and was not restricted in the type of insulin used during the study. For patients on CIPII a continuation phase and a maintenance phase were implemented after the study phase of 360 days. Patients received Insuman Implantable 400 IU/ml for another 12 months before transferring to Insuplant 400 IU/ml for 12 months.

Primary efficacy parameters in MIP 310 were HbA1c and number of severe hypoglycaemic events. Secondary efficacy parameters were self-monitored blood glucose measurements, mean amplitude of glycaemic excursions, low blood glucose index and relative pump refill error.

The primary efficacy results are described in the following table:

Table 1 Average HbA1C by Treatment Group and Visit

Timepoint	HbA1c Values (%)			
	As-Treated Data Set		Intent-to-Treat Data Set	
	CIPII (n = 52)	SC (n = 48)	CIPII (n = 52)	SC (n = 52)
Visit 3 - Start of Treatment Mean ± SD Median (min, max)	n = 52 8.06 ± 0.77 7.9 (6.6, 10.3)	n = 48 8.12 ± 0.76 8.0 (6.5, 10.3)	n = 52 8.06 ± 0.77 7.9 (6.6, 10.3)	n = 52 8.15 ± 0.77 8.0 (6.5, 10.3)
Visit 5 Mean ± SD Median (min, max)	n = 52 7.64 ± 0.67 7.7 (5.6, 9.0)	n = 48 8.03 ± 0.75 8.0 (6.7, 10.6)	n = 52 7.64 ± 0.67 7.7 (5.6, 9.0)	n = 52 8.06 ± 0.76 8.0 (6.7, 10.6)
Visit 6 - Change of Insulin Mean ± SD Median (min, max)	n = 51 7.75 ± 0.85 7.7 (6.2, 10.1)	n = 47 8.00 ± 0.66 8.0 (6.5, 9.6)	n = 52 7.66 ± 0.84 7.7 (6.2, 10.1)	n = 52 8.08 ± 0.76 8.0 (6.5, 10.6)
Visit 7 Mean ± SD Median (min, max)	n = 50 8.01 ± 0.99 8.0 (5.8, 11.1)	n = 47 8.18 ± 0.81 8.2 (6.5, 9.9)	n = 51 7.99 ± 0.99 7.9 (5.8, 11.1)	n = 47 8.18 ± 0.81 8.2 (6.5, 9.9)
Visit 8 - End of Study Mean ± SD Median (min, max)	n = 49 7.78 ± 1.04 7.9 (5.1, 9.6)	n = 47 8.19 ± 0.87 8.3 (6.1, 9.6)	n = 51 7.75 ± 1.03 7.9 (5.1, 9.6)	n = 47 8.19 ± 0.87 8.3 (6.1, 9.6)

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Two important studies were submitted (Study MIP 310 and HUBIN). In addition, 6 other studies are considered supportive by the applicant; however, these studies are of limited relevance as these studies only used Insuplant.

HUBIN Study: Comparative Phase

Patient populations in the Insuman Implantable and Insuplant groups were similar in terms of baseline characteristics including duration of diabetes, duration of CIPII and reason for treatment with CIPII (**Table 2**).

Table 2. Treatment before implantation in mITT population for HbA1c

Treatment before implantation		Insuman N = 84	Insuplant N = 84	mITT population for HbA1c N = 168
Treatment before implantation				
	N	81	82	163
Subcutaneous multi-injection		16 (19.8 %)	13 (15.9 %)	29 (17.8 %)
Continuous subcutaneous insulin infusion		57 (70.4 %)	61 (74.4 %)	118 (72.4 %)
Continuous intraperitoneal insulin infusion		4 (4.9 %)	7 (8.5 %)	11 (6.7 %)
Subcutaneous multi-injection and CSPII (*)		4 (4.9 %)	1 (1.2 %)	5 (3.1 %)
Reason for initiation of CIPII				
	N	81	80	161
Insulin peripheral resistance		3 (3.7 %)	5 (6.3 %)	8 (5.0 %)
Hypoglycaemia		23 (28.4 %)	24 (30.0 %)	47 (29.2 %)
Brittle diabetes		51 (63.0 %)	50 (62.5 %)	101 (62.7 %)
Hypoglycaemia and brittle diabetes		4 (4.9 %)	1 (1.3 %)	5 (3.1 %)

On average 49% of the population was female, time from current pump implantation was 2.38 ± 1.75 years, 78% had at least one diabetic late complication. The average baseline HbA1c value (at V1) was

7.74±1.04 %. The average refill accuracy in the per protocol population for refill accuracy was 0.30±5.81 at V1.

The inclusion criteria possibly introduced bias in this study. The inclusion criteria were HbA1c ≤9% and percentage error at refill equal or below 20%. The HbA1c at baseline was slightly worse at 8.03% (N=138) in the Insuplant non-comparative phase compared to 7.76% for Insuman and 7.72% for Insuplant at baseline (mITT for HbA1c) in the comparative phase. The refill accuracy was also slightly worse at 3.59 (N=124, 24% missing data) compared to -1.27 for Insuman and -1.83 for Insuplant (mITT for refill accuracy; 8% and 22% missing data in the mITT) at baseline for the comparative phase.

This is not expected to have an influence on the non-inferiority of Insuman Implantable versus Insuplant. However, this has a small influence on the safety and reliability of the therapy in the true therapeutic population.

In the 6 months preceding the inclusion visit 5% of the patients (4 in each treatment group) presented at least one severe hypoglycaemia; 29 (17.3%) of the patients had at least one medical/surgical history of the current pump.

Patients were excluded from the mITT population for refill accuracy if they had inconsistencies in measurement of their refill accuracy at any post-baseline visit and therefore no post-baseline refill values recorded. For these reasons, there were 66 out of 84 Insuman Implantable patients and 64 out of 85 Insuplant patients included in mITT population for refill accuracy. In addition, patients with any major protocol deviation were excluded from mITT population. For this reason, there were only 62 patients in the Insuman Implantable and 56 patients in the Insuplant for PP population of the refill accuracy. Refill accuracy will therefore be overestimated due to exclusion of patients with inconsistent refill values.

HUBIN Study: Insuplant Non-Comparative Phase

In the non-comparative phase of the HUBIN trial investigators followed their standard practice. The recommended rinsing procedure when refill accuracy error percentage was greater than 15 % was done in few patients: 2/10 patients (20 %) at V1, 4/17 patients (23.5 %) at V2, 5/15 patients (33.3 %) at V3, 2/7 patients (28.6 %) at V4 and 4/11 patients (36.4 %) at V5. Rinsing procedures were also performed based on clinical evaluation (e.g. at V2, 9 rinsings were performed with a refill accuracy error percentage ≤ |15| %.).

A protocol amendment was made: Pump refill was performed every 40 +/- 5 days, except for insuplant non-comparative phase (usual duration). The mean time between refills was 47±16 days in the non-comparative Insuplant arm.

There is a difference in baseline population characteristics between the patients in the comparative phase of the HUBIN trial and the remaining patient population on CIPII in the non-comparative Insuplant phase.

- In the comparative phase 49% of the population was female, while in the non-comparative Insuplant phase, 70% of the population was female.
- Time from current pump implantation was 3.95±2.77 years in the non-comparative Insuplant group while it was 2.38 ± 1.75 years in the comparative arm.
- 78% of the patients in the comparative phase had at least one diabetic late complication. In the non-comparative Insuplant phase, this was a little lower: 74%.

- Reason for initiation in the patients in the comparative phase was insulin peripheral resistance for 5%, and hypoglycaemia (alone and in combination with brittle diabetes) for 32%. In the study population in the non-comparative Insuplant phase, this was insulin peripheral resistance in 13.5% (alone or in combination with brittle diabetes) and hypoglycaemia in 26% (alone or in combination with brittle diabetes). In the remaining part of the population it was 'brittle diabetes' (Table 3).

Table 3. Treatment before implantation in analysis population

Treatment before implantation		Analysis population N = 164
Treatment before implantation		
	N	163
• Subcutaneous multi-injection		26 (16.0 %)
• Continuous subcutaneous insulin infusion		117 (71.8 %)
• Continuous intraperitoneal insulin infusion		10 (6.1 %)
• Subcutaneous multi-injection and CSPII (*)		10 (6.1 %)
Reason for initiation of CIPII (*)		
	N	163
• Insulin peripheral resistance		18 (11.0 %)
• Hypoglycaemia		40 (24.5 %)
• Brittle diabetes		98 (60.1 %)
• Insulin periph resistance and brittle diabetes		4 (2.5 %)
• Hypoglycaemia and brittle diabetes		3 (1.8 %)

- At inclusion, refill accuracy error percentage was in average 3.59 ± 7.91 % (median: 3.15 %) and HbA1c 8.03 ± 1.18 % (median: 7.70 %). The average baseline refill accuracy error percentage in the comparative phase was -1.54 and the HbA1c value 7.74±1.04 %.

HUBIN Study: Insuman Non-Comparative Phase

In the interim analysis all patients treated with Insuman, both from the comparative phase of the HUBIN trial and the non-comparative phase, were considered since their first fill with Insuman until the cut-off date for the interim analysis.

Outliers were checked during the Data Review. Experts checked refill accuracy values. All outliers were defined as invalid values.

The mean time between insulin refill, known for 407 patients, was 46 ± 13 days (median: 43 days).

With regards to the baseline characteristics, the ITT population was composed of 36.9 % males and 63.1 % females, with a mean age of 51.2 years. About half of the patients (48.5 %) had a normal weight, 32.2 % were overweight and 16.8 % were obese.

The mean time from the diagnosis of Type 1 diabetes was 30.7 years and the treatment with CIPII was started on average 10.7 years before the start of the study. Current pump was implanted since 3.3 years on average and current insulin (Insuplant) was started 9.1 years before the start of the study. The following table shows the main treatments before implantation and the reasons for initiation of CIPII.

Table 4. Treatment before implantation in ITT population

Treatment before implantation		ITT population N = 417
Treatment before implantation		
	N	409
• Subcutaneous multi-injection		66 (16.1 %)
• Continuous subcutaneous insulin infusion (CSII)		244 (59.7 %)
• Continuous intraperitoneal insulin infusion (CIPII)		25 (6.1 %)
• Intramuscular multi-injections		1 (0.2 %)
• Subcutaneous multi-injection and CSII		71 (17.4 %)
• Subcutaneous multi-injection and CSII and CIPII		2 (0.5 %)
Reason for initiation of CIPII		
	N	408
• Insulin peripheral resistance		49 (12.0 %)
• Hypoglycaemia		90 (22.1 %)
• Brittle diabetes		254 (62.3 %)
• Insulin peripheral resistance and brittle diabetes		4 (1.0 %)
• Hypoglycaemia and brittle diabetes		11 (2.7 %)

Ref.: Statistical Report T09

Most of the patients (74.1 %) presented at least one diabetic late complication that mainly consisted of diabetic retinopathy and diabetic neuropathy. In addition, 19.7 % of patients had at least one medical or surgical history related to the current pump in the last six months.

At baseline, refill accuracy error percentage was in average 4.40 ± 9.86 % (median: 3.35 %) and HbA1c 7.92 ± 1.28 % (median: 7.70 %).

It should be highlighted that there were differences with the baseline characteristics in the comparative phase.

- 63 % of the patients the Insuman non-comparative phase were female. This is more than in the comparative phase of the HUBIN trial.
- On average the current pump was implanted since 3.30±2.48 years, which is longer than in the comparative phase.
- Reason for initiation in the patients in the comparative phase was insulin peripheral resistance for 5%, and hypoglycaemia (alone and in combination with brittle diabetes) for 32%. In the Insuman non-comparative analysis 13% was included due to insulin peripheral resistance (alone or in combination with brittle diabetes) and 25% due to hypoglycaemia (alone or in combination with brittle diabetes).
- Refill accuracy error percentage at inclusion was 4.40 ± 9.86 % for the Insuman non-comparative phase and 0.30±5.81 in the comparative phase.
- The baseline HbA1c was 7.92 ± 1.28 % in the Insuman non-comparative phase and 7.74±1.04 in the comparative phase.

The mean time between refills was 41±3 days in the comparative phase of the HUBIN study and shifted to 46±13 days (N=407; median: 43 days) in the non-comparative Insuman analysis

The baseline HbA1c in the Insuplant comparative phase was 7.72 ± 1.15, in the Insuplant non-comparative phase this was 8.03 ± 1.18. According to the Applicant this is a non-significant difference. However, this most probably reflects the inclusion criterion of the comparative phase (HbA1c ≤ 9). The same is true for Insuman: 7.76 ± 0.92 in the comparative phase and 7.92 ± 1.28 for all the patients on Insuman.

Study MIP 310

The difficulty associated to the design of study MIP310 was that it complicated the assessment of the benefit/risk of the studied product. First, effects of product and pump cannot be separated all the time and second, the test product is compared to Insuplant, which is approved in France, but not in other European countries. The two insulins in the CIPII group were not randomized (sequence) nor double blind. All patients in the CIPII group started with the Insuplant insulin. Therefore all start-related AEs were in this group. Randomization of the sequence would have prevented this problem. In addition, not all patients in the study belonged to the target population, inclusion criteria permitted patients to entry the study when not sufficiently controlled after at least three months of intensive insulin treatment. This period is too short to start the rather invasive therapy of CIPII. The appropriate patient population has been studied in the HUBIN trial.

A hierarchical testing procedure has been employed with first testing primary hypotheses, and if statistically significant, secondary hypotheses could be tested. Note that the statistical plan did not explicitly specify whether non-inferiority was claimed if both or either of the two primary endpoints would be statistically significant. Since both endpoints are designated primary, both endpoints have to show non-inferiority.

Efficacy data and additional analyses

Overall, the only difference between Insuplant and Insuman Implantable is the origin of the Insulin. It is porcine for Insuplant and recombinant insulin for Insuman. Insuplant is registered in France since 1998, which is a reassuring element. The fact that the manufacturing of Insuplant has been discontinued is an element of major importance for the evaluation of this file, as the patients which are already using the implantable pump need an insulin formulation that can be used with the pump. There are no objections for the new formulation of insulin itself, and the pump is already registered. This assessment however, covers the evaluation of the whole system of administration.

The comparative phase of the HUBIN study provides data on comparison between Insuplant and Insuman IP administration. As noted above the findings are reassuring and Insuman and Insuplant are considered interchangeable.

Although the HbA1c values were higher in the non-comparative phases of the Hubin trial, they remained stable during the study phase.

The refill accuracy error percentage did not substantially change in the Insuman non-comparative phase. However, the error percentages were higher than in the Insuman comparative phase. Possibly due to a selection bias related with the inclusion criteria of the comparative phase.

In the Insuman non-comparative phase of the HUBIN trial, actual and theoretical daily insulin doses and the dose used during the last 24 hours of each cycle did shift from cycle 8 to 10. This most likely represents the heterogeneity of the insulin need of patients at different cycles in this study arm.

As obese subjects need larger amounts of insulin the Applicant performed an analysis of the reduction in HbA1c and AEs according to BMI category. Efficacy and safety were comparable for the different categories. No differences between weight classes were observed for refill accuracy.

As data are understandably limited on IP insulin administration, it should be clear that the marketing authorisation only concerns patients in which SC treatment by insulin pump has become problematic.

Only type 1 diabetics have been included in the HUBIN trial. Historical data also provide very limited data in regard to treatment of type 2 diabetes patients and to our knowledge no PK data exist, which might be of relevance as visceral fat may influence PK in type 2 diabetes patients. In addition, insulin

requirements are often higher in type 2 diabetic patients because of hepatic and peripheral insulin resistance. This would render pump refills and subsequent risk of infection more frequent and thus affect the risk/benefit profile of IP insulin administration. Furthermore, problematic glycaemic fluctuations and severe hypoglycaemia are much rarer in type 2 patients. This is probably reflected by the fact that only type 1 diabetics were available for recruitment in the HUBIN trial and is reflected in the SmPC. In addition, in type 2 diabetes non-alcoholic steatohepatitis is much more frequent than in type 1 diabetics, adding to the concern of a potential risk for liver steatosis when insulin is administered through IP route.

Given the high risk associated with CIPII, it is clear that the marketing authorisation should be very restricted and limited to the type 1 diabetic or c-peptide negative population as represented in the HUBIN trial. IP insulin administration has only limited historical data and the HUBIN trial understandably is also limited due to its size. This is a reflection of the limited population in which IP administration is truly advisable. It should be a last resort in patients unresponsive to SC insulin treatment, including subcutaneous pump therapy, with subcutaneous insulin resistance, or high and unexplained glycaemic fluctuations leading to frequent and unpredictable severe hypoglycaemia and/or recurrent severe hyperglycaemia.

In study MIP 310 comparing CIPII to SC administration, the results on HbA1C of Insuman Implantable 400 IU/ml were not very strong. At the end of the study the HbA1C was 7.78 in the CIPII group and 8.19 in the SC group (as treated analysis). The results in the CIPII group are sufficiently good as SC treatment but the power of this trial was not ideal: it should be noted that the number of patients treated with Insuman Implantable is small: 52 patients treated for 6 months. However, if the indication for the CIPII with Insuman Implantable is limited to a population in which SC administration has become problematic, this is sufficient. The Applicant has performed a post-hoc analysis in a sub-group of patients with use of CSII, HbA1c >7.5%, mean self-monitored plasma glucose (SMPG) value >180 mg/dL. It can be debated whether this is the real EVADIAC group; however, in any case these are patients with insufficient glycaemic control. Effect on HbA1c with IP treatment was superior to that with SC treatment.

The inclusion criteria were HbA1c $\leq$9% and percentage error at refill equal or below 20%. The HbA1c values were indeed higher in the Insuman non-comparative phase than in the comparative phase. This is not expected to have an influence on the non-inferiority of Insuman Implantable versus Insuplant. However, this has a small influence on the safety and reliability of the therapy in the true therapeutic population.

In the HUBIN comparative phase, one fifth of the study population was excluded from the ITT population for refill accuracy due to "no valid post-baseline refill value". For each patient, the experts – blinded from the treatment allocation – did consider whether the refill accuracy error percentage values pattern was consistent or if one or several values had to be invalidated. This was not related to the actual value. Due to the limited number of points for each patient (5) when more than 2 values were suspicious, it was decided to invalidate the whole patient as it was impossible to determine which values were reflecting the reality. Refill accuracy will therefore be overestimated due to exclusion of patients with a bad refill accuracy.

Also in the Insuman non-comparative phase of the Hubin trial about 15 to 20% of the patients in the different cycles were not included in the population used for evaluation of refill accuracy. In the Insuplant non-comparative phase, HbA1c measurements were not performed at each refill cycle, which explains the lower number of data points.

In the comparative phase of the Hubin trial there were similar rates of patients in the two treatment groups who received at least one other insulin injection "rescue insulin" during the study: 11/84 patients of the Insuman Implantable group versus 10/84 patients of the Insuplant group.

Subcutaneous "rescue insulin" was used most of the time during delivery system dysfunction (catheter occlusion, PPC issue): 9/11 patients in the Insuman group and 7/10 patients in the Insuplant group. In the Insuman non-comparative phase, 39.1 % of the ITT population used subcutaneous insulin at least once during the study phase. Subcutaneous insulin was used most of the time during delivery system dysfunction (62% of the cases) and metabolic control issues.

The applicant commits to submit the integrated report containing the complete data of all phases of the HUBIN study (Insuplant non-comparative phase, Insuman/Insuplant comparative phase and Insuman non-comparative phase) as this is not yet available. The applicant is requested to submit this report in October 2014 as a post authorisation commitment.

2.5.3. Conclusions on the clinical efficacy

Given the high risk associated with CIPII, it is clear that the marketing authorisation should be very restricted. It should be a last resort in patients unresponsive to SC insulin treatment, including subcutaneous pump therapy, presenting with frequent, otherwise unexplained severe hyper- and/or hypoglycaemia.

On the basis of the current evidence, Insuman Implantable and Insuplant are considered interchangeable.

The HbA1c values in the patients in the Hubin trial treated with Insuman Implantable via CIPII were stable. The mean refill accuracy error percentage did not change substantially.

Exclusion of patients with invalid post-baseline refill values due to inconsistent refill accuracy error percentages will select the patient population with less variability.

2.6. Clinical safety

Several risks of using Insuman Implantable are similar to those observed with insulin in general, such as severe hypoglycaemia, antigenicity, hypersensitivity and hyperglycaemia which are also identified risks for Insuman with SC routes of administration. Since Insuman Implantable is administered through an implanted intra-peritoneal pump there are additional risks related to the placement of the pump and device issues. Additionally, focal hepatic steatosis has been observed with CIPII using Insuplant when the catheter was positioned very close to or in a liver capsule and is a risk with Insuman Implantable.

The safety evaluation includes the two main studies (HUBIN and MIP 310), which were studies in type 1 diabetes to demonstrate efficacy and safety of Insuman Implantable 400 IU/mL and Insuplant 400 IU/mL in an intra-peritoneal pump, the MIP 2007 pump model. Additional safety information is provided from additional Insuplant studies. Particular attention is paid to metabolic and nutritional AE/SAE including their relationship to ADAs (anti-insulin antibodies) levels. No special approaches to monitoring were used.

Patient exposure

The patient exposure of the studies that contributed to the safety database is presented in the following table:

Table 5: Patient exposure in all studies

Study	Insulin	Device	Inclusion Criterion	Total Number of Patients	Number of Males (n)+	Number of Females (n)+	Mean Age	Mean Duration of Diabetes	Total Patient Years
Pivotal Study									
Study HUBIN	Insuman Implantable 400 IU/mL and Insuplant 400 IU/mL	MIP 2007	Type 1 Diabetes	417	154	263	51.2	30.7	435
Supportive Study									
Study MIP 310 (CIPII)	Study Phase Insuman Implantable 400 IU/mL and Insuplant 400 IU/mL	MIP 2007	Type 1 Diabetes	52	21	31	43.3	23.0	49.1
Study MIP 310 (SC)	Patient's Current	CSII or MDI		52	19	33	39.5	16.9	46.6
Supportive Studies (Studies supporting the use of Insuman Implantable by describing the efficacy and safety of Insuplant administered with the MIP in type 1 diabetes mellitus)									
Study 303a	Insuplant 400 IU/mL	MIP 2007	Type 1 Diabetes	420	168 (n=383)	215 (n=383)	45.8 (n=384)	24.8	1274.05
Study 302	Insuplant 400 IU/mL	MIP 2001 (different models during trial)	Type 1 Diabetes	260	143	117	38.5 (n=259)	18.35	1435.1
Study 302H	Insuplant 400 IU/mL	MIP 2001	Type 1 Diabetes	15	6	9	41.5	23.77	98.5
Study CU	Insuplant 400 IU/mL	MIP 2001	Type 1 Diabetes (unable to achieve stable glycaemic control under standard care)	252	60 (n=123)	63 (n=123)	38.6 (n=136)	NAV	485
Study 303	Insuplant 400 IU/mL	MIP 2007	Type 1 Diabetes	345	67 (n=143)	76 (n=143)	39.2 (n=165)	NAV	965.44
Study 307	Insuplant 400 IU/mL	MIP 2001	Type 1 Diabetes	110	20 (n=41)	21 (n=41)	40.9 (n=50)	NAV	83.45

* = CIPII group only, including 12-month follow-up period
NAV = Not Available
(n) =Total number of patients with information documented

On average the patients in HUBIN were older with longer duration of diabetes and more complications than MIP 310 and would therefore be expected to have more AEs and more hypoglycaemia. The primary safety evaluation was based on the HUBIN study, which provides the safety assessment of Insuman Implantable 400 IU/mL compared to Insuplant 400 IU/mL, of Insuplant in the non-comparative phase and of Insuman Implantable throughout the entire study. The safety assessment was based on the safety population, which was composed of all randomized patients exposed to the study drug, i.e., who received at least one administration of the study drug.

Patients in MIP 310 had type 1 diabetes, HbA1c levels ≥7.5% and had been receiving intensive SC insulin therapy, CSII or MDI, for at least three months prior to enrolment. In MIP 310, the CIPII and SC groups were comparable with regard to baseline and demographic characteristics.

The safety assessment in MIP 310 is also based on the safety population, which was defined as all patients who completed Visit 3 (Start of Treatment). For the study phase, the safety data was primarily summarized by comparing CIPII and SC treatments. Additional summaries of AEs in the CIPII group during the Insuplant treatment period (first 6 months of the study phase) and the Insuman Implantable treatment period (the second 6 months of the study phase) were also provided. For continuation and maintenance phases, AEs from the continuation phase (Insuman Implantable treatment) and the maintenance phase (Insuplant treatment) were summarized.

In study MIP 310, patients implanted with the Medtronic MiniMed Pump, received two insulin formulations via the MIP 2007 model during the 360 day study phase; Insuplant 400 IU/mL for the first 180 days and Insuman Implantable 400 IU/mL for the second 180 days. Only 51 of the 52 randomized patients received Insuman Implantable. Forty-nine (49) patients then entered a continuation phase with Insuman Implantable up to 1 year. The overall extent of exposure to Insuman Implantable was 109.75 patient-years.

In supportive studies 302, 302H, CU, 303 and 307, in type 1 diabetic patients, study populations were comparable in their extent of exposure in clinical trials.

The comparative and non-comparative Insuplant phases of study HUBIN (Insuman Implantable 400 IU/mL versus Insuplant 400 IU/mL for 6 months and Insuplant 400 IU/mL for 6 months) have been completed. Eighty four (84) patients were exposed to Insuman Implantable. The overall extent of exposure to Insuman Implantable was 37.33 patient-years.

To ensure treatment continuation of all patients using a Medtronic MiniMed Implantable insulin pump system after the discontinuation and end of availability of Insuplant in June 2011, the patients are receiving Insuman Implantable in an open-label Insuman Implantable non-comparative extension phase of the HUBIN study, which is planned to run until the product is approved and marketed. An interim analysis was performed on 417 patients included. The mean time on the study drug, known for 409 patients was 388 ± 100 days (median: 370 days). This population is closely followed every 45 days at time of pump refill.

Given the small number of subjects in the target population for CIPII, this small number is justified. The Insuman Implantable non-comparative phase of HUBIN provides data on 412 patients. Patients will enter a registry to further characterize the safety of this treatment in real life practice. This registry is part of the pharmacovigilance plan; it is planned to run for 10 years with interim analysis reported on a yearly basis.

Adverse events

HUBIN Study: Comparative phase

Overall, the nature and the frequency of treatment emergent adverse events (TEAEs) in the HUBIN study were in accordance with the safety profile of any insulin therapy, and globally, display of treatment-emergent adverse events was well balanced between the two treatment groups.

During treatment period, TEAEs were reported in 52.4% of the patients of the safety population (56% in Insuman Implantable group versus 48.8% in Insuplant group) and were considered as possibly related for 11.3% (14.3% in Insuman Implantable group versus 8.3% in Insuplant group, **Table 6**). The respective incidences are shown in **Table 7**. The rate of possibly related TEAEs was 0.45 per patient-year exposure for the Insuman comparative phase and 0.37 for the Insuplant comparative phase. The statistical and clinical significance of this small difference in TEAEs and possibly related TEAEs in the two groups is not known since the groups are small and the trial was only over 4 refill cycles of 160 days.

Table 6. TEAEs in the HUBIN comparative phase in the Safety population

Treatment-emergent adverse events (TEAE)	Insuman (N=84)	Insuplant (N=84)
Patients with any TEAE	47 (56.0%)	41 (48.8%)
Patients with at least one possibly related TEAE	12 (14.3 %)	7 (8.3 %)
Patients with at least one treatment emergent SAE	14 (16.7%)	12 (14.3%)
Patients with at least one TEAE leading to death	0 (0.0%)	0 (0.0%)
Patients with at least one TEAE leading to permanent treatment discontinuation	1 (1.2%)	1 (1.2%)

Source: Statistical Report T35 to T39

Table 7. Incidence of TEAEs in the HUBIN comparative phase

Rate/patient-year	Insuman (N = 84)	Insuplant (N = 84)	All Comparative phase (N=168)
TEAE	2.09	2.03	2.06
Possibly related TEAE	0.45	0.37	0.41
Treatment emergent SAE	0.61	0.53	0.57
TEAE leading to death	0.00	0.00	0.00
TEAE leading to permanent treatment discontinuation	0.03	0.03	0.03

Rate/patient-year was calculated by Number of events / patient-years of exposure.

The most frequent TEAEs were infections and infestations (21.4% of the patients), metabolism and nutrition disorders (13.7%), musculoskeletal and connective tissue disorders (7.1%) and general disorders and administration site conditions (6.5%)(Table 8).

Table 8. TEAEs by SOC

Adverse events TEAEs	Insuman (N = 84)	Insuplant (N = 84)	Safety population N = 168
At least one TEAE	47 (56.0 %)	41 (48.8 %)	88 (52.4 %)
INFECTIONS AND INFESTATIONS	18 (21.4 %)	18 (21.4 %)	36 (21.4 %)
METABOLISM AND NUTRITION DISORDERS	11 (13.1 %)	12 (14.3 %)	23 (13.7 %)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5 (6.0 %)	7 (8.3 %)	12 (7.1 %)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6 (7.1 %)	5 (6.0 %)	11 (6.5 %)
GASTROINTESTINAL DISORDERS	4 (4.8 %)	6 (7.1 %)	10 (6.0 %)
NERVOUS SYSTEM DISORDERS	4 (4.8 %)	4 (4.8 %)	8 (4.8 %)
SURGICAL AND MEDICAL PROCEDURES	4 (4.8 %)	2 (2.4 %)	6 (3.6 %)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (3.6 %)	2 (2.4 %)	5 (3.0 %)
EYE DISORDERS	2 (2.4 %)	1 (1.2 %)	3 (1.8 %)
PSYCHIATRIC DISORDERS	2 (2.4 %)	0 (0.0 %)	2 (1.2 %)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (2.4 %)	0 (0.0 %)	2 (1.2 %)
ENDOCRINE DISORDERS	1 (1.2 %)	0 (0.0 %)	1 (0.6 %)
HEPATOBILIARY DISORDERS	0 (0.0 %)	1 (1.2 %)	1 (0.6 %)
IMMUNE SYSTEM DISORDERS	0 (0.0 %)	1 (1.2 %)	1 (0.6 %)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0 %)	1 (1.2 %)	1 (0.6 %)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (1.2 %)	0 (0.0 %)	1 (0.6 %)

Source: Statistical Report T35

At least one TEAE was considered as possibly related to the insulin and/or to the pump in 19 patients (11.3 %): 12 patients from the Insuman Implantable 400 IU/mL group (14.3%) and 7 patients from the Insuplant 400 IU/mL group (8.3%) (Table 9).

Table 9. Possibly related TEAEs by SOC

TEAEs possibly related to the insulin and/or to the pump	Insuman (N = 84)	Insuplant (N = 84)	Safety population N = 168
At least one possibly related TEAE	12 (14.3 %)	7 (8.3 %)	19 (11.3 %)
METABOLISM AND NUTRITION DISORDERS	7 (8.3 %)	4 (4.8 %)	11 (6.5 %)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (4.8 %)	2 (2.4 %)	6 (3.6 %)
GASTROINTESTINAL DISORDERS	2 (2.4 %)	1 (1.2 %)	3 (1.8 %)
NERVOUS SYSTEM DISORDERS	1 (1.2 %)	2 (2.4 %)	3 (1.8 %)
HEPATOBILIARY DISORDERS	0 (0.0 %)	1 (1.2 %)	1 (0.6 %)
SURGICAL AND MEDICAL PROCEDURES	0 (0.0 %)	1 (1.2 %)	1 (0.6 %)

Source: Statistical Report T36

The System Organ Class most often affected by possibly related TEAEs was metabolism and nutrition disorders (8.3 % [7/84] of the patients in Insuman Implantable 400 IU/mL group and 4.8% [4/84] of the patients in the Insuplant 400 IU/mL group), which included hyperglycaemia (3 patients treated with Insuman versus 2 patients treated with Insuplant), acetonaemia (1 patient treated with Insuman versus 3 patients treated with Insuplant), hypoglycaemic unconsciousness (2 patients treated with Insuman versus 1 patient treated with Insuplant), hypoglycaemia (1 patient treated with Insuman), and hypoglycaemic seizure (1 patient treated with Insuman).

General disorders and administrative site conditions were considered as possibly related to treatment in 4.8% of the patients in Insuman group and 2.4% of the patients in Insuplant group; these patients presented device occlusion (3.6% (N=3) in Insuman group versus 2.4% (N=2) in Insuplant group) or catheter site pain (1.2% (N=1) in Insuman group versus 0% in Insuplant group).

Other TEAE possibly related to the insulin and/or to the pump were nervous system disorders (1.2% in the Insuman group versus 2.4% in the Insuplant group), which were hypoglycaemic comas in 1 patient treated with Insuman and 2 patients treated with Insuplant and gastrointestinal disorders (2.4% in the Insuman group versus 1.2% in the Insuplant group), which were abdominal pain (2 patients treated with Insuman) and umbilical hernia (1 patient treated with Insuplant). Hepatic steatosis was considered as related to the study drug in 1 patient of the Insuplant 400 IU/mL group (without known hepatic steatosis reported at inclusion); as was medical device change (pump change) in 1 patient of the same treatment group.

No clinically significant changes in weight, mean systolic and diastolic blood pressure were observed at V2, V3, V4 and V5.

Hypoglycaemia and hyperglycaemia

In the HUBIN study the incidence of severe hypoglycaemia was a safety endpoint. The definition of serious hypoglycaemia was similar of the other studies in that the event led to loss of consciousness requiring administration of a parenteral countermeasure by a third party, seizure, or a visit to an emergency department.

Table 10. Hyperglycaemias and hypoglycaemias in the HUBIN comparative phase

Rate/patient-year	Insuman (N = 84)	Insuplant (N = 84)	All Comparative phase (N=168)
Hyperglycaemia	27.67	20.39	24.02
Hyperglycaemia with ketonemia	3.21	1.37	2.29
Severe hypoglycaemia	0.45	0.34	0.40

The number of patients with symptomatic hypoglycaemia and their number of events during the week before each post-treatment visit was summarized and no clinically significant difference was observed between the two treatment groups. During the comparative phase, there were 12 patients (14.3%) in Insuman Implantable group and 11 patients (13.1%) in Insuplant group who presented with at least one severe hypoglycaemic event. One patient in Insuman Implantable group and 3 patients in the Insuplant group had at least one nocturnal severe hypoglycaemic event

The number of patients experiencing at least one episode of severe hypoglycaemia in the comparative arm of HUBIN was balanced between the 2 groups. Annual incidence of severe hypoglycaemia was 0.451 vs. 0.343 episodes per patient-year for Insuman Implantable versus Insuplant.

There were 5 patients in each arm that had serious AEs for hypoglycaemia, and most frequent serious TEAEs were metabolism and nutrition disorders in 6.0% of patients (5 patients) in both the Insuman Implantable and Insuplant groups: hypoglycaemic unconsciousness for 3 patients in each group, hypoglycaemia for 1 patient in each group and hypoglycaemic seizure for 1 patient of each group.

Sixty nine (69) patients (82.1%) in the Insuman Implantable group and 67 patients (79.8%) in the Insuplant group had at least one hyperglycaemia event during the comparative phase. Among them, 13 Insuman Implantable patients (15.5%) and 15 Insuplant patients (17.9%) had at least one event of hyperglycaemia with ketonemia. Hyperglycaemia and hyperglycaemia with ketonemia were not required to be reported as AEs unless specific criteria were met. Ketonemia >0.5 mmol/L had to be reported as AE. None of the events were reported as SAEs. Only diabetic ketoacidosis would be reported as an SAE and there were no events in either group during the comparative phase of HUBIN.

The incidence of hyper- and hypoglycaemia observed in the comparative phase of the study is higher compared to the incidence observed in the other observational phases (described below). However, after review of the events, no meaningful differences among the study phases were noted.

HUBIN study: Insuplant Non-Comparative Phase

The following tables present an overall summary of the TEAEs together with their incidence rates.

Table 11. TEAEs in the HUBIN Insuplant non-comparative phase

Overall summary of safety results	Analysis population N = 164
Patients with any TEAE(*)	66 (40.2 %)
Patients with at least one possibly related TEAE (*)	18 (11.0 %)
Patients with at least one treatment emergent SAE (including fatal event)	30 (18.3 %)
Patients with at least one TEAE(*) leading to death(1)	1 (0.6 %)
Patients with at least one TEAE(*) leading to permanent treatment discontinuation	4 (2.4 %)
Patients with at least one severe hypoglycaemia	6 (3.7 %)
Patients with at least one hyperglycaemia	80 (49.1 %)
Patients with at least one hyperglycaemia with ketonemia	10 (6.1 %)

(*) Treatment Emergent Adverse Event
(1) Lung neoplasm malignant with liver and bone metastases

Table 12. Incidence of TEAEs in the HUBIN Insuplant non-comparative phase

Number of events (rate/patient-year)	All Insuplant Non-Comparative Phase (N=164)
TEAE	1.57
Possibly related TEAE	0.31
Treatment emergent SAE	0.64
TEAE leading to death	0.02
TEAE leading to permanent treatment discontinuation	0.06

Rate/patient-year was calculated by Number of events / patient-years of exposure

The nature and the frequency of treatment emergent adverse events were in accordance with the known safety profile of insulin. Treatment-emergent adverse events were reported in 40.2 % of the patients and were considered as possibly related to insulin and/or pump for 11.0 % of the patients. The incidence of possibly related TEAEs was 0.31 per patient-year exposure. Possibly related TEAE were mainly TEAE related to the pump: administration site disorders in 10 patients (6.1 %) and medical device change or removal in 5 patients (3.0 %). Other TEAE possibly related to the insulin and/or to the pump were hyperglycaemia in 2 patients (1.2 %), acetonaemia in 1 patient (0.6 %) and brittle diabetes in 1 patient (0.6 %).

No clinically significant changes in mean weight, systolic and diastolic blood pressure was observed at V2, V3, V4, V5 and V6.

Hypoglycaemia and hyperglycaemia

An increase of the rate of patients with symptomatic hypoglycaemia was observed at 2nd (58.9 %), 3rd (64.5 %) and 4th (58.4 %) cycle compared to 1st cycle (46.4 %).

Table 13. Hypoglycaemia and hyperglycaemia in the HUBIN Insuplant non-comparative phase

	Insuplant non-comparative phase
Number of hyperglycaemias per patient-year	8.272
Number of hyperglycaemias with ketonemia per patient-year	0.187
Number of severe hypoglycaemias per patient-year	0.140

Six patients (3.7 %) presented at least one severe hypoglycaemia during the study phase. The number of severe hypoglycaemias per patient-year was 0.140. In 5 patients (3.1 %) the severe hypoglycaemia was diurnal and in 1 patient the moment was not determined. Four of these 6 patients had high level ($\geqslant$ 10 %) of free anti-insulin antibodies (AIA) at inclusion.

About half of the patients (49.1 %) presented at least one hyperglycaemia during the study phase and 10 patients (6.1 %) at least one hyperglycaemia with ketonemia. The number of hyperglycaemia per patient-year was 8.272 and the number of hyperglycaemia with ketonemia per patient-year 0.187. No patient experienced protocol defined diabetic ketoacidosis (pH < 7.25).

HUBIN STUDY: Insuman Treated Patients

Table 14 gives an overview of the adverse event profile of Insuman in the ITT population.

Table 14. TEAEs in the HUBIN Insuman non-comparative phase

Overall summary of safety results	ITT population (N = 417)
Patients with any TEAE(*)	319 (76.5 %)
Patients with at least one possibly related TEAE (*)	117 (28.1 %)
Patients with at least one treatment emergent SAE (including fatal event)	172 (41.2 %)
Patients with at least one TEAE(*) leading to death(1)	2 (0.5 %)
Patients with at least one TEAE(*) leading to permanent treatment discontinuation	10 (2.4 %)
Patients with at least one severe hypoglycaemia	62 (14.9 %)
Patients with at least one hyperglycaemia	318 (77.2 %)
Patients with at least one hyperglycaemia with ketonemia	78 (18.9 %)

(*) Treatment Emergent Adverse Event
(1) Cerebrovascular accident for one patient, atrial fibrillation with ventricular dysfunction for the other

Table 15. Incidence of TEAEs in the HUBIN Insuman non-comparative phase

Rate/patient-year	Insuman patients from Insuman arm of the comparative phase (N=83)	Insuman patients from Insuplant arm of the comparative phase (N=82)	Insuman patients from Insuplant non-comparative phase (N=252)	All Insuman non-comparative phase patients (N=417)
TEAE	1.94	1.46	2.16	1.96
Possibly related TEAE	0.49	0.52	0.58	0.54
Treatment emergent SAE	0.79	0.74	1.07	0.93
TEAE leading to death	0.00	0.01	0.01	0.01
TEAE leading to permanent treatment discontinuation	0.01	0.09	0.04	0.04

The incidence of possibly related TEAEs were overall similar in all treatment groups, regardless whether or not they had been enrolled in the comparative phase.

Overall, 76.5 % of the ITT population reported at least one TEAE, at least one TEAE was considered as possibly related to treatment in 28.1 % of patients, and as serious adverse events in 41.2% of patients.

No clinically significant change from baseline was observed at each cycle for weight, systolic and diastolic blood pressure.

Table 16 gives an overview of the possibly related TEAEs by SOC and PT.

Table 16. Possibly related TEAEs by SOC and PT

Possibly related TEAEs	ITT population N = 417
At least one possibly related TEAE	**117 (28.1 %)**
Surgical and medical procedures	**45 (10.8 %)**
Medical device change	43 (10.3 %)
Medical device implantation	2 (0.5 %)
Medical device removal	1 (0.2 %)
General disorders and administration site conditions	**41 (9.8 %)**
Device occlusion	20 (4.8 %)
Device failure	4 (1.0 %)
Catheter site pain	3 (0.7 %)
Device electrical finding	3 (0.7 %)
Device malfunction	3 (0.7 %)
Device battery issue	2 (0.5 %)
Medical device complication	2 (0.5 %)
Device dislocation	1 (0.2 %)
Device inversion	1 (0.2 %)
Implant site inflammation	1 (0.2 %)
Injection site haemorrhage	1 (0.2 %)
Injection site inflammation	1 (0.2 %)
Injection site pain	1 (0.2 %)
Metabolism and nutrition disorders	**36 (8.6 %)**
Hyperglycaemia	16 (3.8 %)
Hypoglycaemia	7 (1.7 %)
Hypoglycaemic unconsciousness	5 (1.2 %)
Diabetes mellitus inadequate control	4 (1.0 %)
Acetonaemia	4 (1.0 %)
Ketoacidosis	2 (0.5 %)
Ketosis	2 (0.5 %)
Hypoglycaemic seizure	2 (0.5 %)
Infections and infestations	**7 (1.7 %)**
Implant site infection	5 (1.2 %)
Device related infection	1 (0.2 %)
Diabetic foot infection	1 (0.2 %)
Gastrointestinal disorders	**4 (1.0 %)**
Abdominal pain	4 (1.0 %)
Diarrhoea	1 (0.2 %)
Nervous system disorders	**4 (1.0 %)**
Hypoglycaemic coma	3 (0.7 %)
Loss of consciousness	1 (0.2 %)
Investigations	**3 (0.7 %)**
Blood glucose fluctuation	3 (0.7 %)
Skin and subcutaneous tissue disorders	**3 (0.7 %)**
Erythema	1 (0.2 %)
Scar	1 (0.2 %)
Skin erosion	1 (0.2 %)

n : patients with at least one event belonging to the SOC/PT % = 100 x n / N

Possibly related TEAE were mainly TEAE related to the pump:

- Medical device change, implantation or removal in 45 patients (10.8 %).
- Administration site disorders in 41 patients (9.8 %), half of these device occlusion (20 patients: 4.8 %).

Other TEAE possibly related to the insulin and/or to the pump were:

- Metabolism and nutrition disorders in 36 patients (8.6 %): hyperglycaemia (16 patients: 3.8 %), hypoglycaemia (7 patients: 1.7 %), diabetes inadequate control (4 patients: 1.0 %), acetonaemia (4 patients: 1.0 %), ketoacidosis (2 patients: 0.5 %), ketosis (2 patients: 0.5 %) hypoglycaemic unconsciousness (5 patients: 1.2 %) and hypoglycaemic seizure (2 patients: 0.5 %).

• Infections in 7 patients (1.7 %), including implant site infection (5 patients: 1.2 %), device related infection (1 patient: 0.2 %) and diabetic foot infection (1 patient: 0.2 %).

• Gastro-intestinal disorders in 4 patients (1.0 %), including abdominal pain (4 patients: 1.0 %) and diarrhoea (1 patient: 0.2 %).

• Nervous system disorders in 4 patients (1.0 %), including hypoglycaemic coma (3 patients: 0.7 %) and loss of consciousness (1 patient: 0.2 %).

• Blood glucose fluctuation in 3 patients (0.7 %).

• Skin disorders in 3 patients (0.7 %), including erythema (1 patient: 0.2 %), skin erosion (1 patient: 0.2 %) and scar (1 patient: 0.2 %).

No hepatobiliary disorder was related to insulin or pump.

Hypoglycaemia and hyperglycaemia

Table 17. Hypoglycaemia and hyperglycaemia in the HUBIN Insuman non-comparative phase

Rate/patient-year	Insuman patients om insuman arm of the comparative phase (N=83)	Insuman patients from insuplant arm of the comparative phase (N=82)	Insuman patients from insuplant non-comparative phase (N=252)	All Insuman non-comparative phase patients (N=417)
Hyperglycaemia	14.75	7.62	6.98	9.28
Hyperglycaemia with ketonemia	1.65	1.27	0.46	0.95
Severe hypoglycaemia	0.32	0.12	0.20	0.22

The rate of patients with at least one symptomatic hypoglycaemia during the last week of each cycle did not significantly change. It was 58.1 % at baseline (cycle 0) and then varied between 54.2 % and 61.2 %.

62 patients (14.9 %) presented at least one severe hypoglycaemia and 96 episodes were reported during the study phase. In 45 patients (10.8 %) the severe hypoglycaemia were only diurnal, in 14 patients (3.4 %) only nocturnal and 3 patients (0.7 %) had severe hypoglycaemia diurnal and nocturnal. The number of severe hypoglycaemia per patient-year was 0.218.

During the study phase, 318 patients (77.2 %) presented at least one hyperglycaemia, and 78 patients (18.9 %) at least one hyperglycaemia with ketonemia. The number of hyperglycaemia per patient-year was 9.276 and the number of hyperglycaemia with ketonemia per patient-year 0.952. Compared to the Insuplant non-comparative phase, the number of hyperglycaemia per patient year was higher during the Insuman non-comparative phase (9.276 versus 8.272) as well as the number of hyperglycaemia with ketonemia per patient-year (0.952 versus 0.187).

None of the patients of the ITT population presented protocol defined diabetic ketoacidosis during the study phase.

Study – MIP 310

Study Phase

In the study MIP 310, done in patients with type 1 diabetes who were naive to intra-peritoneal insulin, the incidence of 'severe hypoglycaemic events' was a primary efficacy parameter. Severe hypoglycaemic events were defined as 'a clinical episode of hypoglycaemia that required assistance from another person' in the MIP 310 clinical study report (CSR).

The available data are not sufficient to test the statistical difference between the CIPII and SC groups in MIP 310.

The analysis and reporting of events of (non-severe) hypoglycaemia were not officially required in MIP 310 and, in accordance with this, there is no definition of (non-severe) hypoglycaemia in the MIP 310 CSR. Adverse events of 'hypoglycaemia' were however reported in the MIP 310 CSR. In MIP 310, there were 25 events of hypoglycaemia; 23 in the CIPII group and 2 in the SC group.

In the CIPII group alone, there were 13 AEs of hypoglycaemia during 6 months of Insuplant 400 IU/mL treatment and 10 AEs of hypoglycaemia during 6 months of Insuman Implantable 400 IU/mL treatment.

There were 6 events of severe hypoglycaemia in 4 patients during MIP 310; 2 events in 2 patients in the CIPII group and 4 events in 2 patients in the SC group. The available data are not sufficient to test the statistical difference between the 2 groups.

In the CIPII group alone, there were 2 severe hypoglycaemic events during 6 months of treatment with Insuplant 400 IU/mL and no severe hypoglycaemic events during 6 months of treatment with Insuman Implantable 400 IU/mL.

Continuation and Maintenance Phases

There were 191 AEs during the continuation and maintenance Phases (134 during the continuation phase, 57 during the maintenance phase). The frequency of these AEs per 100 patient-years was 151.5 (155.6 during the continuation phase, 142.6 during the maintenance phase). The frequency of AEs was higher in the continuation phase than the maintenance phase.

There were 46 AEs probably or possibly related to the MIP System or study insulin (37 during the continuation phase, 9 during the maintenance phase). The frequency of these AEs per 100 patient years was 38.1 (43.0 during the continuation phase, 22.5 during the maintenance phase). The frequency of AEs probably or possibly related to the MIP System or study insulin was higher in the continuation phase than the maintenance phase.

Serious adverse event/deaths/other significant events

No patient died during the comparative phase of the Hubin study or during the MIP 310 study.

In the Insuplant non-comparative phase of the Hubin trial, one patient died due to a malignant lung neoplasm with liver and bone metastases.

In the Insuman non-comparative phase of the Hubin trial, 2 patients (0.5%) died due to severe cardiac disorders for one and a cerebrovascular accident for the other.

Pivotal Study – HUBIN: Comparative phase

In the Hubin study, 15.5% of the patients (16.7% (14 patients) in Insuman Implantable and 14.3% (12 patients) in Insuplant) reported at least one serious treatment-emergent adverse event during the study (Table 18).

Table 18. Serious treatment emergent adverse events

Serious TEAEs	Insuman (N = 84)	Insuplant (N = 84)	Safety population N = 168
At least one serious TEAE	**14 (16.7 %)**	**12 (14.3 %)**	**26 (15.5 %)**
METABOLISM AND NUTRITION DISORDERS	5 (6.0 %)	5 (6.0 %)	10 (6.0 %)
HYPOGLYCAEMIC UNCONSCIOUSNESS	*3 (3.6 %)*	*3 (3.6 %)*	*6 (3.6 %)*
HYPOGLYCAEMIA	*1 (1.2 %)*	*1 (1.2 %)*	*2 (1.2 %)*
HYPOGLYCAEMIC SEIZURE	*1 (1.2 %)*	*1 (1.2 %)*	*2 (1.2 %)*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (6.0 %)	3 (3.6 %)	8 (4.8 %)
DEVICE OCCLUSION	*4 (4.8 %)*	*2 (2.4 %)*	*6 (3.6 %)*
CATHETER SITE PAIN	*1 (1.2 %)*	*0 (0.0 %)*	*1 (0.6 %)*
IMPAIRED HEALING	*0 (0.0 %)*	*1 (1.2 %)*	*1 (0.6 %)*
NERVOUS SYSTEM DISORDERS	2 (2.4 %)	2 (2.4 %)	4 (2.4 %)
HYPOGLYCAEMIC COMA	*2 (2.4 %)*	*2 (2.4 %)*	*4 (2.4 %)*
INFECTIONS AND INFESTATIONS	1 (1.2 %)	1 (1.2 %)	2 (1.2 %)
ABSCESS	*0 (0.0 %)*	*1 (1.2 %)*	*1 (0.6 %)*
HERPES ZOSTER	*1 (1.2 %)*	*0 (0.0 %)*	*1 (0.6 %)*
SURGICAL AND MEDICAL PROCEDURES	1 (1.2 %)	1 (1.2 %)	2 (1.2 %)
DRUG DELIVERY DEVICE REMOVAL	*1 (1.2 %)*	*0 (0.0 %)*	*1 (0.6 %)*
MEDICAL DEVICE CHANGE	*0 (0.0 %)*	*1 (1.2 %)*	*1 (0.6 %)*
GASTROINTESTINAL DISORDERS	0 (0.0 %)	1 (1.2 %)	1 (0.6 %)
IMPAIRED GASTRIC EMPTYING	*0 (0.0 %)*	*1 (1.2 %)*	*1 (0.6 %)*
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0 %)	1 (1.2 %)	1 (0.6 %)
LACERATION	*0 (0.0 %)*	*1 (1.2 %)*	*1 (0.6 %)*
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (1.2 %)	0 (0.0 %)	1 (0.6 %)
PERIARTHRITIS	*1 (1.2 %)*	*0 (0.0 %)*	*1 (0.6 %)*
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0 %)	1 (1.2 %)	1 (0.6 %)
MYELODYSPLASTIC SYNDROME	*0 (0.0 %)*	*1 (1.2 %)*	*1 (0.6 %)*
PSYCHIATRIC DISORDERS	1 (1.2 %)	0 (0.0 %)	1 (0.6 %)
DEPRESSION	*1 (1.2 %)*	*0 (0.0 %)*	*1 (0.6 %)*

Ref.: Statistical Report T37

Most frequent serious TEAEs were metabolism and nutrition disorders in 6.0 % (5 patients) in each group: hypoglycaemic unconsciousness for 3 patients in each group, hypoglycaemia for 1 patient in each group and hypoglycaemic seizure for 1 patient of each group.

The other SOCs with the highest incidences of SAEs were:

1. General disorders and administration site conditions in 5 patients in the Insuman Implantable group and 3 patients in the Insuplant group (6.0% versus 3.6%): device occlusion in 4 patients in the Insuman Implantable group and 2 patients in the Insuplant group, catheter site pain in 1 patient in the Insuman Implantable group and impaired healing (of the skin after pump re-implantation) in 1 patient in the Insuplant group.
2. Nervous system disorders for 2 patients in each treatment group (2.4%) who experienced hypoglycaemic coma.
3. Infections and infestations for 1 patient with herpes zoster in the Insuman Implantable group (1.2 %) and 1 patient with abscess in the Insuplant group (1.2 %).
4. Surgical and medical procedures for 1 patient whose drug delivery device was removed in the Insuman Implantable group (1.2 %) and for 1 patient whose medical device was changed in the Insuplant group (1.2 %).

Pivotal Study – HUBIN: Insuplant non-comparative phase

One patient died due to a malignant lung neoplasm with liver and bone metastases.

Serious treatment emergent adverse event were experienced by 18.3 % of the patients. About half of the serious TEAE were events concerning the pump (14 patients – 8.5 %) and most often serious TEAE were related to the pump and not the insulin (13 patients – 7.9 %). One device occlusion was related to the insulin and to the pump and 1 hypoglycaemic coma to the insulin but not to the pump.

Pivotal Study – HUBIN: Insuman non-comparative phase

Two patients (0.5 %) died during the non-comparative phase Insuman (before the cut-off date 30 June 2012): one due to cerebrovascular accident, the other due to atrial fibrillation with ventricular dysfunction. None of these fatal events was reported as related to the insulin or to the pump.

- A 69 year old female patient who started Insuman with Medtronic Mini Med Implantable Pump on 16-Jun-2011 and experienced severe stroke and heart attack leading to 360 days after the first Insuman administration. This cerebrovascular accident was considered as not associated with the insulin and not associated with the pump.
- A 64 year old female patient who started Insuman with Medtronic Mini Med Implantable Pump on 29-Jun-2011 and experienced, first, a cerebrovascular accident after atrial fibrillation (AF) 138 days after first Insuman administration, then, died 169 days after the first Insuman administration secondary to tachycardia, AF and bad function of the left ventricle. These were considered as not associated with the insulin and not associated with the pump.

An overview of the serious TEAEs is given in Table 19. Overall, 172 patients (41.2 %) presented at least one serious TEAE (including the fatal events) during the Insuman non comparative phase (before the cut-off date for interim analysis).

Most frequent serious TEAEs were in relation with the pump:

- Surgical and medical procedures (58 patients: 13.9 %) mainly composed of medical device changes, implantations or removals (53 patients: 12.7 %).
- General disorders and administration site conditions (40 patients: 9.6 %) including almost exclusively medical device occlusion, failure, malfunction and complications (with the exception of general physical health deterioration in 1 patient, chest pain in 1 patient and oedema peripheral in 1 patient).

Serious TEAEs were most often determined to have a causal relationship with the pump and not with the insulin, or neither with the pump nor with the insulin.

Only, 14 patients (3.4 %) experienced a serious TEAE related to the insulin and not to the pump:

- Hypoglycaemia in 4 patients
- Hyperglycaemia in 2 patients
- Hypoglycaemic unconsciousness in 4 patients
- Hypoglycaemic coma in 2 patients
- Loss of consciousness in 1 patient
- Hypoglycaemic unconsciousness and hypoglycaemic seizure in 1 patient

And, 5 patients (1.2 %) experienced Serious TEAE related to the insulin and the pump:

- Hypoglycaemic coma in 1 patient;
- Hypoglycaemia in 1 patient;
- Device occlusion in 1 patient;
- Medical device change in 1 patient;
- Hypoglycaemic seizure, diabetes mellitus inadequate control, medical device complication and device occlusion in 1 patient.

Table 19. Serious TEAEs

Serious TEAEs	ITT population N = 417
At least one serious TEAE	**172 (41.2 %)**
Surgical and medical procedures	58 (13.9 %)
General disorders and administration site conditions	40 (9.6 %)
Metabolism and nutrition disorders	40 (9.6 %)
Nervous system disorders	21 (5.0 %)
Infections and infestations	16 (3.8 %)
Injury, poisoning and procedural complications	12 (2.9 %)
Gastrointestinal disorders	8 (1.9 %)
Cardiac disorders	7 (1.7 %)
Psychiatric disorders	6 (1.4 %)
Musculoskeletal and connective tissue disorders	5 (1.2 %)
Eye disorders	2 (0.5 %)
Investigations	2 (0.5 %)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.5 %)
Renal and urinary disorders	2 (0.5 %)
Skin and subcutaneous tissue disorders	2 (0.5 %)
Vascular disorders	2 (0.5 %)
Ear and labyrinth disorders	1 (0.2 %)
Pregnancy, puerperium and perinatal conditions	1 (0.2 %)
Reproductive system and breast disorders	1 (0.2 %)
Respiratory, thoracic and mediastinal disorders	1 (0.2 %)

n : patients with at least one event belonging to the SOC % = 100 x n / N

In the Insuman non-comparative phase, the incidence rate of SAEs was slightly higher in patients from the non-comparative Insuplant arm (1.07 per patient-year exposure) than in patients from the Insuman comparative arm (0.79 per patient-year exposure) or from the Insuplant comparative arm (0.74 per patient-year exposure).

The rate of SAEs was higher in the Insuman non-comparative phase (0.93 per patient-year exposure) than in the comparative study phase (0.57 per patient-year exposure) and in the Insuplant non-comparative phase (0.64 per patient-year exposure).

Study – MIP310

In MIP 310, there were more SAEs in the CIPII group (12 SAEs in 9 patients) than the SC group (9 SAEs in 7 patients) during the treatment period.

Six of the 12 SAEs in the CIPII group were possibly associated with implantation surgery and/or device maintenance (SAE Verbatim: 'skin erosion at pump site' x 2, 'post infection of pump pocket', 'laparoscopy to reposition catheter' and 'device explant' x 2). Of the 6 SAEs, the relationship of 5 of the SAEs to the study device was described as 'probable'. There was no information on the relationship of the remaining SAE to the study device. Three of the 12 SAEs in the CIPII group were associated with the acute complications of diabetes or the treatment of diabetes with insulin (SAE Verbatim: 'hypoglycaemia', 'severe hypoglycaemia requiring assistance' and 'hyperglycaemia'). Of the 3 SAEs, the relationship to the study drug was described as 'probable' for 2 SAEs and 'unlikely' for 1 SAE.

Seven of 9 SAEs in the SC group were associated with the acute complications of diabetes or the treatment of diabetes with insulin (SAE Verbatim: 'hypoglycaemia' x 2, 'severe hypoglycaemia' x 2, 'elevated blood sugar requiring hospitalization' [Preferred Term: hyperglycaemia], 'diabetes out of control', 'dehydration/pump malfunction/catheter kink/ketoacidosis' [Preferred Term: hyperglycaemia]), although the relationship of 6 of the 7 SAEs to comparator drug and/or comparator device was described as 'none'.

In the CIPII group alone, there were 5 SAEs in patients receiving Insuplant 400 IU/mL during 6 months of treatment and 7 SAEs in patients receiving Insuman Implantable 400 IU/mL during

6 months of treatment. Of the 5 SAEs in CIPII patients receiving Insuplant 400 IU/mL there were 2 SAEs of 'severe hypoglycemia'. Of the 7 SAEs in CIPII patients receiving Insuman Implantable 400 IU/mL there were no SAEs of 'severe hypoglycemia'.

In MIP 310, 12 patients discontinued during the study; 5 patients in the CIPII group and 7 patients in the SC group. Most patients in the CIPII group, 4 of 5 patients, discontinued due to events associated with implantation surgery or device maintenance ('device complication' x 2, 'pump pocket infection' x 1 and 'patient request' x 1 following catheter occlusion and swelling at the site of surgery). The fifth patient (patient request) discontinued following randomization but prior to start of treatment. Most patients in the SC group, 5 of 7 patients, were discontinued due to 'non-compliance/lost to follow-up'.

Continuation and Maintenance Phases
There were 40 SAEs during the continuation (Insuman 12 months) and maintenance (Insuplant 12 months) phases (30 during the continuation phase, 10 during the maintenance phase). The frequency of SAEs per 100 patient-years was 31.7 (34.8 during the continuation phase, 25.0 during the maintenance phase). The frequency of SAEs was higher in the continuation phase than the maintenance phase.

There were 26 SAEs probably or possibly related to the MIP System or study insulin (21 during the continuation phase, 5 during the maintenance phase). The frequency of SAEs probably or possibly related to the MIP System or study insulin per 100 patient-years was 20.6 (24.4 during the continuation phase, 12.5 during the maintenance phase). The frequency of SAEs probably or possibly related to the MIP System or study insulin was higher in the continuation phase than the maintenance phase.

Overall, in the MIP 310 study, the higher number of SAEs in the IP group might be expected since CIPII patients underwent a surgical procedure for the implantation of the device. Six of the SAEs were possibly associated with implantation surgery and/or device maintenance. Although the SAEs cannot be attributed to the insulin used, they are the consequence of the method used and as such are relevant for the comparison with current treatment methods (SC).

Device interventions and infectious complications

Device interventions
In the comparative phase of HUBIN the refill cycle was 40 days ± 5 days, in the non-comparative Insuman arm this was 45 days, both are of shorter duration compared to MIP 310 where the refills were done every 90 days. A 10 minute rinse was done at study entry into the comparative phase for all patients prior to randomization and no prophylactic rinses were done in either the comparative phase or the Insuman Implantable non-comparative phase. Reactive rinses in both phases of the study were done in response to a change in refill accuracy, change in insulin dose or persistent hyperglycemia.

In the comparative phase of HUBIN, 9 patients (10.7%) in both treatment groups needed at least one extra refill during the study. Twelve (12) patients (14.3%) of the Insuman Implantable 400 IU/mL group and 18 (21.4%) of the Insuplant 400 IU/mL group had at least one rinsing procedure during the study and 1 patient (1.2%) of the Insuman Implantable 400 IU/mL group and 2 patients of the Insuplant 400 IU/mL group had at least one pump blockage, defined as blockage after a 4 hour NaOH rinse. In some cases pump blockage occurred during or just after the rinsing procedure required at study entry. There were a total of 19 patients (11.3%) that needed at least one device intervention during the study, that consisted of either pump, catheter, or PPC interventions; 8 (9.5%) of the patients of the Insuman Implantable 400 IU/mL group and 11 (13.1%) of the patients of the Insuplant

400 IU/mL group. An overview of the incidences of device interventions in the comparative phase is given in Table 20.

Table 20. Incidence of device interventions in the HUBIN comparative phase

Rate/patient-year	Insuman (N = 84)	Insuplant (N = 84)	All Comparative phase (N=168)
Extra refill	0.24	0.19	0.21
Pump blockage	0.03	0.05	0.04
Pump explantation	0.00	0.08	0.04
Pump intervention	0.08	0.13	0.11
Catheter intervention	0.11	0.13	0.12
PPC intervention	0.03	0.19	0.11

Rate/patient-year was calculated by Number of events / patient-years of exposure.

In the Insuman non-comparative arm of HUBIN, 170 patients (40.8%) needed 255 extra-refill, 6 patients (1.4%) experienced a pump blockage and 70 pump explantations were performed in 68 patients (16.3%), two patients having experienced two pump explantations. An overview of the incidences of device interventions in the Insuman non-comparative phase is given in Table 21.

Table 21. Incidence of device interventions in the HUBIN Insuman non-comparative phase

Rate/patient-year	Insuman patients from Insuman arm of the comparative phase (N=83)	Insuman patients from Insuplant arm of the comparative phase (N=82)	Insuman patients from Insuplant non-comparative phase (N=252)	All Insuman non-comparative phase patients (N=417)
Insulin extra refill	0.35	0.33	0.50	0.43
Pump blockage	0.01	0.01	0.02	0.01
Pump explantation	0.06	0.13	0.22	0.16
Pump intervention	0.11	0.16	0.54	0.35
Catheter intervention	0.15	0.29	0.50	0.36
PPC intervention	0.09	0.24	0.25	0.20

Rate/patient-year was calculated by Number of events / patient-years of exposure.

Patients enrolled directly in Insuman non-comparative phase without entering Insuplant non-comparative phase were included in 'Insuman patients from insuplant non-comparative phase' column considering most patients were on Insuplant before entering the study.

344 patients (82.5%) needed 572 rinsing procedures. The mean delay of rinsing procedures after the preceding one was 151 days for the first, 191 days for the second, 151 days for the third and 88 days for the fourth. The reasons for rinsing procedures are tabulated in Table 22. The main reason of rinsing procedures was an increase of refill accuracy error percentage (53.6% of the rinsing procedures).

Table 22. Reasons of rinsing procedures - ITT population

	Rinsing procedure
Reason of rinsing procedure	
N	526
Error percentage increase	282 (53.6 %)
Increase in insulin need	56 (10.6 %)
Other	176 (33.5 %)
Error percentage increase and increase in insulin need	8 (1.5 %)
Increase in insulin need and other	4 (0.8 %)
Error percentage increase specify	
N	234
Instable glycaemia control	*52 (22.2 %)*
Hba1c increase	*2 (0.9 %)*
Hyperglycaemia	*146 (62.4 %)*
Other	*31 (13.2 %)*
Hba1c increase and other	*1 (0.4 %)*
Hyperglycaemia and other	*2 (0.9 %)*

186 patients (44.6%) needed at least one other device intervention during Insuman non-comparative phase, that consisted of either pump interventions (121 patients – 29.0%), catheter interventions (133 patients – 31.9%), or PPC interventions (78 patients – 18.7%). There was no case of intervention for refill kit or MiniMed needle.

The number of device interventions during the Insuman non-comparative phase were generally higher in patients previously treated with Insuplant in the Insuplant non-comparative phase (or directly enrolled in Insuman non-comparative phase) when compared with other groups. This could be due to different baseline characteristics, e.g. the larger time from current pump implantation in the Insuplant non-comparative phase than in the comparative phase. The high number of device events reflects the complexity of the technique (even if it could also be explained by the fact that 14% of patients had a pump older than 6 years at study entry).

The incidence of device interventions in the HUBIN Insuplant non-comparative phase is summarized in Table 23.

Table 23. Incidence of device interventions in the HUBIN Insuplant non-comparative phase

Rate/patient-year	All Insuplant Non-Comparative Phase (N=164)
Extra refill	0.23
Pump blockage	0.00
Pump explantation	0.19
Pump intervention	0.23
Catheter intervention	0.34
PPC intervention	0.16

Rate/patient-year was calculated by Number of events / patient-years of exposure.

The incidence rates for Insuman and Insuplant non-comparative phases are comparable, but there was a higher number of extra refills in the Insuman non-comparative phase.

In MIP 310, there were 79 device interventions with a similar number of catheter complications (n=35) and pump complications (n=32) and fewer PPC complications (n=12). There were device interventions which were described as such, but were done routinely.

The Applicant has explained that 35 device interventions in the MIP 310 Study Phase were no real complications but routine procedures done at refill. From the genuine device interventions (44), underdelivery of insulin was the most occurring complication (15 events in 10 patients) followed by occlusion (7 events in 6 patients). With shortening of the refill procedure and the prophylactic sodium

hydroxide rinse procedure introduced in later phases of the study, the number of flush and rinse interventions decreased. Data from the Continuation and Maintenance Phases of the MIP 310 study indicate that the most common AEs were hyperglycaemia and hypoglycaemia. The incidence of hyperglycaemia due to underdelivery and occlusion can be expected to be less in the current situation with the improved prophylactic rinse procedure.

Infectious complications

Infectious complications may result in pump explantation. In the comparative phase of HUBIN, one patient (Insuman Implantable group) had the pump explanted for 5 months due to pocket infection. The patient was treated with antibiotics and the pump was re-implanted without additional complications prior to the end of the comparative phase. This subject was considered a protocol deviation for use of rescue insulin for more than 7 days and was excluded from efficacy analysis. A second patient (Insuplant group) experienced a cutaneous infection at the pump site. The infection was treated with antibiotic for 7 days and the patient recovered. The patient remained on pump treatment during the course of the event.

In MIP 310, the three pump pocket infections led to pump explantation; 1 pump was replaced, and 2 other pumps were not replaced.

In earlier studies using only Insuplant (studies 302, 302H, CU, 303 and 307), the number of device events per patient-year decreased in accordance with the study chronology (start of study) from 2.08 events per patient year in Study 302 to 0.36 events per patient year in Study 307. These studies were carried out between 1989 and 2000. This decrease could reflect the development of the MIP and the insulin formulation.

Anti-Insulin Antibodies

Anti-insulin antibodies (ADAs) may result in hyperglycaemia or hypoglycaemia. In general, levels of ADAs rise with initiation of any insulin treatment, which is exaggerated when intra-peritoneal insulin is used.

Pivotal Study – HUBIN: Comparative Phase

In HUBIN, patients were already on established treatment with an intra-peritoneal pump and would be expected to have elevated anti-insulin antibody titers and would not be expected to have a further rise in titers during the trial given the similarity of Insuman Implantable and Insuplant.

The numbers of patients with normal and abnormal levels of ADAs at each visit are presented in Table 24. The repartition of patients in each free ADAs class was slightly different between the two groups. However, no specific evolution was detected during the comparative phase for both of them.

Table 24. Number of patients with normal and abnormal levels of ADAs at each visit -Safety population

		Insuman N = 84	Insuplant N = 84	Safety population N = 168
ADAs (ELISA) at V1				
	N	83	84	167
	Missing	1	0	1
NORMAL : < 5.0 KU/L		36 (43.4 %)	36 (42.9 %)	72 (43.1 %)
ABNORMAL : ≥ 5.0 KU/L		47 (56.6 %)	48 (57.1 %)	95 (56.9 %)
ADAs (ELISA) at V2				
	N	82	83	165
	Missing	2	1	3
NORMAL : < 5.0 KU/L		33 (40.2 %)	35 (42.2 %)	68 (41.2 %)
ABNORMAL : ≥ 5.0 KU/L		49 (59.8 %)	48 (57.8 %)	97 (58.8 %)

ADAs (ELISA) at V3				
	N	78	78	156
	Missing	6	6	12
NORMAL : < 5.0 KU/L		36 (46.2 %)	31 (39.7 %)	67 (42.9 %)
ABNORMAL : ≥ 5.0 KU/L		42 (53.8 %)	47 (60.3 %)	89 (57.1 %)
ADAs (ELISA) at V4				
	N	81	82	163
	Missing	3	2	5
NORMAL : < 5.0 KU/L		32 (39.5 %)	39 (47.6 %)	71 (43.6 %)
ABNORMAL : ≥ 5.0 KU/L		49 (60.5 %)	43 (52.4 %)	92 (56.4 %)
ADAs (ELISA) at V5				
	N	81	78	159
	Missing	3	6	9
NORMAL : < 5.0 KU/L		36 (44.4 %)	38 (48.7 %)	74 (46.5 %)
ABNORMAL : ≥ 5.0 KU/L		45 (55.6 %)	40 (51.3 %)	85 (53.5 %)

There was globally no clinically significant difference in the repartition of ADAs (ELISA) values between the treatment groups whatever the visit (Table 25).

Table 25. Occurrence of Serious Adverse Events according to ADA level

	ADA (Elisa) < 5 kU/L	ADA (Elisa) [5 ; 30 [kU/L	ADA (Elisa) [30 ; 100] kU/L	ADA (Elisa) > 100 kU/L	Missing
Patient (N)	74	48	23	14	9
Serious adverse Event (N)	8	14	8	3	3
Patient with at least 1 SAE	7	9	6	1	3

Pivotal Study – HUBIN: Insuplant Non-Comparative Phase

An overview of abnormal free anti-insulin antibodies (⩾ 2.5 %) values is given in Table 26. The rate of patients with abnormal values of free AIAs did not change substantially, between 75 % and 87 %, during the Insuplant non comparative phase. The only exception was at V6; however, the small number of evaluated patients at V6 prevents a meaningful comparison.

Table 26. Number of patients with abnormal level of Free AIAs at each visit

Patients (number and %) with abnormal value of Free AIAs at each visit			Analysis population N = 164
Free AIA at V1		N	67
	Abnormal : ≥ 2.5 %		50 (74.6 %)
Free AIA at V2		N	21
	Abnormal : ≥ 2.5 %		18 (85.7 %)
Free AIA at V3		N	56
	Abnormal : ≥ 2.5 %		42 (75.0 %)
Free AIA at V4		N	31
	Abnormal : ≥ 2.5 %		27 (87.1 %)
Free AIA at V5		N	29
	Abnormal : ≥ 2.5 %		22 (75.9 %)
Free AIA at V6		N	2
	Abnormal : ≥ 2.5 %		2 (100.0 %)

Pivotal Study – HUBIN: Insuman Non- Comparative Phase

The rate of patients with abnormal values of free AIAs (≥2.5%) or AIAs (ELISA, ≥5.0KU/L) did not change substantially during the Insuman non comparative phase:

- 88.1 % at baseline (cycle 0), then, between 76.2 % and 90.0 % from cycle 1 to cycle 13 for free AIAs

- 50.3 % at baseline, then, between 50.0 % and 69.2 % from cycle 1 to cycle 13 for AIAs (ELISA).

Four patients in the Insuman non-comparative phase of the HUBIN trial had a history of anti-insulin antibody syndrome.

Study MIP 310

In MIP 310, the CIPII group reported much higher mean ADAs values, and frequencies of values outside the reference range, compared to both baseline values and SC group values during the 360 day study phase (Table 27). Levels of ADAs rose according to baseline stratification. Evaluation of the relationship between ADAs values and HbA1c values phase showed no clear correlation between these factors. A medical review of all patients in MIP 310 revealed that while some patients exhibited elevated ADAs values there was no correlation with clinical signs of Insulin Antibody Syndrome.

Table 27. Descriptive Statistics for special interest laboratory values by treatment group and study visit

	IP Group				SC Group			
	N	Mean ± SD Median (min, max)	High Alert n (%)	Low Alert n (%)	N	Mean ± SD Median (min, max)	High Alert n (%)	Low Alert n (%)
Visit 3	50	61.89±137.65 11.50 (2.10, 707.00)	34 (68.0)	N/A	49	30.62±57.85 10.0 (2.10, 317.0)	34 (69.4)	N/A
Visit 5	50	87.44±185.09 29.0 (2.00, 973.00)	46 (92.0)	N/A	46	25.87±40.58 10.5 (2.2, 197.00)	29 (63.0)	N/A
Visit 6	51	69.66±74.77 42.00 (3.30, 399.00)	48 (94.10)	N/A	45	30.77±61.31 6.10 (2.30, 342.00)	27 (60.0)	N/A
Visit 7	50	222.13±1036.3 36.50 (2.50, 7374.0)	47 (94.0)	N/A	46	26.09±51.35 9.05 (2.10, 303.00)	30 (65.2)	N/A
Visit 8	49	234.11±918.49 38.00 (2.10, 6379.0)	43 (87.8)	N/A	44	25.39±47.08 9.20 (2.10, 224.00)	27 (61.4)	N/A

Hepatic Steatosis

Two patients were diagnosed with hepatic steatosis during the HUBIN study, both patients were on Insuplant at the moment of diagnosis. Based on the information provided in the first case the patient had a history of unspecified hepatopathy prior to enrolment in the HUBIN study. The patient was treated with CIPII for 5 years prior to the diagnosis of hepatopathy. Medical history and use of concomitant medications may provide an alternative explanation for the aggravation of preexisting hepatic condition. In the second case it seems that the catheter was in very close proximity to the liver causing focal hepatic steatosis. In both cases it seems that steatosis was not clinically relevant since there were no additional AEs or SAEs that could be considered as potentially related to the event.

Additionally, at the beginning of the study, 8 patients had a history of hepatic steatosis and 4 patients of focal hepatic steatosis. Based on the data available, patients had a long standing diagnosis of steatosis, ranging since 1983 and 2010. In 11 patients steatosis was deemed as ongoing and in one case the event resolved. In 9 patients elevated liver enzymes were not observed while 3 patients had GGT increased (one of those patients had increased ALT). Adverse and serious adverse events that were observed in HUBIN study do not seem to be related to the issue of hepatic steatosis.

According to the Applicant, there is no additional clinical relevance of hepatic steatosis. The clinical features of subjects with and without steatosis are similar.

According to Regnell and Lernmark (Regnell & Lernmark, 2011) however, insulin can have a role in the stimulation of fat synthesis and steatosis. The cases above indicate that there is a potential for the

development of hepatic and focal steatosis. Additionally, the overall and liver-related mortality are increased in patients with nonalcoholic steatohepatitis compared to the general population (Pais & Ratziu, 2012).

The CHMP agreed that the consequences of the accumulation of liver fat remain poorly understood and the long term effects such as patients with non-alcoholic steatohepatitis potentially developing cirrhosis, endstage liver disease and hepatocellular carcinoma, should be considered.

The applicant aims to better characterize the risk of focal hepatic steatosis related to the use of Insuman Implantable 400 IU/mL in the MiniMed Implantable Pump by means of the following additional pharmacovigilance activities:

• Non-comparative pre-authorization efficacy and safety study until the actual availability of Insuman Implantable on the market

• Insuman Implantable registry when Insuman Implantable is available on the market

Laboratory findings

Pivotal Study – HUBIN

There were no laboratory tests measured.

Study – MIP 310

There were only slight variations between treatment groups and within groups for urine creatinine and microalbumin. The urine microalbumin/creatinine ratio was similar in the CIPII and SC groups at baseline, in terms of actual values and frequency of values outside the reference range. The SC group reported a mean ratio of 100.41 and 16 (30.8%) high alerts and the CIPII group reported a mean ratio of 98.76 with 15 (30.0%) high alerts at Visit 1. However, at Visit 5, while the SC group reported a decrease in mean ratio to 79.65 and decrease in number of high alerts to 10 (22.2%), the mean ratio in the CIPII group increased to 156.68 as did the number of high alerts to 18 (36%). This difference in ratio values between the SC and CIPII groups remained consistent at Visit 8. The statistical and clinical significance of this data is not known. There was no difference in AST and ALT between IP insulin and SC insulin. From other studies no data are available on renal function. The Applicant will collect microalbumin/creatinine ratio in the registry study which is planned to start once the product is marketed.

Safety in special populations

Use in the Elderly

Efficacy for both co-primary endpoints change in HbA1c from baseline to V5 and refill accuracy at V5 was similar in patients <65 and ≥65. The number of SAEs was slightly higher in those over 65.

Use in Pregnancy and Lactation

Patients who were pregnant or lactating were excluded from participating in all the studies described in this report. No pregnancies occurred in the comparative phase of HUBIN or in any of the phases of MIP 310. However, pregnancies did occur during Study 303a. Of the 6 SAEs in the SOC 'pregnancy, puerperium and perinatal conditions', 4 were considered to be 'not related' to study drug and/or study device. The relationship of the event of 'foetal macrosomia' to study drug and/or study device was described as 'unlikely' and the relationship of the event 'uterine contractions during pregnancy' to study drug and/or device was described as 'unlikely'. The safety of CIPII with Insuman Implantable 400 IU/mL or Insuplant 400 IU/mL in pregnant or lactating patients has not been established. The appropriate warnings to this respect have been added to section 4.6 of the SmPC.

A protocol amendment was made for the non-comparative Insuman phase to allow Insuman Implantable use in pregnancy. No specific problems have been reported after this amendment.

Use in Paediatric Patients

Paediatric patients were excluded from the studies listed in this line extension. However, there is one subject in the non-comparative phase of HUBIN who is less than 18. The safety of CIPII with Insuman Implantable 400 IU/mL or Insuplant 400 IU/mL in paediatric patients cannot be considered to be established. Due to the large size of the implantable pump, implantation in children who have not reached adult size may not be feasible. As such a contraindication has been included in section 4.3 of the SmPC. References to the paediatric population can also be found in sections 4.2 and 4.4 of the SmPC.

Use in obese patients

Subset analysis was not done in those patients with BMI >30 Kg/m^2 in the comparative phase of HUBIN. Data from 12 obese patients in the IP group and 6 obese patients in the SC group in the study phase of MIP 310 showed similar efficacy data assessed as HbA1c in those with BMI >30 Kg/m^2. This is evidence that the efficacy is not related to the route of administration.

Safety related to drug-drug interactions and other interactions

None other than those generally reported for all insulin preparations.

Discontinuation due to adverse events

In the safety population of the HUBIN comparative phase, only 2 patients (1.2%) presented at least one adverse event leading to study drug withdrawal: 1 patient whose drug delivery device was removed for personal convenience in the Insuman Implantable 400 IU/mL group and 1 patient with an impaired healing of the skin after re-implantation in the Insuplant 400 IU/mL group.

In the Insuplant non-comparative phase of the HUBIN trial, 4 patients (2.4 %) presented at least one adverse event leading to study drug withdrawal: 2 patients (1.2 %) with medical device occlusion, 1 patient (0.6 %) with medical device removal and 1 patient (0.6 %) with hyperglycaemia.

In the ITT population treated with Insuman Implantable in the HUBIN trial, 10 patients (2.4 %) presented at least one adverse event leading to study drug withdrawal.
For 7 patients (1.7 %), the adverse events were in relation with the pump (device battery issue: 1 patient, device dislocation: 1 patient, drug delivery device removal: 1 patient, implant site inflammation: 1 patient, device related infection: 1 patient, implant site infection: 1 patient and skin erosion due to pump: 1 patient).
For the 3 other patients (0.4 %), the adverse events were:

- Hyperglycaemia with ketosis and cognitive disorders: 1 patient
- Hypoglycaemia: 1 patient
- Cerebrovascular accident: 1 patient

2.6.1. Discussion on clinical safety

An important consideration to bear in mind regarding this clinical program is that the number of patients is limited due to the small number of patients in the target population.

Overall, it is clear that an intraperitoneal pump needs to be implanted and regular interventions are necessary for refill and flushing. A high number of patients treated with Insuman Implantable in the HUBIN study, 44.6%, needed at least one device intervention on an average exposure of 388 days per patient. Any problem with the device may have serious consequences. In addition, device interventions

are a burden for patients. These device interventions can only be performed in a few specialized centres in Europe.

In the Insuman non-comparative phase of the HUBIN trial there was a high number of device events. The number of device interventions during the Insuman non-comparative phase were generally higher in patients previously treated with Insuplant in the Insuplant non-comparative phase (or directly enrolled in Insuman non-comparative phase) when compared with other groups. This could be due to different baseline characteristics, e.g. the larger time from current pump implantation in the Insuplant non-comparative phase than in the comparative phase. Possibly related TEAEs were mainly related to the pump: medical device change, implantation or removal in 10.8% and administration site disorders in 9.8%, half of these device occlusions. Other possibly related TEAEs were metabolism and nutrition disorders (8.6%) and infections in 1.7%, 6 of these 7 patients this was device or implant site related.

During the treatment period in MIP 310, there were more serious adverse events in the CIPII group (12 SAEs in 9 patients) than the SC group (9 SAEs in 7 patients). In addition, there were 40 SAEs during the continuation and maintenance phases (30 during the continuation phase, 10 during the maintenance phase). In study 310, the incidence of *severe* hypoglycaemia was not different between the IP group and the SC group; but numbers were small. Incidence of hypoglycaemia other than severe is also an important parameter. Hypoglycaemia was not explicitly defined in the study protocol. Nevertheless, in the study phase of MIP 310, there were 25 events of hypoglycaemia; 23 in the CIPII group and 2 in the SC group. The increased risk of hypoglycaemia with IP insulin is a serious issue. There were no clinically relevant differences in device interventions and infections between Insuman and Insuplant.

In the comparative part of the HUBIN trial, there were more adverse events with Insuman than with Insuplant (56.0 vs. 48.8%). In addition, more patients had adverse events possibly related to the insulin and/or to the pump during treatment with Insuman compared to Insuplant (12 patients (14.3%) vs. 7 patients (8.3%)). These findings suggest that Insuman may have disadvantages in comparison to Insuplant.

In the comparative part of the HUBIN study, the System Organ Class most often affected by possibly related TEAEs was metabolism and nutrition disorders (8.3 % [7/84] with Insuman and 4.8% [4/84] with Insuplant), which included glucose abnormalities. Annual incidence of severe hypoglycaemia was 0.451 episodes per patient-year with Insuman Implantable and 0.343 episodes per patient-year with Insuplant. In the pharmacokinetic study, Cmax and AUC0-4h of Insuman Implantable seemed to be higher compared to Insuplant with respectively 70% and 40%. Also in the non-comparative arms the number of severe hypoglycaemia was higher with Insuman Implantable than with Insuplant (0.218 per patient-year versus 0.140 per patient-year). Although the numbers were small and the differences were not statistically significant, Insuman may be associated with a higher risk for hypoglycaemia.

Compared to the Insuplant non-comparative phase, the number of hyperglycaemia per patient-year was higher during the Insuman non-comparative phase (9.276 versus 8.272) as well as the number of hyperglycaemia with ketonemia per patient-year (0.952 versus 0.187).

In rats and humans, it has been demonstrated that high local insulin levels may induce a focal reversible hepatic steatosis. Insulin can have a role in the stimulation of fat synthesis and steatosis. (Regnell & Lernmark, 2011) The long term effects of IP insulin on the liver are unknown. In the HUBIN and MIP 310 study, hepatic steatosis was reported in one patient. No AE were observed during the study in this patient. However, laboratory measurements demonstrated no differences in liver enzymes between IP insulin and SC insulin.

In the Insuplant non-comparative phase of the HUBIN trial, one patient died due to a malignant lung neoplasm with liver and bone metastases. In the Insuman non-comparative phase of the HUBIN trial, 2

patients (0.5%) died due to severe cardiac disorders for one and a cerebrovascular accident for the other.

There was an increase in the urine microalbumin/creatinine ratio with intraperitoneal insulin treatment compared to SC treatment. The clinical significance is unclear, but harmful effects in the long term should not be excluded; this will be monitored in the planned registry study. There is limited data on renal function while on CIPII and this data is from MIP310. Prevalence of nephropathy, use of concomitant medications affecting the renin angiotensin system and Treatment Emergent Adverse Events (TEAEs) related to renal function in the trials are similar to the rates seen in Epidemiology of Diabetes Interventions and Complications (EDIC) extension of the Diabetes Control and Complications Trial (DCCT). The Applicant will collect the microalbumin/creatinine ratio from the sites when available per standard of care. Those data will be collected in registry study.

There was a higher number of anti-insulin antibodies with intraperitoneal insulin treatment compared to subcutaneous insulin. The clinical significance is unclear, but there may be harmful effects in the long term. There were no clinically relevant differences in antibodies between Insuman and Insuplant. IP treatment may cause an exaggerated rise in IA titre. However, this may return to normal with time and there does not seem to be a clinical significance of increased IA in the patients treated with CIPII.

Given the larger amount of insulin that is needed in obese patients, a subset analysis according to BMI with respect to efficacy and safety was performed. This analysis revealed that efficacy and safety were comparable for the different categories. No differences between weight classes were observed for refill accuracy.

The applicant commits to submit the integrated report containing the complete data of all phases of the HUBIN study (Insuplant non-comparative phase, Insuman/Insuplant comparative phase and Insuman non-comparative phase) as this is not yet available. The applicant will submit this report in October 2014.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Intraperitoneal insulin is only used by a very small group of patients. Compared to subcutaneous insulin, intraperitoneal insuman has several disadvantages. IP insulin is associated with more device interventions, administration site conditions, infections, hypoglycaemia, microalbuminuria and anti-insulin antibodies. Information regarding safety in pregnancy/lactation, long-term safety, long-term exposure to phenol in intraperitoneal region, and safety in the paediatric population are still missing (see section 2.8, Risk Management Plan).

The CHMP considers the following measures necessary to address the safety data in the context of a MA:

• Non-comparative pre-authorization efficacy and safety study until the actual availability of Insuman Implantable on the market - Submission of the integrated report containing the completed data of all phases of the HUBIN study (Insuplant non-comparative phase, Insuman/Insuplant comparative phase and Insuman non-comparative phase) in October 2014.

• Insuman Implantable registry when Insuman Implantable is available on the market – the registry will last for 10 years. Interim analyses will be addressed on a yearly basis.

The CHMP considers the above activities sufficient to further characterize the aforementioned important identified and potential risks of the product, as well as the missing information on the product.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1.1 the PRAC considers by consensus that the risk management system for insulin human (Insuman) in 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 is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Summary of the Safety Concerns

Important identified risks	Severe hypoglycemia Hyperglycemia (caused by insulin underdelivery due to pump jamming or catheter occlusion) Antigenicity Pump pocket infection Abnormal healing Skin erosion
Important potential risks	Hypersensitivity to Insuman Hypersensitivity to pump material Focal hepatic steatosis Long-term local reactions Transmission of infectious agent Medication errors
Missing information	Safety in pregnancy/lactation Long-term safety Long-term exposure to phenol in intraperitoneal region Safety in pediatric population

The PRAC agreed.

Pharmacovigilance plans

Ongoing and planned studies in the PhV development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Pre-authorization study (HUBIN_L_05335 – Insuman non-comparative phase): Evaluation of Insuman Implantable 400 IU/mL in patients with Type 1 diabetes treated with the Medtronic MiniMed Implantable Pump System using Insuplant 400 IU/mL.	To gain additional information on the efficacy and safety of Insuman implantable	Collection of all adverse events	Ongoing	October 2014
Registry (**HUBINC06380**): Post Authorization Safety Study (PASS): European observational cohort of patients with type 1 diabetes treated with Insuman Implantable 400 IU/mL in an intra-peritoneal pump.	To better characterize some of the risks related to the use of Insuman Implantable 400 IU/mL in the MiniMed Implantable Pump and gain additional safety data.	With the exclusion of antigenicity, transmission of infectious agent, medication errors and long-term local reactions (assessed by routine pharmacovigilance), all other risks will be followed in the registry.	Planned to start as soon as the product is marketed	Registry will last for 10 years. Interim analyses will be addressed in RMP on a yearly basis.

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation activities	Additional risk minimisation activities
Important identified risks		
Severe hypoglycemia	**SmPC** • SmPC *Section 4.2 Posology and method of administration* explains that blood glucose monitoring is essential to monitor glycemic control, to determine insulin doses and to detect possible malfunction of the pump. • SmPC *Section 4.4 Special warnings and precautions for use* describes situation where hypoglycemia could occur, consequences and *Section 6.6 Special precautions for disposal and other handling* how to manage the pump in such a situation. • SmPC Section 4.5 *Interaction with other medicinal products and other forms of interaction*, describes the list of substances that may enhance the blood glucose-lowering. This is also mentioned in section 2 of the package leaflet. • SmPC Section 4.8 Undesirable effects lists hypoglycemia. This is also explained in section 4 of the package leaflet.	Educational program for HCPs (training, physician manual, physician quick guide) Educational program for patients (training, patient manual) Patient emergency information card Alarm and display message
Hyperglycemia caused by insulin underdelivery	**SmPC** • SmPC *Section 4.4 Special warnings and precautions for use* explains mechanisms of insulin underdelivery, the way to manage them and highlights that patients should correct resistant hyperglycemia with SC insulin • SmPC *Section 6.6 Special precautions for disposal and other handling* describes in which situations insulin under-delivery should be suspected, and summarize the diagnostic pump procedures to be performed.	Important patient information leaflet Educational program for HCPs (training, physician manual, physician quick guide) Educational program for patients (training, patient manual) Patient emergency information card
Antigenicity	**SmPC** • SmPC *Section 4.2 Posology and method of administration* explains how to closely monitor patients requiring high level of insulin because of the presence of insulin antibodies • SmPC *Section 4.4 Special warnings and precautions for use* gives information on antibodies to insulin and recommendations for dose adjustment. • SmPC *Section 4.8 Undesirable effects* informs about the risk related to anti-insulin antibodies formation (immune system disorders).	Educational program for HCPs (training, physician manual, physician quick guide)
Infection of the pump pocket	**SmPC** • SmPC *Section 4.4 Special warnings and precautions for use* describes prophylactic measures to be taken at time of pump implantation to reduce the risk of infectious complications • SmPC *Section 4.8 Undesirable effects* informs about the risk of pump pocket infection. • SmPC Section *6.6 Special precautions for disposal and other handling* describes precautions to be taken at time of pump refill to reduce the risk of infectious complications.	Educational program for HCPs (training, physician manual, physician quick guide) Educational program for patients (training, patient manual)
Abnormal healing	**SmPC** SmPC *Section 4.4 Special warnings and precautions for use* describes prophylactic measures to be taken at time of pump implantation to reduce the risk of abnormal healing.	Educational program for HCPs (training, physician manual, physician quick guide) Educational program for patients (training, patient manual)

Safety concern	Routine risk minimisation activities	Additional risk minimisation activities
Skin erosion	**SmPC** • SmPC *Section 4.4 Special warnings and precautions for use* describes prophylactic measures to be taken at time of pump implantation to reduce the risk of skin erosion • SmPC *Section 4.8 Undesirable effects* informs about the risk of skin erosion at pump site implantation).	Educational program for HCPs (training, physician manual, physician quick guide) Educational program for patients (training, patient manual)
Important potential risks		
Hypersensitivity reactions to Insuman	**SmPC** • SmPC *Section 4.3 Contraindications* lists hypersensitivity to the active substance or to any of the excipients as a contraindication. • SmPC *Section 4.4 Special warnings and precautions for use* explains that patients hypersensitive to Insuman Implantable for whom no better tolerated medicinal product is available must only continue treatment under close medical supervision and – if necessary – in conjunction with anti-allergic treatment • SmPC Section 4.8 Undesirable effects informs about the risk of immediate type allergic reactions.	Educational program for HCPs (training, physician manual, physician quick guide) Educational program for patients (training, patient manual)
Hypersensitivity reactions to pump material	**SmPC** SmPC *Section 4.3 contraindications* lists hypersensitivity to titanium alloy, polysulfone or silicone materials used in the implanted components of the pump as a contraindication.	Educational program for HCPs (training, physician manual, physician quick guide)
Long term local reactions	No specific information is required.	Educational program for HCPs (training, physician manual, physician quick guide)
Focal hepatic steatosis	**SmPC** SmPC *Section 4.4 Special warnings and precautions* for use explains that focal hepatic steatosis has been observed with IP Insulin and that after stopping insulin infusion or removal or reposition of the peritoneal catheter, focal hepatic steatosis seems to be reversible and without clinical consequence. SmPC Section 4.8 *Undesirable effects* informs about the risk of focal hepatic steatosis	Educational program for HCPs (training, physician manual, physician quick guide)
Transmission of infectious agent	No specific information is required. Any potential risk of microbiological contamination is handled by full compliance to Good Medical Practices and due reporting of any case.	None

Safety concern	Routine risk minimisation activities	Additional risk minimisation activities
Medication errors	**SmPC** • SmPC *Section 1.NAME OF THE MEDICINAL PRODUCT* uses the qualifier "Implantable" joined to the name of the product. • SmPC Section 4.2 Posology and method of administration states that: o Insuman Implantable 400 IU/mL has been specifically formulated for use with a Medtronic MiniMed Implantable Pump supplied by Medtronic MiniMed and for patients who require treatment with insulin via the intraperitoneal continuous infusion route, o the prescription of Insuman Implantable 400 IU/mL for intraperitoneal use should be supervised by a physician experienced in diabetes and competent in using IP insulin, and limited to those hospital units that have received adequate training in the use of the Medtronic MiniMed Implantable Pump • SmPC *Section 4.2 Pososlogy/mode of administration* and section 6.6 *special precautions for disposal and other handling* contraindicates the use of Insuman Implantable 400 IU/mL with any other pumps (external or implantable) or with any other medical devices including syringes • SmPC *Section 4.4 Special warnings and precautions for use* requests to always check insulin label before each administration • SmPC *Section 6.6 Special precautions for disposal and other handling* reminds that only Insuman Implantable must be used with this pump (pump refill section) **Specific qualifier** Specific qualifier "Implantable" as part of the trade name (Insuman Implantable 400 IU/mL) links this formulation with the intraperitoneal implanted pump.	Educational program for HCPs (training, physician manual, physician quick guide) Educational program for patients (training, patient manual)
	Packaging • Use of black colour specific to Insuman Implantable on packaging (carton and label). • The statements "Intraperitoneal use" is displayed in bolded red and "Use only with Medtronic MiniMed Implantable pump" in bold, both on the carton main panel and the vial label to increase prominence of the route of administration. • The strength 400 IU/mL has been further highlighted by the use of a contrasted display: black printing on a white box, over a black background in order to increase its prominence, both on the carton and the vial label. • A specific warning on the higher concentration has been added on the carton: "CAUTION high insulin concentration" in bolded red and partly upper case print. • The invented name, the qualifier, the strength and the pharmaceutical form are being repeated in an additional panel (top opening flap) i.e. the name of the product now appears 3 times on 3 panel sides, instead of previously twice in order to improve differentiation	
Missing information		
Long-term safety	None	Educational program for HCPs (training, physician manual, physician quick guide)

Safety concern	Routine risk minimisation activities	Additional risk minimisation activities
Long-term exposure to phenol in intraperitoneal region	None	Educational program for HCPs (training, physician manual, physician quick guide)
Safety in pregnancy/lactation	**SmPC** SmPC *Section 4.6 Fertility, pregnancy and lactation* informs about the lack of data in pregnancy. It states that women of childbearing potential, implanted or candidates for implantation must inform their physician if they are contemplating pregnancy, and that Insuman Implantable should not be used during pregnancy unless the clinical condition of the woman requires treatment with Insuman Implantable. No effects on nursing child are anticipated, Insuman Implantable can be used during breast-feeding.	Educational program for HCPs (training, physician manual, physician quick guide) Educational program for patients (training, patient manual)
Safety in pediatric population	**SmPC** • SmPC Section 4.2 Posology and method of administration informs about the lack of data in paediatric patients. Due to the large size of the implantable pump, Insuman Implantable should not be used in paediatric patients who have not reached adult size • Use in paediatric patients who have not reached adult size is a contraindication listed in the SmPC *Section 4.3 Contraindications.* • SmPC *Section 4.4 Special warnings and precautions for use* states that due to the large size of the implantable pump, Insuman Implantable should not be used in paediatric patients who have not reached adult size.	Educational program for HCPs (training, physician manual, physician quick guide)

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice with changes. These changes concerned the following elements of the Risk Management Plan: inclusion of additional risk minimisation measures to Annex II.

The CHMP justified these changes as follows:

The RMP contained additional risk minimisation activities consisting of education materials. Of these, the physician and patient manuals have been reviewed by the notified body (GMED) and the CHMP agreed that there is no further need for this technical material to be further reviewed at Member State level. In addition to this, the CHMP also agreed that the Physician and Patient Quick Guides, due to their technical nature, do not require further review by the Member State.

Annex II

Additional risk minimisation measures

The following conditions of the MA refer to the Insuman Implantable 400 IU/ml strength solution for infusion.

The MAH shall implement a controlled distribution system for the Insuman Implantable 400 IU/ml strength solutions for infusion to ensure that the medicinal product is only available to centres with current certification by Medtronic as having the appropriate facilities and staff who have received adequate training in the use of the Medtronic MiniMed Implantable Pump and the Personal Pump Communicator (PPC).

The MAH shall ensure that the training programme for centres includes the following key elements:

- Device components
- Patient selection criteria
- Warnings and precautions when using an implantable pump
- Device programming
- Refill procedure
- Rinse and flush procedure, stroke measurement and pump management including troubleshooting
- Alarms and messages displayed by the device and the appropriate actions to take
- Recognition of signs and symptoms of under or no delivery of insulin and the appropriate actions to take
- Recognition of signs and symptoms of severe hypoglycaemia and the appropriate actions to take
- Training of patients and the key information that patients need to be aware of
- Ensuring that each patient receives the patient manual, the patient quick guide and the important patient information leaflet for the Medtronic MiniMed implantable insulin pump system and the patient emergency information card
- Information on the risk management plan, the safety concerns and the risk minimisation measures
- Information on the registry including how to, and the importance of, entering patients in it
- Surgical aspects of implantation

The MAH shall ensure that all centres are adequately supplied with the following in the appropriate national language(s):

- SmPC and patient information leaflets
- Patient emergency information cards
- The important patient information leaflets for the Medtronic MiniMed implantable insulin pump system. The MAH shall ensure the patient information leaflets include the following key messages:
    - The system does not check your blood glucose; therefore you need to **check your blood glucose at least 4 times a day** according to the method and frequency recommended by your physician;
    - You need to program boluses and temporary basal rates with your PPC;
    - You need to replace the 1.5V AA battery in the PPC every 4 weeks.
    - Every 40 to 45 days, a refill of insulin at the hospital is needed.
    - Running a diagnostic test of your pump system is needed if you think the pump may have been damaged by water, a sporting incident, electrotherapy (cardiac defibrillator), diagnostic ultrasound or radiation (X-ray).

    - You need to carry the completed Patient Emergency Information Card with you always.
    - You need to carry alternative insulin and the means to administer it with you always.
    - You need to keep some form of fast-acting sugar with you at all times.
- Implantable Insulin Pump System: Patient manuals
- Implantable Insulin Pump system: Physician Manuals
- Physician quick guides on the main programming functions
- Patient quick guides on the main programming functions

These materials shall contain content closely similar to the mock-ups provided in the currently approved risk management plan annexes.

The MAH shall ensure that all patients receive training in the following key elements regarding the Insuman Implantable Pump 400 IU/ml:

- Patients' responsibilities regarding insulin treatment as well as refill frequency and maintenance of the pump as outlined in the key messages in the patient information leaflet;
- Training on how to set up the pump with the PPC;
- Conduct of all procedures required for the correct management and maintenance of the Medtronic MiniMed Implantable Pump and the PPC, including rinsing procedures and instructions as to how to handle messages, alarms and routine warnings issued by the PPC;
- The potential for surgical and clinical complications and how to respond in the event any such complications arise.

Legal status:

Insuman Implantable is reserved for treatments which can only be followed in a hospital environment, because of its pharmaceutical characteristics.

The legal status of Insuman Implantable differs from the other Insuman products. As the product will be used in specialized centers, the CHMP agreed with the change in legal status from "subject to medical prescription" to "subject to restricted medical prescription" for Insuman Implantable only. The prescription of Insuman Implantable is restricted to centers certified by Medtronic as having received adequate training in the use of Insuman Implantable.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Insulin can be delivered into the intra-peritoneal cavity via an implanted pump device (MiniMed). Insuplant was being used as a concentrated insulin formulation in these pumps. Insuplant contains porcine-derived semi-synthetic human insulin as an active substance and received Marketing Authorisation in France in August 1998. The manufacturing of this porcine-derived insulin was recently stopped due to the insulin being a chemically modified porcine insulin. The recombinant human insulin Insuman Implantable was developed as a replacement therapy for Insuplant. The intended use for Insuman Implantable, is 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.

Severe hypoglycaemia is defined here according to the EMA Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev.1): "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."

In the present application, two pivotal studies using Insuman have been submitted (HUBIN and Study MIP 310). In addition to these, 6 other studies are considered supportive by the applicant; however, these studies are of limited relevance as these studies only used intraperitoneal administration of Insuplant.

The newly submitted HUBIN study was performed in order to directly compare Insuman and Insuplant. This was a randomised non-inferiority trial comparing 84 patients using Insuman with 84 patients using Insuplant during 6 months. The patients in this study are relevant for the use of Insuman in clinical practice. The number of patients completing the HUBIN study was similar with Insuman and Insuplant. After 6 months, HbA1c was 0.1% lower with Insuman compared to Insuplant. Non-inferiority of the HbA1c change from baseline after 4 refill cycles was reached. The upper limit of the 95% CI was 0.11% in the per protocol population.

The Insuman non-comparative continuation phase of the HUBIN trial showed that the HbA1c values remained stable for 14 refill cycles, although these were higher than in the comparative phase.

In randomized study MIP 310, treatment with intraperitoneal insulin was compared to subcutaneous treatment during 1 year. The 52 patients in the intraperitoneal group were using Insuplant for the first 6 months and Insuman for the last 6 months. Study MIP 310 suggests that intraperitoneal insulin administration using the MiniMed pump and Insuman/Insuplant can be used for the treatment of diabetes type 1. After treatment with intraperitoneal Insuplant for 6 months, in the as treated dataset HbA1c was 0.32% lower compared to subcutaneous insulin (95% CI 0.662 to 0.018). After treatment with intraperitoneal Insuman, HbA1c was 0.410% lower compared to subcutaneous insulin (95% CI -0.786 to -0.034). The design of study MIP 310 did not permit a good differentiation between the effects of Insuplant and Insuman as administration of these insulins was not randomized in sequence or double blind.

Uncertainty in the knowledge about the beneficial effects.

Insuplant has only been approved in France. Therefore, although the Hubin trial may have demonstrated non-inferiority of Insuman in comparison to Insuplant, this does not necessarily result in a positive benefit-risk ratio.

In clinical practice, intraperitoneal insulin administration is a last resort in patients unresponsive to SC insulin treatment (demonstrated resistance to SC treatment, problematic absorption profile of SC insulin and as a consequence problematic fluctuations in glycaemia). The marketing authorisation should be limited to this restricted type 1 diabetic population. It is important to note that not all patients in Study 310 belonged to the target population. The inclusion criteria of study MIP 310 allowed T1DM patients to start this rather invasive therapy when they are insufficiently controlled after only three months of intensive insulin treatment.

The HUBIN study is a trial that contains a non-inferiority comparative phase comparing Insuman and Insuplant. The comparative phase was single blind as a double blind was not technically feasible due to the short timelines. The inclusion criteria (HbA1c $\leq$ 9% and percentage error at refill equal or below 20%) introduced bias in the HUBIN trial.

In the comparative phase of the HUBIN study, non-inferiority was reached between Insuman and Insuplant for the refill accuracy. The refill accuracy error percentage did not substantially change in the Insuman non-comparative phase. However, the error percentages were higher than in the Insuman comparative phase, possibly due to a selection bias related with the inclusion criteria of the comparative phase. Moreover, refill accuracy is overestimated due to the exclusion of all patients with inconsistent refill accuracy values.

In study 310, the non-inferiority margin of 0.5% is considered too wide. A difference of 0.5% in HbA1c is not clinically irrelevant. A margin of 0.3% or 0.4% would have been more acceptable. Nevertheless, HbA1c was lower in the IP group, so the difference is in favour of IP treatment. However, 11/52 patients needed rescue insulin treatment in the IP group for an average of 24 days. These patients could be considered treatment failures. In addition, patients in the IP group completed more blood glucose tests compared to the subcutaneous group. This may have decreased the HbA1c values in the IP group in comparison to the SC group. A further efficacy analysis has been performed in relation to those patients using non-study insulin ("insulin analysis"). This analysis showed superiority for the IP treatment in the device analysis; non-inferiority was not shown for the insulin analysis. Therefore superiority cannot be claimed.

Risks

Unfavourable effects

The number of patients in the studies is limited, due to the small number of patients in the target population.

It is clear that an intraperitoneal pump needs to be implanted and regular interventions are necessary for refill and flushing. A high number of patients treated with Insuman Implantable in the HUBIN study, 44.6%, needed at least one device intervention on an average exposure of 388 days per patient. Any problem with the device may have serious consequences. In addition, device interventions are a burden for patients. These device interventions can only be performed in a few specialized centres in Europe.

In the Insuman non-comparative phase of the HUBIN trial there was a high number of device events. Possibly related TEAEs were mainly related to the pump: medical device change, implantation or

removal in 10.8% and administration site disorders in 9.8%, half of these were device occlusions. Other possibly related TEAEs were metabolism and nutrition disorders (8.6%) and infections in 1.7%, for 6 of these 7 patients this was device or implant site related.

During the treatment period in MIP 310, there were more serious adverse events in the CIPII group (12 SAEs in 9 patients) than the SC group (9 SAEs in 7 patients). In study 310, the incidence of severe hypoglycaemia was not different between the IP group and the SC group. The incidence of hypoglycaemia other than severe is also an important parameter which should be considered. Hypoglycaemia was not explicitly defined in the study protocol. Nevertheless, in the study phase of MIP 310, there were 25 events of hypoglycaemia; 23 in the CIPII group and 2 in the SC group.

There were no clinically relevant differences in device interventions and infections between Insuman and Insuplant. There were no clinically relevant differences in antibodies between Insuman and Insuplant.

In rats and humans, it has been demonstrated that high local insulin levels may induce a focal reversible hepatic steatosis. Insulin can have a role in the stimulation of fat synthesis and steatosis. (Regnell & Lernmark, 2011). The long term effects of IP insulin on the liver are unknown. In the HUBIN and MIP 310 study, hepatic steatosis was reported in one patient. No AE were observed during the study in this patient. Laboratory measurements demonstrated no differences in liver enzymes between IP insulin and SC insulin.

In the Insuplant non-comparative phase of the HUBIN trial, one patient died due to a malignant lung neoplasm with liver and bone metastases. In the Insuman non-comparative phase of the HUBIN trial, 2 patients (0.5%) died due to severe cardiac disorders for one and a cerebrovascular accident for the other.

Uncertainty in the knowledge about the unfavourable effects

In the comparative part of the HUBIN trial, there were more adverse events with Insuman than with Insuplant (56.0 vs. 48.8%). In addition, more patients had adverse events possibly related to the insulin and/or to the pump during treatment with Insuman compared to Insuplant (12 patients (14.3%) vs. 7 patients (8.3%)). These findings suggest that Insuman may have some disadvantages in comparison to Insuplant.

In the comparative part of the HUBIN study, the System Organ Class most often affected by possibly related TEAEs was metabolism and nutrition disorders (8.3 % [7/84] with Insuman and 4.8% [4/84] with Insuplant), which included glucose abnormalities. Annual incidence of severe hypoglycaemia was 0.451 episodes per patient-year with Insuman Implantable versus 0.343 episodes per patient-year with Insuplant. In the pharmacokinetic study, Cmax and AUC0-4h of Insuman Implantable seemed to be higher compared to Insuplant with respectively 70% and 40%. Also in the non-comparative arms the number of severe hypoglycaemia was higher with Insuman Implantable than with Insuplant (0.218 per patient-year versus 0.140 per patient-year). Although the numbers were small and the differences were not statistically significant, Insuman may be associated with a higher risk for hypoglycaemia.

Compared to the Insuplant non-comparative phase, the number of hyperglycaemic events per patient-year was higher during the Insuman non-comparative phase (9.276 versus 8.272) as well as the number of hyperglycaemic events with ketonemia per patient-year (0.952 versus 0.187).

Given the larger amount of insulin that is needed in obese patients, a subset analyses according to BMI is important with respect to efficacy and safety. This analysis revealed that efficacy and safety were comparable for the different categories. No differences between weight classes were observed for refill accuracy.

In MIP 310, there was an increase in the urine microalbumin/creatinine ratio with intraperitoneal insulin treatment compared to SC treatment. The clinical significance is unclear, but harmful effects in the long term should be excluded. There also was an increase in the number of anti-insulin antibodies with intraperitoneal insulin treatment compared to subcutaneous insulin. The clinical significance is unclear, but there may be harmful effects in the long term. Of note, in the Hubin study there were no differences between Insuman and Insuplant with respect to anti-insulin antibodies. The urinary microalbumin/creatinine ratio was not measured in this study. The Applicant will collect the microalbumin/creatinine ratio from the sites when available per standard of care. Those data will be collected in the registry study.

Study MIP 310 was carried out between 2002 and 2004 and the procedure of continuous intraperitoneal insulin infusion (CIPII) has undergone further developments with changes in pump handling that could affect both the benefit and the risk of procedure of continuous intraperitoneal insulin infusion (CIPII).

Benefit-risk balance

Importance of favourable and unfavourable effects

The HUBIN study demonstrates that with respect to HbA1c, both Insuplant and Insuman can be used for the treatment of diabetes type 1 in patients undergoing continuous intraperitoneal insulin infusion (CIPII). In the comparative phase of this study, Insuman and Insuplant were non-inferior with respect to HbA1c and refill accuracy. However, refill accuracy is overestimated due to the exclusion of all patients with a bad refill accuracy (38 of the 169 patients). In order to make a benefit risk assessment, a realistic estimate of the refill accuracy should be taken into account.

There was a higher risk for hypoglycaemia and treatment related adverse events metabolism and nutrition disorders with Insuman compared to Insuplant in the HUBIN comparative phase. Also in the non-comparative arms the number of severe hypoglycaemia was higher with Insuman Implantable than with Insuplant (0.218 per patient-year versus 0.140 per patient-year). Given the results of the pharmacokinetic study, it may be that Insuman is associated with a higher risk for hypoglycaemia. Compared to the Insuplant non-comparative phase, the number of hyperglycaemic events per patient-year was higher during the Insuman non-comparative phase (9.276 versus 8.272) as well as the number of hyperglycaemic events with ketonemia per patient-year (0.952 versus 0.187).

Given the larger amount of insulin that is needed in obese patients, a subset analysis according to BMI was performed. Efficacy (HbA1c) and safety were similar in each category. No differences between weight classes were observed for refill accuracy.

Insuplant so far has only been approved in France and is not manufactured anymore; the benefit/risk of Insuman should therefore be assessed within the context of its intraperitoneal administration. IP insulin administration has only been used in a small group of patients in a few centres in France and Holland. Currently in Europe, 404 patients are being treated with IP insulin using the MiniMed pump. In study MIP 310, HbA1c after treatment with intraperitoneal Insuman was 0.41% lower than after treatment with subcutaneous insulin. However, this study was only in part performed in the target population. The Applicant has performed a post-hoc analysis in a sub-group of patients with use of continuous subcutaneous insulin infusion (CSII), HbA1c >7.5%, mean SMPG value >180 mg/dL. It can be debated whether this is the real EVADIAC group; however, in any case these are patients with insufficient glycaemic control. The effect on HbA1c with IP treatment was superior to that with SC treatment.

Many patients needed rescue insulin during treatment. This is not very serious in clinical practice, but these patients could be considered treatment failures. In the MIP 310 study, patients in the IP group completed more blood glucose tests compared to the subcutaneous group. Due to these issues, superiority cannot be claimed. In the Insuman non-comparative phase of the HUBIN trial, 39.1% of the ITT population used subcutaneous insulin, in 62% of these cases due to delivery system dysfunction.

Several important disadvantages are obvious from this study. Surgical implantation is necessary. There is an increased risk of infections, and regular refills and flushes should be performed. Further disadvantages of the use of IP Insuman compared to SC insulin are the higher risk of serious adverse events and hypoglycaemia. Also an increased risk for anti-insulin antibodies and urinary microalbuminuria was observed. CIPII has been associated with hepatic steatosis in one patient. The clinical relevance of these findings is not clear, but these findings may be important, especially for long-term safety.

In general, these disadvantages hamper its use in larger patient groups. Nowadays CIPII is mainly used in patients with so called "brittle diabetes" who fail to reach adequate glycaemic control while on intensive SC insulin therapy. The majority also failed CSII. Therefore, the approved indication is "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".

Although the design of study MIP 310 does not allow for a full comparison between intensive intraperitoneal and subcutaneous administration of Insuman, this study does not show that the benefits of Insuman administered by CIPII outweigh the risks. However, this study was carried out between 2002 and 2004 and the number of pump dysfunction and pump explantations have decreased thereafter. Also in the Insuman treated patients in the HUBIN trial 44.6 % needed a device intervention during mean study period of 388±100 days.

Benefit-risk balance

Discussion on the benefit-risk balance

CIPII with Insuman is currently applied in a few centres in Europe. The safety and efficacy of Insuman Implantable administered by CIPII are fully established in the therapeutic population. Many device interventions were necessary (in 44.6% of the patients on Insuman in the HUBIN trial) and complications, in particular infections, occurred regularly with an increased risk of hypoglycaemia. The benefit/risk of CIPII is positive in a sufficiently restricted patient group. It should be a last resort in patients that cannot be controlled with subcutaneous insulin (including pump) therapy, presenting with frequent, otherwise unexplained severe hyper- and/or hypoglycaemia.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by concensus that the risk-benefit balance of Insuman Implantable in 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 is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The following conditions of the MA refer to the Insuman Implantable 400 IU/ml strength solution for infusion.

The MAH shall implement a controlled distribution system for the Insuman Implantable 400 IU/ml strength solutions for infusion to ensure that the medicinal product is only available to centres with current certification by Medtronic as having the appropriate facilities and staff who have received adequate training in the use of the Medtronic MiniMed Implantable Pump and the Personal Pump Communicator (PPC).

The MAH shall ensure that the training programme for centres includes the following key elements:

- Device components
- Patient selection criteria
- Warnings and precautions when using an implantable pump
- Device programming
- Refill procedure
- Rinse and flush procedure, stroke measurement and pump management including troubleshooting
- Alarms and messages displayed by the device and the appropriate actions to take

- Recognition of signs and symptoms of under or no delivery of insulin and the appropriate actions to take
- Recognition of signs and symptoms of severe hypoglycaemia and the appropriate actions to take
- Training of patients and the key information that patients need to be aware of
- Ensuring that each patient receives the patient manual, the patient quick guide and the important patient information leaflet for the Medtronic MiniMed implantable insulin pump system and the patient emergency information card
- Information on the risk management plan, the safety concerns and the risk minimisation measures
- Information on the registry including how to, and the importance of, entering patients in it
- Surgical aspects of implantation

The MAH shall ensure that all centres are adequately supplied with the following in the appropriate national language(s):

- SmPC and patient information leaflets
- Patient emergency information cards
- The important patient information leaflets for the Medtronic MiniMed implantable insulin pump system. The MAH shall ensure the patient information leaflets include the following key messages:
    - The system does not check your blood glucose; therefore you need to **check your blood glucose at least 4 times a day** according to the method and frequency recommended by your physician;
    - You need to program boluses and temporary basal rates with your PPC;
    - You need to replace the 1.5V AA battery in the PPC every 4 weeks.
    - Every 40 to 45 days, a refill of insulin at the hospital is needed.
    - Running a diagnostic test of your pump system is needed if you think the pump may have been damaged by water, a sporting incident, electrotherapy (cardiac defibrillator), diagnostic ultrasound or radiation (X-ray).
    - You need to carry the completed Patient Emergency Information Card with you always.
    - You need to carry alternative insulin and the means to administer it with you always.
    - You need to keep some form of fast-acting sugar with you at all times.
- Implantable Insulin Pump System: Patient manuals
- Implantable Insulin Pump system: Physician Manuals
- Physician quick guides on the main programming functions
- Patient quick guides on the main programming functions

These materials shall contain content closely similar to the mock-ups provided in the currently approved risk management plan annexes.

The MAH shall ensure that all patients receive training in the following key elements regarding the Insuman Implantable Pump 400 IU/ml:

- Patients' responsibilities regarding insulin treatment as well as refill frequency and maintenance of the pump as outlined in the key messages in the patient information leaflet;
- Training on how to set up the pump with the PPC;
- Conduct of all procedures required for the correct management and maintenance of the Medtronic MiniMed Implantable Pump and the PPC, including rinsing procedures and instructions as to how to handle messages, alarms and routine warnings issued by the PPC;
- The potential for surgical and clinical complications and how to respond in the event any such complications arise.