EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 February 2015
EMA/157145/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Toujeo

International non-proprietary name: insulin glargine

Procedure No. EMEA/H/C/000309/X/0079/G

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

AE	adverse event
AHA	antihyperglycaemic agents
AIA	anti-insulin antibody
ATC	anatomical therapeutic chemical
BG	blood glucose
BMI	body mass index
CGM	continuous glucose monitoring
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CV	cardiovascular
DCCT	Diabetes Control and Complications Trial
DTSQs	Diabetes Treatment Satisfaction Questionnaire (status)
e-CRF	electronic case report form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GIR-AUC_{0-24h}	area under the body weight standardized glucose infusion rate versus time curve from time zero to 24 hours post dosing
GIR-AUC_{0-36h}	area under the body weight standardized glucose infusion rate versus time curve from time zero to 36 hours post dosing
GIR_{max}	maximum glucose infusion rate
GLP-1	glucagon-like peptide-1
ICH	International Conference on Harmonization
IMP	investigational medicinal product
IND	Investigational New Drug
INS-AUC_{0-24}	area under the serum insulin glargine concentration versus time curve from time zero to 24 hours post dosing
INS-AUC_{0-36}	area under the serum insulin glargine concentration versus time curve from time zero to 36 hours post dosing
IVRS/IWRS	interactive voice/web response system
LC-MS/MS	liquid chromatography tandem mass spectrometry

LOCF	last observation carried forward
LS	least square
MDRD	modification of diet in renal disease formula
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
NDA	New Drug Application
NGSP	National Glycohemoglobin Standardization Program
NIMP	non-investigational medicinal product
NPH	neutral protamine Hagedorn
OAD	oral antihyperglycaemic drug
PCSA	potentially clinically significant abnormality
PD	pharmacodynamic
PK	pharmacokinetic
PSP	Paediatric Study Plan
PT	preferred term
RR	relative risk
SAE	serious adverse event
SE	standard error
SHRB	Severe Hypoglycaemia Review Board
SMPG	self-monitored plasma glucose
SMQ	standardized MedDRA query
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
U100	Insulin glargine 100 U/ml (HOE901-U100)
U300	Insulin glargine 300 U/ml (HOE901-U300)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sanofi-aventis Deutschland GmbH submitted to the European Medicines Agency on 25 April 2014 an extension of the existing marketing authorisation of Optisulin to register an additional form 300 units/ml grouped with a Type IAIN variation to change the invented name from Optisulin to Toujeo.

The applicant applied for an addition of a new strength/potency (300 units/ml), grouped with a change in the (invented) name of the medicinal product (Toujeo). The applicant applied initially for the following indication for the new strength/potency: Treatment of diabetes mellitus in adults.

The legal basis for this application refers to:

Annex I of Regulation (EC) No 1234/2008, point (c) - Extensions of marketing authorisations

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

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.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff

Co-Rapporteur: Kristina Dunder

CHMP Peer reviewer: n/a

- The application was received by the EMA on 25 April 2014.
- The procedure started on 28 May 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 August 2014.
- PRAC RMP Advice and assessment overview adopted by PRAC on 11 September 2014
- During the meeting on 25 September 2014, 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 26 September 2014.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 November 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 December 2014.
- PRAC RMP Advice and assessment overview adopted by PRAC on 9 January 2015.
- During the CHMP meeting on 22 January 2015, 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 26 January 2015.
- PRAC RMP Advice and assessment overview adopted by PRAC on 12 February 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 11 February 2015.
- During the meeting on 26 February 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting an extension of the Marketing Authorisation for Toujeo.

2. Scientific discussion

2.1. Introduction

Background

Diabetes mellitus is a chronic disease characterized by hyperglycaemia from defects in insulin secretion, insulin action, or both.

Type 1 diabetes mellitus (T1DM) usually begins at a young age (<20 years) and is mainly due to autoimmune destruction of the pancreatic ß-cells that produce insulin. As a result, patients with T1DM require lifelong insulin supplementation for survival.

In type 2 diabetes mellitus (T2DM),, the most common form of diabetes accounting for over 90% of all diabetes cases , the combined impact of impaired insulin secretion and insulin resistance results in elevated blood glucose (BG) levels. Due to the latter, hyperglycaemia may prevail despite plasma insulin levels exceeding those in non-diabetic individuals. Treatment initially involves changes in lifestyle (diet, exercise), with oral antihyperglycaemic drugs (OADs) added as necessary to maintain adequate BG control. Other injectable therapeutic agents, such as the glucagon-like peptide-1 (GLP-1) receptor agonists may be an option before or in addition to insulin in some patients. Ultimately, due to the progressive β-cell failure in T2DM, insulin replacement is indicated in patients to manage hyperglycaemia. As many patients with T2DM maintain some residual endogenous insulin secretion, the insulin treatment regimen in T2DM may be less complex than in T1DM .

It has been established in T1DM and T2DM that uncontrolled, high levels of BG are a factor for chronic microvascular and macrovascular complications that can result in retinopathy, nephropathy, neuropathy and premature cardiovascular (CV) morbidity and mortality. Studies have shown that improving the control of BG levels in both T1DM , and T2DM reduces the risk of these complications.

About the product

Insulin is the most effective available glucose-lowering treatment. Insulin preparations differing both in their time of onset and duration of action are available for insulin substitution therapy. Of the different therapeutic options, basal-bolus regimens try to closely mimic physiological insulin concentrations by injections of long-acting insulin products for basal insulin supply (comprising insulin glargine, insulin detemir, degludec or human insulin [neutral protamine Hagedorn-insulin; NPH-insulin]) and premeal (bolus) injections of short- or short- and rapid-acting insulin products (comprising human insulin or human insulin analogues aspart, lispro or glulisine). The combined time-action profiles of the basal insulin dose(s) and the short-acting insulin products are to match fasting and prandial glucose load; inappropriately high or low insulin levels may lead to hypoglycaemia or hyperglycaemia.

Insulin glargine is a recombinant analogue of human insulin.

Toujeo (Insulin glargine 300 U/mL, HOE901-U300 in this document: U300).) is indicated in diabetes mellitus where treatment with insulin is required. U300 has the same composition as Lantus and Optisulin, which were the commercial formulations of insulin glargine 100 U/mL available when the studies included in this dossier were performed, except for adjustment of 3 times the amount of active pharmaceutical ingredient and corresponding zinc content.

Insulin glargine as Lantus [EMEA/H/C/000284] and Optisulin [EMEA/H/C/000309] has been authorised in the EU since June 2006. The efficacy and safety of insulin glargine are well known through extensive data collection involving over 200 000 patients included in clinical trials and observational studies.

In the subsequent text insulin glargine 100 U/mL is also referred to as U100 or as Lantus (a commercial formulation of insulin glargine 100 U/mL available when the studies included in this dossier were performed).

2.2. Quality aspects

2.2.1. Introduction

The U300 pen injector is a multiple-dose, disposable insulin pen injection system for single patient use. Insulin glargine is available as solution for injection containing 10.91 mg/mL insulin glargine [equivalent to 300 U (units) of insulin glargine/mL]. The finished product is to be administered subcutaneously. The total content of the 1.5 ml cartridge is 450 insulin units. The injection system provides a maximum of 80 units in one dosing. The dose for injection is adjusted in 1U increments.

2.2.2. Active Substance

General information

Insulin glargine, is a known active substance used for the approved solution for injection containing 100 U/mL. No further data was provided regarding the active substance for this line extension application as the active substance has been approved for manufacturing 100 U/mL solution for injection finished product preparations. The active substance used in this formulation is of the same quality as that used for the manufacture of the already approved 100 U/mL solution for injection, thus no new information or assessment is required.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The 300U pen contains 1.5 mL of solution for injection, which is equivalent to 450 Units (450U is indicated on the pen). Each mL contains 300 Units insulin glargine (equivalent to 10.91 mg).

The registered Insulin glargine 100U/mL solution for injection is a 3 mL cartridge containing 100U/mL. Compared to the 100U/mL presentation, the 300U/mL presentation contains a threefold amount of insulin glargine as well as a threefold amount of zinc chloride per mL. The amounts of other excipients are similar to the 100U/mL composition.

The insulin glargine finished product is contained in a sealed cartridge assembled into a pen injector. The pen injector is operated fully mechanically and does not contain electronics. The construction of the U300 pen injector is based on SoloStar®, an insulin injection device which is marketed world-wide by Sanofi since 2007.

Manufacture of the product and process controls

The manufacturing process and the process controls correspond to those approved for the marketed insulin glargine solution for injection 100 U/mL process. During development only minor changes were made in the manufacturing procedure to adapt the process to the scaled up batch sizes. The presentation was changed from a 3 mL to a 1.5 mL cartridge.

The manufacturing process is described in detail. The critical process controls in place are deemed sufficient.

No animal and/or human derived material is used. No novel excipients are used.

Product specification

Overall the finished product is considered sufficiently controlled. The analytical procedures are sufficiently described and appropriately validated.

The end of shelf life specifications are brought in line with the specifications for the 100U/ml presentation.

Stability of the product

Overall the stability (and in-use stability) of Insulin Glargine (300U/ml) filled in the 1.5 ml cartridge has been sufficiently demonstrated for its intended use. The stability data provided supports the proposed shelf life of 30 months at +2°C to 8°C and an in-use period of 4 weeks at up to 30°C.

Adventitious agents

No materials of human or animal origin are used during manufacture. There is no viral safety risk since the same active substance is used as for the approved insulin glargine 100U/mL and the manufacturing process and the process controls of the insulin glargine 300 U/mL correspond to insulin glargine 100U/mL.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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

Compared to the registered 100U/mL insulin glargine presentation, the 300U/mL line extension contains a threefold amount of insulin glargine as well as a threefold amount of zinc chloride per mL. The amounts of other excipients remain the same. No further development has been performed.

The manufacturing process is deemed sufficiently described and validated. 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 company presents the 300U pen injector as a 1U-80U dosing system and the accuracy of the 1U-80U dosing is suited for its purpose.

Overall the stability (and in-use stability) of Insulin Glargine (300U/mL) filled in the 1.5 mL cartridge is sufficiently demonstrated for its intended use. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

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.

2.3. Non-clinical aspects

2.3.1. Introduction, Pharmacology and Pharmacokinetics

Given the drug substance is the same in HOE901-U100 formulation and HOE901-U300 formulation, the nonclinical profile of insulin glargine has been well characterized. Therefore, no additional nonclinical studies were performed with the HOE901-U300 formulation, except for a local tolerance study.

2.3.2. Toxicology

Local Tolerance

Both HOE901 formulations (100 U/mL and 300 U/mL), did not cause any local effects at the injection sites different from saline solution-treated injection sites. The U300 formulation showed the same good local tolerability as the U100 formulation following subcutaneous administration, which is the intended route of clinical use. Following intramuscular, intravenous and paravenous administration, representing the potential false administration routes, also a good tolerability was seen.

2.3.3. Ecotoxicity / environmental risk assessment

Insuline glargine is a protein which will rapidly be degraded in the environment.

Furthermore, insulin glargine is already used in existing marketed products and no significant increase in environmental exposure is anticipated, since patients who switch to a different strength will not start using more insulin glargine.

Therefore insulin glargine is not expected to pose a risk to the environment.

2.3.4. Discussion on non-clinical aspects

Repeat-dose toxicity of insulin glargine (HOE901-U100) has been studied in the mouse (up to 20 U/kg/day), rat (up to 50 U/kg/day) and dog (up to 5 U/kg/day) previously. The carcinogenic potential was evaluated up to 12.5 U/kg/day in mice and rats. In all studies HOE901 was administered subcutaneously. In all species the toxicological profile was dominated by the exaggerated pharmacological, blood glucose lowering activity of HOE901. Since the drug substance is the same for both formulations, HOE 901-U100 and HOE901-U300, no differences in the nonclinical profile are expected for HOE901-U300.

Given the drug substance is the same in HOE901-U100 formulation and HOE901-U300 formulation, the nonclinical profile of insulin glargine has been well characterized. Because there is already a wealth of human safety experience, the applicant believes that the results of the nonclinical studies conducted with HOE901-U100 and submitted to the original marketing authorization applications and subsequent submissions for the authorized product also apply to HOE901-U300. Therefore, no additional nonclinical studies were performed or are planned with the HOE901-U300 formulation, which was found to be acceptable.

The additional evaluation of local tolerability in one dedicated study conducted in rabbits with the HOE901-U300 formulation to compare this formulation with the HOE 901-U100 formulation was considered to be sufficient by CHMP to complete the nonclinical program for insulin glargine and to support the use of the HOE901-U300 formulation in patients.

2.3.5. Conclusion on the non-clinical aspects

From a non-clinical point of view there were no objections against extending the Marketing Authorisation of the product.

2.4. Clinical aspects

2.4.1. Introduction

In the subsequent text, insulin glargine 100 U/mL is also referred to as U100 or as Lantus (a commercial formulation of insulin glargine 100 U/mL available when the studies included in this dossier were performed).

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

In the HOE901-U300 clinical development program, a total of 1686 patients received at least one dose of U300, 1546 patients were randomized and treated with U300 in the 6-month main study periods of the Phase 3 studies and the 16-week exploratory Phase 2 study.

Table 1- Number of subjects/patients who received at least 1 dose of study treatment (all completed studies)

Phase / Study	Treatment duration	U300	U100(Lantus)	Total
Phase 1 program				
Healthy subjects		23	24	24
T1DM		140	91	142
Total Phase 1		**163**	**115**	**166**
Phase 2/3 program				
Studies in T1DM				
PDY12777	16 weeks	30	29	59
EFC12456	6 months	274	275	549
Total T1DM		**304**	**304**	**608**
Studies in T2DM				
EFC11628	6 months	404	402	806
EFC11629	6 months	403	406	809
EFC12347	6 months	435	438	873
Total T2DM		**1242**	**1246**	**2488**
Total Phase 2/3 T1DM and T2DM		**1546**	**1550**	**3096**

A total of 6 Phase 1 studies were performed with HOE901-U300 providing clinical pharmacology data in this submission; see Table 2. One single-dose study (PKD10086) was conducted in healthy subjects and 2 single-dose studies (PKD11627, PKD12270) and 3 multiple dose studies (TDR11626, PDY12335, and PKD13560) were conducted in patients with T1DM. All studies employed the euglycaemic clamp technique, except PDY12335 which used CGM.

Study PKD10086 examined the bioequivalence and equivalent bioefficacy of the insulin glargine 300 U/mL (U300) and 100 U/mL formulations in 24 healthy male and female subjects following 2 single SC doses of 0.4 U/kg in a crossover design.

Study TDR11626 investigated the safety and tolerability of 8-day repeated dose regimens at 2 dose levels of U300 (0.4 and 0.6 U/kg/day) and compared their PD and PK properties to those of U100 (0.4

U/kg/day) in a crossover euglycaemic clamp setting in steady state conditions, at the end of each treatment period, in 30 patients with T1DM.

Study PKD11627 investigated the glucodynamic activity and exposure of 3 different single SC doses of U300 (0.4 [T_1], 0.6 [T_2], and 0.9 [T_3] U/kg) versus a standard dose of 0.4 U/kg U100 as comparator (R) in a crossover euglycaemic clamp setting in 24 male and female patients with T1DM.

Study PKD13560 was a double-blind, randomized, 2-treatment crossover bioequivalence study comparing 2 different formulations of U300, using the euglycaemic clamp technique, in 50 patients with T1DM.

Study PKD12270 investigated the metabolic effects, the exposure to insulin glargine and the safety and tolerability of single SC doses of U300 in 18 Japanese T1DM patients. Two different SC doses of U300 (0.4 [T_1] and 0.6 [T_2] U/kg) versus a standard dose of 0.4 U/kg U100 as comparator were assessed in a euglycaemic clamp setting.

Study PDY12335 was a randomized, open-label, 2-sequence, 2-period, 2-treatment crossover multiple dosing study in 20 Japanese male and female patients with T1DM comparing 24-hour glycaemic profile in CGM between U300 and U100 at steady state.

Table 2 Overview of the HOE901-U300 Phase 1 clinical development program

Protocol No.	Patients randomized	Reference Therapy	Dose Duration	Main Objectives
Phase 1: Healthy subjects				
PKD10086	24	Lantus	0.4 U/kg Single dose	Bioequivalence
Phase 1: T1DM				
PKD11627	24	Lantus	0.4, 0.6, 0.9 U/kg Single dose	PK/PD
TDR11626	30	Lantus	0.4, 0.6 U/kg once daily 8 days	PK/PD at steady state
PKD13560	50	HOE901-U300 standard formulation versus polysorbate 20 formulation	0.4 U/kg once daily 6 days	Bioequivalence of 2 formulations of HOE901-U300
PKD12270	18	Lantus	0.4, 0.6 U/kg Single dose	PK/PD in Japanese patients
PDY12335	20	Lantus	Once daily, self-titration; 28 days	PK/PD, CGM in Japanese patients

2.4.2. Pharmacokinetics

The pharmacokinetics of insulin glargine is well known. The assessment of the pharmacokinetics was mainly based on comparative bioavailability between the already marketed product with 100 U/ml and the new formulation with 300 U/ml.

Absorption

After administration of the new formulation in equal doses at *steady state* as insulin glargine 100 U/ml, the rate of absorption is considerably lower but the extent is more a less similar (study 11626). The new formulation shows a flatter concentration-time curve reflecting in a low PTF and fluctuation compared with 100U/ml (see figure below)

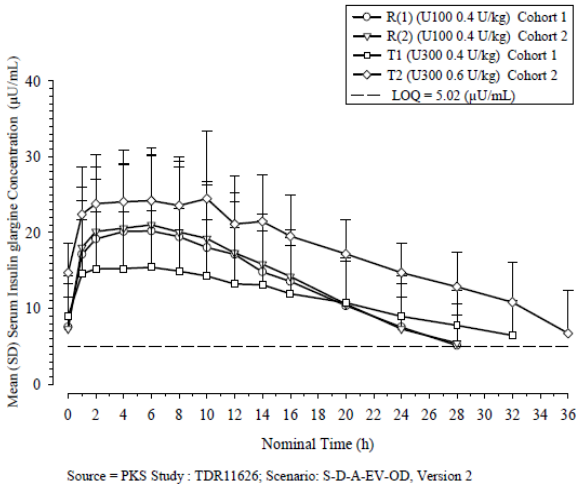


Figure 1 - Mean (± S.D.) insulin glargine concentration time profiles starting with dosing on Day 8 (at steady state) with the old formulation (R) and new formulation (T).

The old formulation of 100 U/ml is not bioequivalent with the new formulation of 300 U/ml after subcutaneous administration of *single equal doses* to healthy subjects (study 10086). The extent of exposure (AUC) after administration of the new formulation with 300 U/ml is only 65% of the exposure after administration of the old formulation of 100 U/ml.

After administration of 0.4 U/kg and 0.6 U/kg of the new formulation (300 U/ml) as single doses (study 11627) to patients with type 1 diabetes, the exposure was nearly similar for the rate as well as for the extent and was half of the value after administration of 0.4 U/kg as insulin glargine 100U/ml. After administration of 0.9 U/kg as the new formulation a comparable exposure was achieved.

The addition of polysorbate to the new formulation (study 13560) did not influence the bioavailability of insulin glargine after subcutaneous administration of 0.4 U/kg. The 90% CI is well within the acceptance range of bioequivalence.

Interactions

No new studies were conducted to evaluate effects of extrinsic factors to support the registration and approval of HOE901-U300. Further information on such studies previously performed and submitted had been assessed in the original marketing application for insulin glargine (HOE901-U100; Lantus [EMEA/H/C/000284] and Optisulin [EMEA/H/C/000309]).

Dose proportionality and time dependencies

With respect to dose proportionality after administration of different doses with the new formulation, no conclusion can be drawn as the absorption from the injection site behaves rather erratic.

After administration of different amount of insulin glargine the following concentration-time curves were determined.

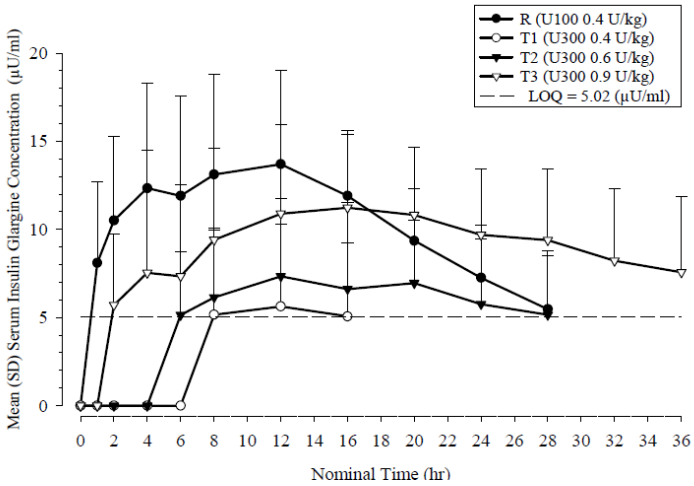


Figure 2 - Mean and S.D plasma concentration- time curves of insulin glargine after subcutaneous administration of three different doses of the new formulation and one dose of the old formulation

Special populations

The lack of studies in special populations is acceptable for this variation.

The studies in Japanese patients did only reveal that the bioavailability between the two different formulations are considerably different and comparable with Caucasian patients. The exposure in Japanese volunteers however is lower. As there is no direct pharmacokinetic comparison, a conclusion on the influence of race is not possible.

2.4.3. Pharmacodynamics

Mechanism of action

Insulin glargine, like human insulin acts via the human insulin receptor system. The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower BG levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

Primary pharmacology

Study PKD10086 (single dose in healthy volunteers) did not demonstrate equivalence in terms of bioavailability or activity between the 300 U/mL and the 100 U/mL solutions for injection, although the 300 U/mL (U300) formulation produced less fluctuation in insulin glargine concentration and activity around the averages compared with the 100 U/mL formulation.

In Study PKD11627 (T1DM) single dose pharmacokinetic and pharmacodynamic profiles for U300 treatments (T_1 to T_3) were flatter and prolonged over the 36 hours observation period as compared to 0.4 U/kg U100 treatment , and the exposure (INS-AUC_{0-36}) and glucose disposal (GIR-AUC_{0-36h}) were lower for matching doses.

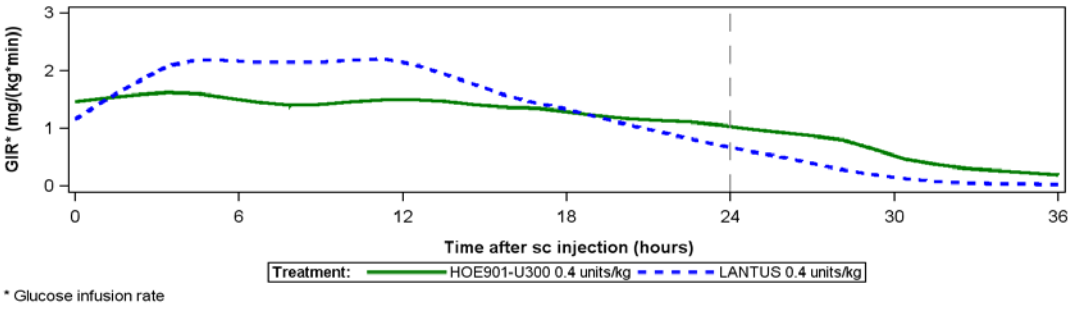
Study TDR11626 investigated the safety and tolerability of 8-day repeated dose regimens at 2 dose levels of U300 (0.4 and 0.6 U/kg/day) and compared their PD and PK properties to those of U100 (0.4 U/kg/day) in a crossover euglycaemic clamp setting in steady state conditions, at the end of each treatment period, in 30 patients with T1DM.

U300 displayed a flatter and more constant serum insulin glargine and glucodynamic profile as compared to Lantus, particularly over the first 24 hours after last dosing.

Insulin glargine exposure was quantifiable in more than 50% of subjects until 32 and 36 hours sampling times post U300 dose, for 0.4 and 0.6 U/kg/day, respectively and U100 was quantifiable until 28 hours post dose. Exposure to insulin glargine and activity was slightly lower within 24 hours with U300 than with U100 with matching doses (INS-AUC_{0-24}; point-estimated treatment ratio 0.83 [90% CI: 0.69 to 1.00)]), with little or no difference within 36 hours (INS-AUC_{0-36}; point-estimated treatment ratio 0.93 [90% CI: 0.77 to 1.12]). The higher dose of U300 produced a correspondingly greater exposure and activity with otherwise similar concentration and activity time profiles.

During the 36-hour clamp period, BG was more tightly controlled and for longer with both doses of U300 than with 0.4 U/kg U100 at or below 110, 130 and 150 mg/dL, as well as at or below the level of euglycaemia (≤105 mg/dL). The end of activity was later for both doses of U300 than for 0.4 U/kg U100.

In addition, the differentiation between parent compound, insulin glargine, and 2 metabolites (M1 and M2) in plasma was generated as supportive data, using a specific LC-MS/MS assay with immunoaffinity enriched metabolites. This analysis confirmed comparable metabolism of insulin glargine regardless of the formulation, with the main metabolite being M1 (21^{A}-Gly-human insulin). Also, steady state (for M1) was reached after 3 to 4 days of treatment with U300 compared with 1 to 2 days with U100.



Local regression smoothing (LOESS), smoothing factor 0.20.

Figure 3 - TDR11626 - 36-hour mean smoothed glucose infusion rate profiles at steady state for 0.4 U/kg U100 and 0.4 U/kg U300

The flatter and prolonged concentration and glucodynamic time profiles observed in study PKD11627 were confirmed in study PKD12270 in Japanese patients with T1DM.

Study PDY12335 was a randomized, open-label, 2-sequence, 2-period, 2-treatment crossover multiple dosing study in 20 Japanese male and female patients with T1DM comparing 24-hour glycaemic profile in CGM between U300 and Lantus at steady state. The mean CGM profiles from Day 2 18:00 to Day 3 24:00 of CGM periods suggest similar BG concentration profiles over time with U300 and U100.

Secondary pharmacology

Of the 100 patients with T1DM participating in the cross-over multiple dose studies of the Phase 1 program and for whom AIA assessments were available, 68 were AIA-negative and 32 AIA-positive prior to treatment. All 32 AIA-positive patients showed cross-reactivity to human insulin. Five patients with a negative AIA status at baseline converted to positive status at the end of the studies. All patients positive prior to treatment remained positive at the end of the studies.

The mean exposure to free insulin glargine for AIA-positive patients receiving U300 or U100 was reduced, and this was more pronounced at a lower dose.

The impact of AIA status on pharmacodynamic responses was less pronounced as on exposure, with no difference between U300 and U100, and became negligible with higher dose.

2.4.4. Discussion on clinical pharmacology

The PD of insulin glargine 300 U/mL (U300) was compared to U100 (Lantus) in 6 phase 1 trials involving 24 healthy subjects and 142 subjects with T1DM using PK assessments and mostly euglycaemic clamps for PD.

The U300 and U100 formulations are not bio-equivalent. The single and multiple dose pharmacokinetic and pharmacodynamic profiles for U300 are flatter and prolonged over the 36 hours observation period as compared to U100.

At steady state with equal doses of the new formulation 300 U/ml and 100 U/ml, the rate of absorption was considerably lower with the new formulation but extent was more or less similar: INS-AUC_{0-24} point-estimated treatment ratio 0.83 (90% CI: 0.69 to 1.00), with little or no difference within 36 hours.

After single dose administration the extent of exposure of the new formulation was only 50-65% of that of 100 U/ml.

Overall it can be concluded that direct switching from the old formulation of 100 U/ml to the new formulation of 300 U/ml with equal doses is not warranted by the pharmacokinetic data after single doses. However, after repeated dosing a lower Cmax is achieved resulting in a less variable plasma-concentration-time curve and a more or less similar extent of exposure.

In all pharmacokinetic studies insulin glargine U300 was administered subcutaneously by injection in the periumbilical area of the abdomen. The SmPC recommends injection in the abdomen wall, the deltoid or the thigh. In the clinical phase 3 studies, no significant differences between HOE901-U300 and U100 was observed in HbA1c or hypoglycaemia when different injections sites (abdomen or thigh) were used. The data for the injection site “upper arm” is scarce but evoke no concern. The same administration recommendations as for Lantus are thus supported.

Further analysis confirmed comparable metabolism of insulin glargine regardless of the formulation, with the main metabolite being M1 (21^{A}-Gly-human insulin). Also, steady state (for M1) was reached after 3 to 4 days of treatment with U300 compared with 1 to 2 days with U100.

In these short-term studies, formation of anti-insulin antibodies was similar between the U100 and U300 formulations. The impact of AIA status on pharmacodynamic responses was less pronounced as on exposure, with no difference between U300 and U100, and became negligible with higher dose.

2.4.5. Conclusions on clinical pharmacology

The new formulation of insulin glargine 300 U/ml is not bioequivalent to the old formulation 100 U/ml. The single and multiple dose pharmacokinetic and pharmacodynamic profiles for U300 are flatter and prolonged over the 36 hours observation period as compared to U100. Direct switching from the old formulation of 100 U/ml to the new formulation of 300 U/ml with equal doses is not warranted by the pharmacokinetic data after single doses. However, after repeated dosing a lower C_{max} is achieved resulting is a less variable plasma-concentration-time curve and a similar extent of exposure.

2.5. Clinical efficacy

Data supporting the efficacy of U300 are based on results from the main 6-month on-treatment period of 4 multinational, open-label, randomized, controlled, Phase 3 studies in patients with T1DM (EFC12456) and T2DM (EFC11628, EFC11629 and EFC12347). In these Phase 3 studies, the objectives were to demonstrate that U300 is as effective as Lantus in terms of HbA_{1c} reduction, and based on the PK/PD profile shown in the euglycaemic clamp studies is associated with a lower risk of hypoglycaemia.

The exploratory Phase 2 study PDY12777 employing CGM provides supportive efficacy data in patients with T1DM. Results from two 3-month administration substudies embedded in the extension periods of studies EFC11628 and EFC11629 in patients with T2DM support the efficacy and safety of U300 when administered at intervals up to 3 hours earlier or later than the patient's usual 24-hour injection interval.

2.5.1. Main studies

An overview of the main studies is presented in Table 3, Table 4 and Table 5.

Table 3 - Overview of Phase 2/3 studies in T1DM

Studies in T1DM	**EFC12456**	**PDY12777**
Phase	3	2 (Exploratory CGM study)
Population	T1DM on basal insulin in combination with mealtime insulin analog	T1DM on basal insulin in combination with mealtime insulin analog
Region	North America, Europe, Japan	USA
Comparator	Lantus	Lantus
Randomization	1:1:1:1 U300 morning injection U300 evening injection Lantus morning injection Lantus evening injection	1:1:1:1 U300 injection sequence: Period A morning → Period B evening Period A evening → Period B morning Lantus injection sequence Period A morning → Period B evening Period A evening → Period B morning
Main Objectives	Efficacy and safety	Efficacy and safety
Route	Once daily SC injection	Once daily SC injection
Injection device:	U300: modified Tactipen Lantus: SoloStar	U300 and Lantus: Half-unit U100-syringe; whole-unit U100-syringe for Lantus doses >30 units
Duration of treatment	6 months (main study period) 6 months comparative extension period[a]	16 weeks (2 x 8 weeks)

Number of patients randomized	U300: 274 Lantus: 275	U300: 30 Lantus: 29

Table 4 - Overview of Phase 3 studies in T2DM

Studies in T2DM	**EFC11628**	**EFC11629**	**EFC12347**
Phase	3	3	3
Population	T2DM on basal insulin in combination with mealtime insulin analog	T2DM on basal insulin in combination with OAD	Insulin-naïve T2DM not adequately controlled on non-insulin AHA
Region	North America, South America, Europe, South Africa	North America, South America, Europe, South Africa	North America, Europe, Japan
Comparator	Lantus	Lantus	Lantus
Randomization	1:1	1:1	1:1
Main Objectives	Efficacy and safety	Efficacy and safety	Efficacy and safety
Route	Once daily SC injection	Once daily SC injection	Once daily SC injection
Injection device	U300:modified Solostar Lantus: Solostar	U300: modified Solostar Lantus: Solostar	U300: modified Tactipen Lantus: Solostar
Duration of treatment	6 months (main study period) 6 months comparative extension period (a)	6 months (main study period) 6 months comparative extension period (a)	6 months (main study period) 6 months comparative extension period (a)
Number of patients randomized	U300: 404 Lantus: 403	U300: 404 Lantus: 407	U300: 439 Lantus: 439

a Extension period ongoing at the time of the dossier cut-off date; results of safety extension periods not included in the dossier; OAD = oral antihyperglycaemic drugs

Table 5 - Overview of Phase 3 sub-studies in T2DM

3-month substudies	**EFC11628**	**EFC11629**
Patient population:	Patients randomized and treated with U300 during the main study period	Patients randomized and treated with U300 during the main study period
Comparison	U300 injection intervals at fixed 24-hour intervals at intervals of 24±3 hours	U300 injection intervals at fixed 24-hour intervals at intervals of 24±3 hours
Randomization	1:1	1:1
Objective:	Efficacy and safety	Efficacy and safety
Duration:	3 months (Month 6 – Month 9 extension period)	3 months (Month 6 – Month 9 extension period)
Number of patients randomized	Fixed intervals: 53 Adaptable intervals:56	Fixed intervals: 44 Adaptable intervals: 45

Methods

The 4 Phase 3 studies were multinational, multicenter, open-label, centrally randomized, comparative, parallel group studies, each comprising a 6-month main study period followed by a 6-month comparative safety extension period. The studies EFC11628 and EFC11629 also included a 4-week post-treatment follow-up period after completion of the 52-week study duration. The active control was Lantus in all studies. The studies utilized a common core protocol that standardized most

aspects of the study design, including the comparator Lantus (insulin glargine 100 U/mL), 1:1 randomization, stratification by screening HbA_{1c} (<8.0% versus ≥8.0%), inclusion/exclusion criteria, targets for fasting pre-breakfast self-monitored plasma glucose (SMPG), recommendations for dosing of U300 and Lantus, primary and secondary efficacy variables and safety variables, including the definitions used for the hypoglycaemia categories and analyses. All 4 Phase 3 studies were designed to show noninferiority of U300 versus Lantus based on the change in HbA_{1c} from baseline to endpoint at Month 6 with a noninferiority margin of 0.4% HbA_{1c}.

In both studies in T1DM (EFC12456, PDY12777) patients were randomized to morning or evening injections of U300 and Lantus to evaluate the efficacy and safety of different injection times of U300. Study PDY12777 was an exploratory, open-label, randomized, parallel-group Phase 2 study to compare the efficacy and safety of U300 and Lantus in patients with T1DM using CGM parameter. Within each treatment group of U300 or Lantus the sequence of the injection time of the basal insulin during the 8-week study period A followed by 8-week study period B was assigned by randomization (morning-evening or evening-morning; 1:1). The study consisted of an up to 4-week screening and training period, a treatment period of 2 x 8 weeks, and a 4-week post-treatment follow-up period. The primary endpoint was the percentage of time in glucose range 4.4 to 7.8 mmol/L (80 to 140 mg/dL) as measured by CGM during the last 2 weeks of both 8-week treatment periods.

The efficacy and safety of U300 when injected at intervals of up to 3 hours earlier or later than the patient's usual once daily injection time was evaluated in 2 substudies embedded in the extension periods of studies EFC11628 and EFC11629 in T2DM. Both substudies were open-label, randomized (1:1), 3-month studies in patients who were randomized and treated with U300 during the main study periods and had completed the 6-month study visit.

All studies comprised an up to 2-week screening period, during which the patients' eligibility criteria were checked and patients were trained on study procedures such as regular SMPG measurements and diary entries. The duration of the pivotal efficacy studies was 6 months (main study periods). The 6-month main study period duration with a "treat-to-target" dosing schedule of the insulin is considered to be sufficient for achieving glycaemic control with U300 or Lantus after changing over from the pre-study basal insulin or initiating basal insulin in previously insulin-naïve patients. The 6-month period enabled an adequate assessment of the changes in HbA_{1c} and the concomitant risk of hypoglycaemia during both the initial period after changing to a new insulin regimen, when most of the adjustment to the insulin dose occurred, and the maintenance period, when only minor refinements of the insulin dose were made.

Study participants

Separate studies were done in T1DM and T2DM due to the different underlying pathophysiologies. Three studies were done in T2DM to cover the broad spectrum of this patient population, including insulin-naïve patients not adequately controlled on non-insulin AHA and requiring insulin, patients already treated with basal insulin in combination with OAD, and patients requiring basal and mealtime insulin for glycaemic control. Adult patients at least 18 years of age with a screening HbA1c in the range of ⩾7.0 to ⩽10.0% for insulin-pretreated patients (EFC11628, EFC11629, EFC12456) and ⩽ 9.0% (PDY12777) or ⩾7.0 to ⩽11.0% in insulin-naïve patients (EFC12347) were eligible for the studies. Patients with T1DM had to be on basal insulin in combination with a mealtime insulin for at least one year, insulin-naïve T2DM patients had to have a known history of T2DM for at least one year and pretreatment with non-insulin AHA for 6 months and sulfonylurea and glinides were to be discontinued at baseline

(EFC12347). T2DM patients pretreated with basal insulin in combination with OAD had to be receiving this insulin regimen for at least 6 months (EFC11629) and patients with T2DM on basal insulin in combination with a mealtime insulin had to be on this regimen for at least 1 year (EFC11628). In studies EFC11628 and EFC11629 in T2DM patients pretreated with basal insulin the daily basal insulin dose had to be at least 42 U.

Study inclusion and exclusion criteria for selecting the patient population were as unrestrictive as possible across the studies to reflect the general population of patients with diabetes mellitus. Only patients with concomitant illnesses or medications that could limit the ability of patients to safely complete the study periods, confound the evaluation of study findings, or that conformed to potential contraindications of insulin therapy, were excluded.

Objectives

The **primary efficacy objective** of the Phase 3 studies was to demonstrate noninferiority of U300 versus Lantus on glycaemic control in adults as measured by:

- EFC12456 (T1DM) and EFC11628, EFC11629, and EFC12347 (all T2DM): change in glycated HbA1c from baseline to endpoint (Month 6) measured in a central laboratory. The studies were designed to show noninferiority of U300 versus Lantus with a noninferiority margin of 0.4% HbA1c.
- Substudies EFC11628 and EFC11629 (T2DM): change in HbA1c from Month 6 (baseline of substudy) to Month 9 (endpoint of substudy).

The **secondary efficacy objectives** for the Phase 3 studies were to compare U300 and Lantus on Nocturnal hypoglycaemia, Pre-injection plasma glucose, Variability of pre-injection plasma glucose Fasting plasma glucose (FPG), % patients overall and without hypoglycaemia reaching HbA1c <7%, % patients reaching FPG target overall and without hypoglycaemia FPG targets (<5.6 mmol/L (100 mg/dL) in studies in T2DM and <7.2 mmol/L, (130 mg/dL) in T1DM), 8-point SMPG profiles (taken at 03:00 hours, before and 2 hours after each main meal, and at bedtime), 24-hour average plasma glucose and variability of 24-hour average plasma glucose.

Outcomes / endpoints

Primary endpoint

In the 4 pivotal Phase 3 studies, the primary efficacy endpoint was change from baseline to endpoint (Month 6) in HbA_{1c}. Noninferiority was tested with a noninferiority margin of 0.4% HbA_{1c}, which was in agreement with the guidance documents of the key regulatory agencies at the time of planning the Phase 3 program. The change in HbA_{1c} from baseline to endpoint (Month 6) was analyzed using a Mixed Model for Repeated Measurements (MMRM) approach under the missing at random framework in the 4 pivotal studies, but was also analyzed using Last Observation Carried Forward (LOCF) imputation in the CSRs for EFC11628 and EFC11629. The primary efficacy analysis was based on the modified intent-to-treat (mITT) population. The mITT population was defined as all randomized patients who received at least one dose of open-label U300 or Lantus study medication, and who had both a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy endpoint.

Secondary endpoints

Secondary endpoints included percentage of patients experiencing at least one nocturnal hypoglycaemia from start of Week 9 to Month 6, severe hypoglycaemia and hypoglycaemia documented by SMPG ≤3.9 mmol/L (70 mg/dL), pre-injection plasma glucose, fasting plasma glucose (FPG), 8-point SMPG profiles, fasting pre-breakfast SMPG and insulin doses.

Statistical methods

In order to investigate the clinical correlates of the flatter profile and longer duration of action of U300 compared with Lantus in the Phase 1 PK/PD studies, 3 main secondary efficacy endpoints were pre-specified in the protocols of the 3 Phase 3 studies in T2DM (EFC11628, EFC11629, EFC12347). Superiority of U300 over Lantus was tested in a pre-specified order of priority only if noninferiority of U300 versus Lantus was demonstrated for the primary endpoint (hierarchical testing strategy). This stepwise closed testing procedure stopped as soon as a test for an endpoint was found not statistically significant. The hypotheses of “less nocturnal hypoglycaemia” and “more sustained duration of action” were sequentially tested in terms of a lower incidence of nocturnal hypoglycaemia, a larger

decrease and lower variability of pre-basal insulin injection plasma glucose. These main secondary efficacy endpoints were not part of a hierarchical testing procedure in study EFC12456 in T1DM, but assessed as other secondary efficacy endpoints.
For the 2 Phase 3 studies (EFC11629 and EFC12347) with non-insulin AHA as background therapy, a meta-analysis based on pooled efficacy data from the main 6-month on-treatment period was also performed.

Results

Participant flow

The distribution of missing data patterns of HbA_{1c} and number of patients excluded from primary efficacy analysis in each treatment group are presented per study with associated reasons (Figure 4, Figure 5, Figure 6, Figure 7).
No differences between U300 and Lantus were found for demographics and baseline characteristics across missing data patterns of $HbA_{1c.}$ Nor was there any difference between treatment groups within each missing data pattern.

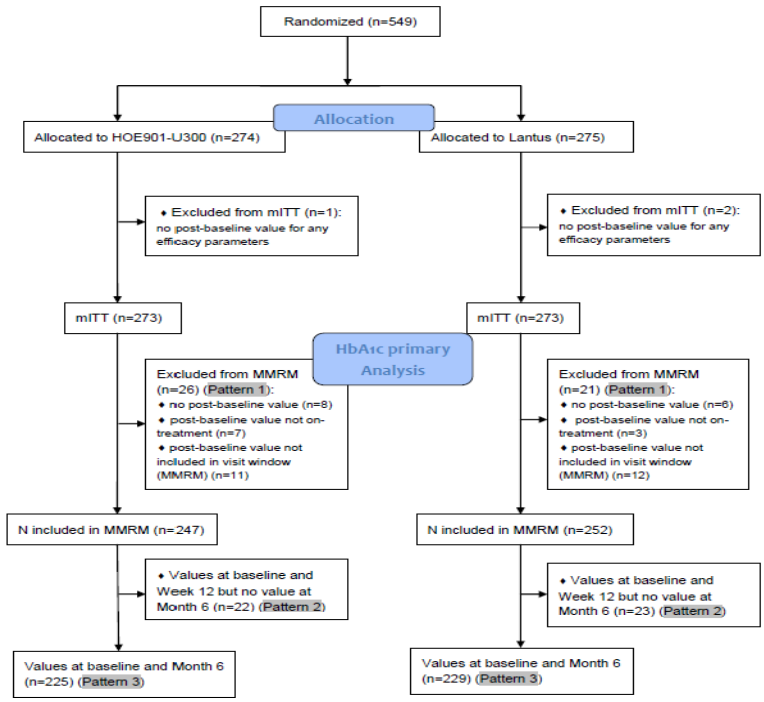


Figure 4 - Disposition of patients in trial EFC12456

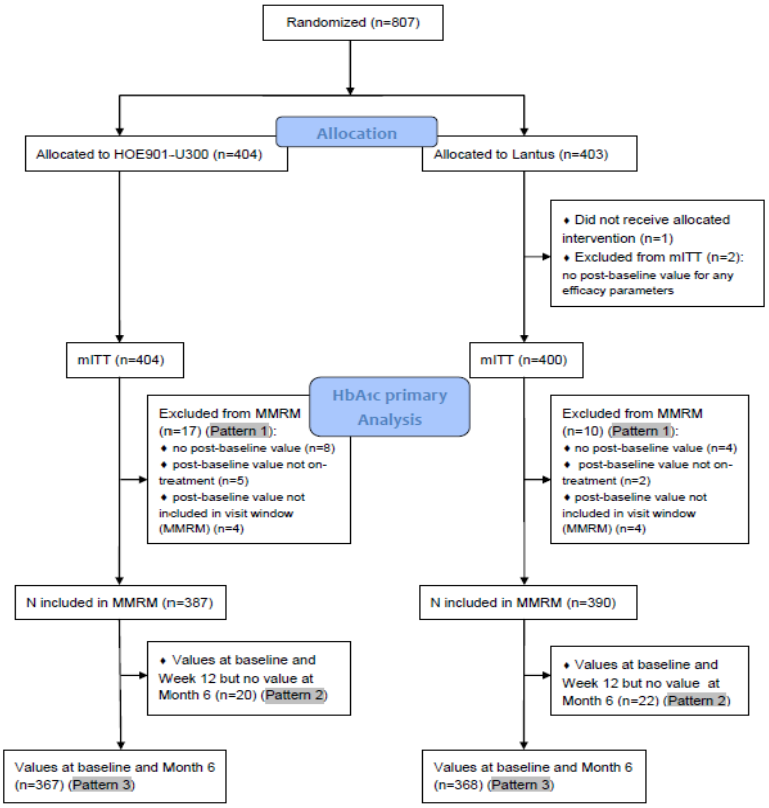


Figure 5 - Disposition of patients in trial EFC11628

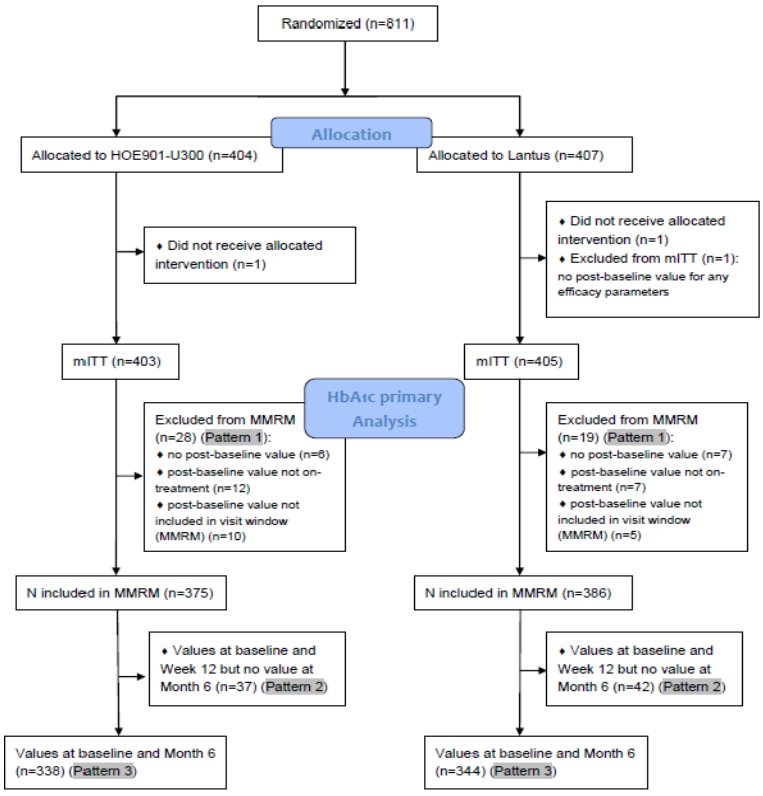


Figure 6 - Disposition of patients in trial EFC11629

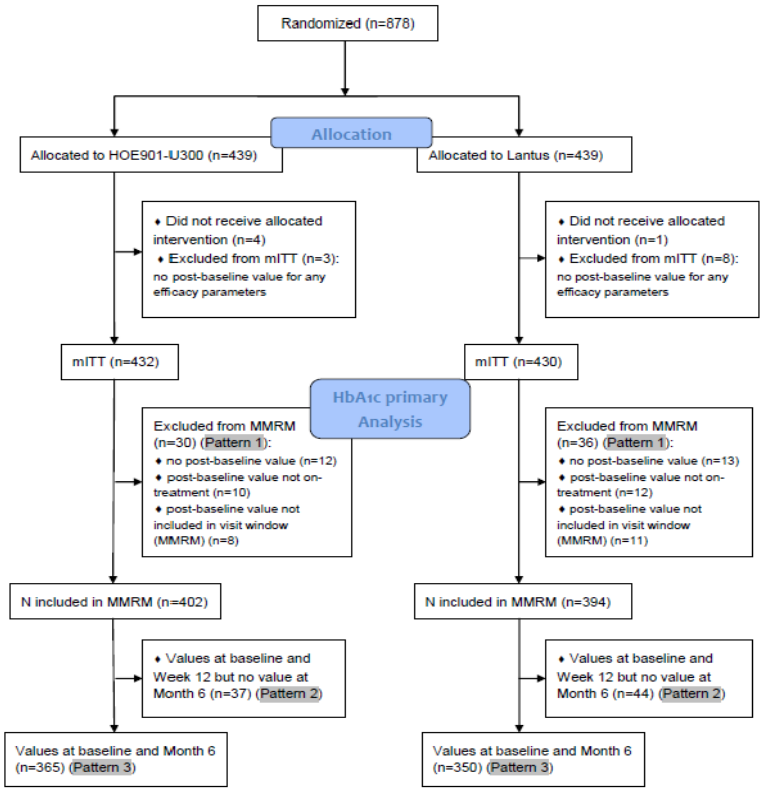


Figure 7 - Disposition of patients in trial EFC12347

Baseline data

All Phase 2/3 studies were well balanced regarding the baseline characteristics. The studies included 608 randomized patients with T1DM and 2496 randomized patients with T2DM; 719 (23.2%) patients were aged 65 years or older, 1872 (75.0%) patients with T2DM had a body mass index (BMI) of at least 30 kg/m² and 495 (15.9%) patients had some degree of renal impairment (GFR [MDRD] ≤60 mL/min). The majority of the patients were Caucasian/white (n=2717; 87.5%), other ethnicities were represented by n=210 (6.8%) Black, n=144 (4.6%) Asian/Oriental, and n=463 (14.9%) Hispanic (Table 6). Geographical areas included North America, South America, Europe, South Africa, and Japan. Overall, patients treated in the 4 pivotal Phase 3 studies adequately represent the patient population who might be expected to receive U300 when marketed after approval.

Table 6 - Summary of study populations

	T1DM		T2DM		
	EFC12456	**PDY12777**	**EFC11628**	**EFC11629**	**EFC12347**
Number of patients randomized	N=549	N=59	N=807	N=811	N=878
Age (years; mean SD)	47.3 (13.7)	44.2 (14.3)	60.0 (8.6)	58.2 (9.2)	57.7 (10.1)
≥ 65 years (%)	55 (10.0%)	2 (3.4%)	246 (30.4%)	190 (23.4%)	226 (25.7)
Male, N (%)	313 (57.0%)	32 (54.2%)	427 (52.9%)	372 (45.9%)	507 (57.7%)
Weight (kg; mean,SD)	81.8 (18.7)	82.1 (17.3)	106.3 (20.8)	98.3 (21.6)	95.3 (22.9)
BMI (kg/m² mean; SD)	27.6 (5.1)	27.3 (5.3)	36.6 (6.4)	34.8 (6.4)	33.0 (6.7)
≥ 30 kg/m²	153 (27.9%)	16 (27.1%)	699 (86.6%)	614 (75.7%)	559 (63.6%)
GFR (MDRD) < 60 mL/min/1.73m²	67 (12.2%)	7 (11.9%)	188 (23.3%)	114 (14.1%)	119 (13.6%)
Duration of diabetes (years; mean SD)	21.0 (12.9)	22.1 (13.8)	15.8 (7.5)	12.6 (7.0)	9.8 (6.4)
≥ 10 years	431 (78.9%)	45 (76.3%)	633 (78.4%)	501 (61.9%)	372 (42.7%)
Total insulin dose prior to study (U/kg; mean) in the last 7 days prior to randomization	0.719 (0.262)	0.603 (0.193)	1.197 (0.466)	0.671 (0.238)	NA
Caucasian/white	467 (85.1%)	59 (100%)	745 (92.3%)	761 (93.8%)	685 (78.0%)
Asian/Oriental	47 (8.6%)	-	11 (1.4%)	10 (1.2%)	76 (8.7%)
Black	26 (4.7%)	-	47 (5.8%)	36 (4.4%)	101 (11.5%)
Hispanic	26 (4.7%)	-	51 (6.3%)	193 (23.8%)	193 (22.0%)

SD=Standard deviation; N=number; GFR= Glomerular filtration rate; MDRD= Modification of diet in renal disease (MDRD) formula; NA = not applicable.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7 - Summary of efficacy for trial EFC12456

Title: A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus Injected in the Morning or Evening in Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period		
Study identifier	EFC12456 (EudraCT: 2012-001524-35)	
Design	This was a Phase 3, 6-month, multicenter, multinational, open-label, randomized, 4-arm parallel-group study followed by a 6-month safety extension period to compare the efficacy and safety of HOE901-U300 and Lantus morning and evening injection in patients with T1DM, and HbA_{1c} in the range of 7% to 10%, who had been on a basal plus mealtime insulin regimen for at least 1 year. Patients were randomized to receive either HOE901-U300 or Lantus as a morning or evening injection (randomization ratio 1:1:1:1). Randomization was stratified by HbA_{1c} obtained at the screening visit (<8.0%, ≥8.0%) and geographical region (Non-Japan; Japan). "Morning" was defined as any time immediately prior to breakfast until lunch and "evening" as any time immediately prior to the evening meal until bedtime.	
	Screening period Main treatment phase Safety extension period Post-treatment follow-up	Up to 2 weeks 6 months 6 months 2 days
Statistical methods	A stepwise closed testing approach was used for the primary efficacy variable to assess noninferiority and superiority sequentially. To assess noninferiority, the upper bound of the two-sided 95% CI for the difference in the mean change in HbA_{1c} from baseline to endpoint between HOE901-U300 overall and Lantus overall was compared with the predefined noninferiority margin of 0.4% HbA_{1c}, a value <0.4% demonstrated noninferiority. If noninferiority was demonstrated, superiority of HOE901-U300 overall over Lantus overall was tested. The superiority of HOE901-U300 overall over Lantus overall was demonstrated if the upper bound of the two-sided 95% CI for the difference in the mean change in HbA_{1c} from baseline to endpoint between HOE901-U300 overall and Lantus overall on mITT population was <0 (zero).	
Treatment groups	HOE901-U300 (insulin glargine, 300 U/mL), modified Tactipen, SC injection every 24 hours in the morning or evening; patients were to continue using their mealtime insulin 274 patients randomized 136 to morning injection 138 to evening injection)	HOE901-U300 starting dose was based on dose of prior total basal insulin and fasting (prebreakfast) SMPG at baseline. Titration to achieve fasting (prebreakfast) SMPG in the range of 4.4 to 7.2 mmol/L (80 to 130 mg/dL) without hypoglycaemia. The titration of mealtime insulin aimed to achieve a 2-hour postprandial SMPG of <8.9 mmol/L (160 mg/dL) while avoiding hypoglycaemia.
	Lantus (insulin glargine 100 U/mL), Solostar, SC injection every 24 hours in the morning or evening; patients were to continue using their mealtime insulin 275 patients randomized: 137 to morning injection 138 to evening injection	Same as HOE901-U300

Title: A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus Injected in the Morning or Evening in Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period		
Study identifier	EFC12456 (EudraCT: 2012-001524-35)	
Endpoints and definitions	Primary efficacy endpoint	
	Change in HbA_{1c} (%)	Change from baseline to (Month 6) in patients with T1DM
	Secondary efficacy endpoints	
	Nocturnal hypoglycaemia	Incidence (%) of patients with at least 1 nocturnal hypoglycaemia, indicated as severe and/or confirmed by plasma glucose ≤3.9 mmol/L (70 mg/dL) that occurred between 00:00 and 05:59 hours, from start of Week 9 to Month 6
	Pre-injection SMPG (mmol/L)	Change in pre-injection SMPG (mmol/L) (obtained within 30 minutes prior to injection of study drug; mean over last 7 days values) from baseline to endpoint (Month 6)
	Variability of pre-injection SMPG (%)	Change in variability of pre-injection SMPG (obtained within 30 minutes prior to injection of study drug; coefficient of variation over last 7 days values) from baseline to endpoint (Month 6)
	Number (%) of patients with target HbA_{1c} <7%	at Month 6 at Month 6 and having experienced no hypoglycaemia event, indicated as severe and/or confirmed by plasma glucose <3.0 mmol/L (54 mg/dL) that occurred during the last 3 months of the main 6-month on-treatment period - any time of the day - between 00:00 and 05:59 hours
	Number (%) of patients with target HbA_{1c} ≤6.5%	at Month 6
	Number (%) of patients with FPG <5.6 mmol/L (100 mg/dL) / FPG <7.2 mmol/L (130 mg/dL)	at Month 6 at Month 6 and having experienced no hypoglycaemia event, indicated as severe and/or confirmed by plasma glucose <3.0 mmol/L (54 mg/dL) that occurred during the last 3 months of the main 6-month on-treatment period - any time of the day - between 00:00 and 05:59 hours
	24-hour plasma glucose (mmol/L)	Change of mean 24-hour plasma glucose based on 8-point SMPG, from baseline to endpoint (Month 6)
	Variability of 24-hour plasma glucose (mmol/L)	Change in variability of 24-hour plasma glucose based on 8-point SMPG
	Daily average total (basal + mealtime) insulin dose (U/kg)	Change in daily average total (basal + mealtime) insulin dose from baseline to Month 6
Results and Analysis		
Analysis description	**Primary Analysis**	

Title: A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus Injected in the Morning or Evening in Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period				
Study identifier	EFC12456 (EudraCT: 2012-001524-35)			
Analysis population and time point description	Modified intention-to-treat (mITT) population – change from baseline to endpoint (Month 6, MMRM0)			
Descriptive statistics, point estimate and effect estimate	Primary endpoint	Comparison groups	HOE901-U300 (N=273)	Lantus (N=273)
	HbA_{1c} (%)	N	225	229
		Endpoint (Month 6): Mean (SD)	7.70 (0.99)	7.68 (0.80)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-0.40 (0.051) [-0.501 to -0.299]	-0.44 (0.051) [-0.543 to -0.344]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 overall versus Lantus overall [95% CI]	0.04 (0.072) [-0.098 to 0.185]	
	Secondary analysis of primary endpoint HbA_{1c} (%)	Change from baseline to endpoint (Month 6): LS mean difference (SE) for morning injection: HOE901-U300 versus Lantus [95% CI]	-0.07 (0.102) [-0.265 to 0.135]	
		Change from baseline to endpoint (Month 6): LS mean difference (SE) for evening injection: HOE901-U300 versus Lantus [95% CI]	0.15 (0.102) [-0.049 to 0.352]	
		Change from baseline to endpoint (Month 6): LS mean (SE) for HOE901-U300: morning versus evening injection [95% CI]	-0.15 (0.102) -0.353 to 0.049]	

Title: A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus Injected in the Morning or Evening in Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period					
Study identifier	EFC12456 (EudraCT: 2012-001524-35)				
	Secondary endpoints		Comparison groups	HOE901-U300 (N=273)	Lantus (N=273)
	Severe and/or confirmed nocturnal hypoglycaemia between start of Week 9 and Month 6		n (%)	162 (59.3)	153 (56.0)
			RR [95% CI] versus Lantus0	1.06 [0.92 to 1.23]	
		Average pre-injection SMPG (mmol/L)	N	117	105
			Month 6: Mean (SD)	9.07 (2.63)	9.29 (2.37)
			Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-1.16 (0.223) [-1.604 to -0.725]	-0.82 (0.233) [-1.277 to -0.357]
			Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 overall versus Lantus overall [95% CI]	-0.35 (0.322) [-0.982 to 0.287]	
		Average pre-injection SMPG (mg/dL)	N	117	105
			Month 6: Mean (SD)	163.40 (47.38)	167.37 (42.75)
			Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-20.97 (4.017) [-28.889 to -13.060]	-14.72 (4.206) [-23.003 to -6.428]
			Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 overall versus Lantus overall [95% CI]	-6.26 (5.799) [-17.686 to 5.168]	
	Variability of pre-injection SMPG (%)		N	117	105
			Month 6: Mean (SD)	30.66 (13.26)	30.60 (13.97)
			Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-3.03 (1.573) [-6.131 to 0.066]	-1.76 (1.651) [-5.014 to 1.491]

Title: A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus Injected in the Morning or Evening in Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period				
Study identifier	EFC12456 (EudraCT: 2012-001524-35)			
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 overall versus Lantus overall [95% CI]	1.27 (2.266) [-5.735 to 3.193]	
	Number (%) of patients at Month 6	HbA_{1c} <7%	46 (16.8)	41 (15.0)
		HbA_{1c} <7% and no emergent severe or confirmed hypoglycaemia	17 (6.2)	16 (5.9)
		HbA_{1c} <7% and no nocturnal emergent severe or confirmed hypoglycaemia	30 (11.0)	29 (10.6)
		HbA_{1c} ≤6.5%	22 (8.1)	15 (5.5)
	Number (%) of patients at Month 6	FPG <5.6 mmol/L (100 mg/dL)	27 (9.9)	35 (12.8)
		FPG <5.6 mmol/L (100 mg/dL) and no emergent severe or confirmed hypoglycaemia	9 (3.3)	12 (4.4)
		FPG <5.6 mmol/L (100 mg/dL) and no nocturnal emergent severe or confirmed hypoglycaemia	22 (8.1)	29 (10.6)
		FPG <7.2 mmol/L (130 mg/dL)	69 (25.3)	70 (25.6)
	Variability of 24-hour plasma glucose based on 8-point SMPG (%)	Change from baseline to endpoint (Month 6): LS mean [95% CI]	-3.92 (1.132) [-6.148 to -1.699]	-2.87 (1.116) [-5.062 to -0.673]
		At endpoint (Month 6): LS mean difference between HOE901-U300 overall and Lantus overall [95% CI]	-1.06 [-4.180 to 2.068]	
	Mean daily total (basal + mealtime) insulin dose (U/kg)	Month 6 OC	0.81	0.73
		Mean change from baseline	0.19	0.10

Title: A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus Injected in the Morning or Evening in Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period	
Study identifier	EFC12456 (EudraCT: 2012-001524-35)
CI: confidence interval, CMH: Cochran-Mantel-Haenszel, FPG: fasting plasma glucose, HbA_{1c}: glycated hemoglobin A_{1c}, LS: least squares, mITT: modified intention-to-treat, MMRM: mixed-model for repeated measurements, N: number of randomized patients, n: number of patients with measurements, OC: Observed Case, SC: subcutaneous, SD: standard deviation, SE: standard error, SMPG: self-monitored plasma glucose, T1DM: type 1 diabetes mellitus, RR: relative risk MMRM analysis with randomized groups (HOE901-U300 morning injection, HOE901-U300 evening injection, Lantus morning injection and Lantus evening injection), randomization strata of screening HbA_{1c} (<8.0, ≥8.0%),randomization strata of geographical region (Non-Japan; Japan), visit (Week 12, Month 6) and visit-by-randomized groups interaction as fixed categorical effects as well as baseline HbA_{1c} value and baseline HbA_{1c}-by-visit interaction as continuous fixed covariates Based on relative risk stratified by randomization strata of screening HbA_{1c} (<8.0, ≥8.0%),randomization strata of geographical region (Non-Japan; Japan), and time of injection (morning, evening) using a CMH methodology	

Table 8 - Summary of efficacy for trial EFC11628

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period		
Study identifier	EFC11628 (EudraCT: 2010-023769-23)	
Design	This was a Phase 3, 6-month, multicenter, randomized, open-label, parallel-group study followed by a 6-month safety extension period to compare the efficacy and safety of HOE901-U300 and Lantus in patients with T2DM, and HbA_{1c} in the range 7% to 10%, injecting at least 42 U Lantus or equivalent NPH insulin. As there were no generally accepted recommendations for the switch from insulin detemir to insulin glargine, insulin detemir was considered a prohibited prior medication in the last 3 months before screening visit for T2DM patients on previous insulin treatment. Patients were randomized in a 1:1 ratio to receive either HOE901-U300 or Lantus. The randomization was stratified by screening HbA_{1c} value (<8%, ≥8%).	
	Screening period Main treatment phase Safety extension period Post-treatment follow-up	2 weeks 6 months 6 months 4 weeks
Statistical methods	A stepwise closed testing approach was used for the primary efficacy variable to assess noninferiority and superiority sequentially. To assess noninferiority, the upper bound of the two-sided 95% CI for the difference in the mean change in HbA_{1c} from baseline to endpoint between HOE901-U300 and Lantus was compared with the predefined noninferiority margin of 0.4% HbA_{1c}, a value <0.4% demonstrates noninferiority. If noninferiority was demonstrated, superiority of HOE901-U300 over Lantus was tested. The superiority of HOE901-U300 over Lantus was demonstrated if the upper bound of the two-sided 95% CI for the difference in the mean change in HbA_{1c} from baseline to endpoint between HOE901-U300 and Lantus on mITT population was <0 (zero).	

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period			
Study identifier	EFC11628 (EudraCT: 2010-023769-23)		
Treatment groups	HOE901-U300 (insulin glargine, 300 U/mL), modified Solostar, SC injection every 24 hours in the evening; patients were to continue using their mealtime insulin 404 patients randomized	HOE901-U300 starting dose was based on dose of prior total basal insulin and fasting (prebreakfast) SMPG at baseline. Titration to achieve fasting (prebreakfast) SMPG in the range of 4.4 to 5.6 mmol/L (80 to 100 mg/dL) without hypoglycaemia. The titration of mealtime insulin aimed to achieve a 2-hour postprandial SMPG of <8.9 mmol/L (160 mg/dL) while avoiding hypoglycaemia.	
	Lantus (insulin glargine 100 U/mL), Solostar, SC injection every 24 hours in the evening; patients were to continue using their mealtime insulin 403 patients randomized	Same as HOE901-U300	
Endpoints and definitions	Primary efficacy endpoint		
	Change in HbA_{1c} (%)	Change from baseline to endpoint (Month 6) in patients with T2DM	
	Secondary efficacy endpoints		
	Nocturnal hypoglycaemia	Incidence (%) of patients with at least 1 nocturnal hypoglycaemia, indicated as severe and/or confirmed by plasma glucose ≤3.9 mmol/L (70 mg/dL) that occurred between 00:00 and 05:59 hours, from start of Week 9 to endpoint (Month 6)	
	Pre-injection SMPG (mmol/L)	Change in pre-injection SMPG from baseline to endpoint (Month 6) obtained within 30 minutes prior to injection of study drug mean value over last 7 days	
	Variability of pre-injection SMPG (%)	Change in variability from baseline to endpoint (Month 6) of pre-injection SMPG obtained within 30 minutes prior to injection of study drug (coefficient of variation of values over last 7 days)	
	Other secondary efficacy endpoints		
	Number (%) of patients with target HbA_{1c} <7%	at endpoint (Month 6) at endpoint (Month 6) and having experienced no hypoglycaemia event, indicated as severe and/or confirmed by plasma glucose <3.0 mmol/L (54 mg/dL) that occurred during the last 3 months of the main 6-month on-treatment period any time of the day - between 00:00 and 05:59 hours	
	Number (%) of patients with target HbA_{1c} ≤6.5%	at endpoint (Month 6)	

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period				
Study identifier	EFC11628 (EudraCT: 2010-023769-23)			
	Number (%) of patients with FPG <5.6 mmol/L (100 mg/dL) / FPG ≤6.7 mmol/L (120 mg/dL)	at endpoint (Month 6) at endpoint (Month 6) and having experienced no hypoglycaemia event, indicated as severe and/or confirmed by plasma glucose <3.0 mmol/L (54 mg/dL) that occurred during the last 3 months of the main 6-month on-treatment period any time of the day - between 00:00 and 05:59 hours		
	24-hour plasma glucose (mmol/L)	Change of mean 24-hour plasma glucose based on 8-point SMPG, from baseline to endpoint (Month 6)		
	Variability of 24-hour plasma glucose (mmol/L) (%)	Change in variability of 24-hour plasma glucose based on 8-point SMPG		
	Daily average total (basal + mealtime) insulin dose (U/kg)	Change in daily average total insulin dose from baseline to endpoint (Month 6)		
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Modified intention-to-treat (mITT) population – change from baseline to endpoint (Month 6, LOCF)			
Descriptive statistics, point estimate, and effect estimate	Primary endpoint	Comparison groups	HOE901-U300 (N=404)	Lantus (N=400)
	HbA_{1c} (%)	N	391	394
		Endpoint (Month 6): Mean (SD)	7.25 (0.85)	7.28 (0.92)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-0.83 (0.060) [-0.946 to -0.709]	-0.83 (0.061) [-0.944 to -0.706]
		Change from baseline to endpoint (Month 6):LS mean difference (SE) HOE901-U300 versus Lantus [95% CI]	-0.00 (0.056) [-0.112 to 0.107]	
	Severe and/or confirmed nocturnal hypoglycaemia between start of Week 9 and endpoint (Month 6)	N	404	400
		n (%) with at least 1 nocturnal hypoglycaemia	146 (36.1)	184 (46.0)
		RR [95% CI] versus Lantus	0.79 [0.67 to 0.93]	
		p-value (CMH)	0.0045	
	Average	N	365	360

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period				
Study identifier	EFC11628 (EudraCT: 2010-023769-23)			
	pre-injection SMPG (mmol/L)	Endpoint (Month 6) Mean (SD)	9.10 (2.42)	9.27 (2.44)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-0.90 (0.182) [-1.260 to -0.544]	-0.84 (0.182) [-1.196 to -0.480]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI]	-0.06 (0.162) [-0.383 to 0.254]	
		p-value (ANCOVA)	0.6909	
	Average pre-injection SMPG (mg/dL)	N	365	360
		Endpoint (Month 6): Mean (SD)	163.98 (43.56)	167.02 (44.05)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-16.25 (3.284) [-22.701 to -9.807]	-15.09 (3.284) [-21.541 to -8.645]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI]	-1.16 (2.920) [-6.895 to 4.571]	
		p-value (ANCOVA)	0.6909	
	Variability of pre-injection SMPG (%)	N	365	360
		Endpoint (Month 6): Mean (SD)	22.21 (11.75)	21.60 (11.52)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-1.10 (1.222) [-3.502 to 1.295]	-1.08 (1.222) [-3.476 to 1.324]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI]	-0.03 (1.087) [-2.161 to 2.107]	
	Other secondary endpoints			
	Number (%) of patients at endpoint (Month 6)	N	365	360
		HbA_{1c} <7%	155 (39.6)	161 (40.9)
		HbA_{1c} <7% and no emergent severe or confirmed hypoglycaemia	100 (25.4)	97 (24.6)

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period				
Study identifier	EFC11628 (EudraCT: 2010-023769-23)			
		HbA_{1c} <7% and no nocturnal emergent severe or confirmed hypoglycaemia	139 (35.5)	144 (36.5)
		HbA_{1c} ≤6.5%	82 (21.0)	85 (21.6)
	Number (%) of patients at endpoint (Month 6)	FPG <5.6 mmol/L (100 mg/dL)	103 (26.5)	91 (23.2)
		FPG <5.6 mmol/L (100 mg/dL) and no emergent severe or confirmed hypoglycaemia	64 (16.3)	57 (14.5)
		FPG <5.6 mmol/L (100 mg/dL) and no nocturnal emergent severe or confirmed (<3.0 mmol/L;<54mg/dL) hypoglycaemia	86 (22.1)	79 (20.2)
		FPG ≤6.7 mmol/L (120 mg/dL)	180 (46.3)	176 (44.9)
	24-hour plasma glucose based on 8-point SMPG (mmol/L)	Change from baseline to endpoint (Month 6)	-0.987 (-17.789)	-1.073 (-19.338)
	Variability of 24-hour plasma glucose based on 8-point SMPG (%)	Change from baseline to endpoint (Month 6): LS mean [95% CI]	-2.26 [-4.474 to -0.052]	-0.33 [-2.559 to 1.893]
		At endpoint (Month 6): LS mean difference HOE901-U300 versus Lantus [95% CI]	-1.93 [-3.913 to 0.053]	
	Mean daily total (basal + mealtime) insulin dose (U/kg)	Month 6 OC	1.54	1.43
		Mean change from baseline	0.35	0.27
ANCOVA: analysis of covariance, CI: confidence interval, CMH: Cochran-Mantel-Haenszel, FPG=fasting plasma glucose, HbA_{1c}: glycated hemoglobin A_{1c}, LOCF: last observation carried forward, mITT: modified intention-to-treat, LS: least squares, N: number of randomized patients, NPH: neutral protamine Hagedorn, n: number of patients with measurements, OC: Observed Case, SC: subcutaneous, SD: standard deviation, SE: standard error, SMPG: self-monitored plasma glucose, T2DM: type 2 diabetes mellitus				

Table 9 - Summary of efficacy for trial EFC11629

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both in combination with oral antihyperglycaemic drug(s) in Patients with Type 2 Diabetes Mellitus with a 6-Month Safety Extension Period		
Study identifier	EFC11629 (EudraCT: 2010-023770-39)	
Design	This was a Phase 3, 6-month, multicenter, randomized, open-label, parallel-group followed by a 6-month safety extension period to compare the efficacy and safety of HOE901-U300 and Lantus in patients with T2DM, and HbA_{1c} in the range 7% to 10%, injecting at least 42 U Lantus or equivalent NPH insulin with OADs. As there were no generally accepted recommendations for the switch from insulin detemir to insulin glargine, insulin detemir was considered a prohibited prior medication in the last 3 months before screening visit for T2DM patients on previous insulin treatment. Patients were randomized in a 1:1 ratio to receive either HOE901-U300 or Lantus. The randomization was stratified by screening HbA_{1c} value (<8%, ≥8%).	
	Screening period Main treatment phase Safety extension period Post-treatment follow-up	2 weeks 6 months 6 months 4 weeks
Statistical methods	A stepwise closed testing approach was used for the primary efficacy variable to assess noninferiority and superiority sequentially. To assess noninferiority, the upper bound of the two-sided 95% CI for the difference in the mean change in HbA_{1c} from baseline to endpoint between HOE901-U300 and Lantus was compared with the predefined noninferiority margin of 0.4% HbA_{1c}, a value <0.4% demonstrates noninferiority. If noninferiority was demonstrated, superiority of HOE901-U300 over Lantus was tested. The superiority of HOE901-U300 over Lantus was demonstrated if the upper bound of the two-sided 95% CI for the difference in the mean change in HbA_{1c} from baseline to endpoint between HOE901-U300 and Lantus on mITT population was <0 (zero).	
Treatment groups	HOE901-U300 (insulin glargine, 300 U/mL), modified Solostar, SC injection every 24 hours in the evening 403 patients randomized	HOE901-U300 starting dose was based on dose of prior total basal insulin and fasting (prebreakfast) SMPG at baseline. Titration to achieve fasting (prebreakfast) SMPG in the range of 4.4 to 5.6 mmol/L (80 to 100 mg/dL) without hypoglycaemia. The titration of mealtime insulin aimed to achieve a 2-hour postprandial SMPG of <8.9 mmol (160 mg/dL) while avoiding hypoglycaemia.
	Lantus (insulin glargine, 100 U/mL), Solostar, SC injection every 24 hours in the evening 405 patients randomized	Same as HOE901-U300
Endpoints and definitions	Primary efficacy endpoint	
	Change in HbA_{1c} (%)	Change from baseline to endpoint (Month 6) in patients with T2DM
	Secondary efficacy endpoints	

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both in combination with oral antihyperglycaemic drug(s) in Patients with Type 2 Diabetes Mellitus with a 6-Month Safety Extension Period		
Study identifier	EFC11629 (EudraCT: 2010-023770-39)	
	Nocturnal hypoglycaemia	Incidence (%) of patients with at least 1 nocturnal hypoglycaemia, indicated as severe and/or confirmed by plasma glucose ≤3.9 mmol/L (70 mg/dL) that occurred between 00:00 and 05:59 hours, from start of Week 9 to endpoint (Month 6)
	Pre-injection SMPG (mmol/L)	Change in pre-injection SMPG (mmol/L) (obtained within 30 minutes prior to injection of study drug; mean over last 7 days values) from baseline to endpoint (Month 6)
	Variability of pre-injection SMPG	Change in variability of pre-injection SMPG (obtained within 30 minutes prior to injection of study drug; coefficient of variation over last 7 days values) from baseline to endpoint (Month 6)
	Other secondary efficacy endpoints	
	Number (%) of patients with target HbA_{1c} <7%	at endpoint (Month 6) at endpoint (Month 6) having experienced no hypoglycaemia event, indicated as severe and/or confirmed by plasma glucose <3.0 mmol/L (54 mg/dL) that occurred during the last 3 months of the main 6-month on-treatment period - any time of the day -between 00:00 and 05:59 hours.
	Number (%) of patients with target HbA_{1c} ≤6.5%	at endpoint (Month 6)
	Number (%) of patients with FPG <5.6 mmol/L (100 mg/dL) / FPG ≤6.7 mmol/L (120 mg/dL)	at endpoint (Month 6) at endpoint (Month 6) having experienced no hypoglycaemia event, indicated as severe and/or confirmed by plasma glucose <3.0 mmol/L (54 mg/dL) that occurred during the last 3 months of the main 6-month on-treatment period at any time of the day.
	24-hour plasma glucose (mmol/L)	Change of mean 24-hour plasma glucose based on 8-point SMPG, from baseline to endpoint (Month 6)
	Variability of 24-hour plasma glucose (mmol/L)	Change in variability of 24-hour plasma glucose based on 8-point SMPG.
	Daily average basal insulin dose (U/kg)	Change in daily average basal insulin dose from baseline to endpoint (Month 6)
Results and Analysis		
Analysis description	**Primary Analysis**	

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both in combination with oral antihyperglycaemic drug(s) in Patients with Type 2 Diabetes Mellitus with a 6-Month Safety Extension Period					
Study identifier	EFC11629 (EudraCT: 2010-023770-39)				
Analysis population and time point description	Modified intention-to-treat (mITT) population – change from baseline to endpoint (Month 6, LOCF)				
Descriptive statistics, point estimate and effect estimate	Primary endpoint		Comparison groups	HOE901-U300 (N=403)	Lantus (N=405)
	HbA_{1c} (%)		n	386	392
			Endpoint (Month 6): Mean (SD)	7.57 (1.02)	7.56 (1.04)
			Change from baseline to endpoint (Month 6): LS Mean (SE) [95% CI]	-0.57 (0.094) [-0.756 to 0.387]	-0.56 (0.093) [-0.744 to -0.379]
			Change from baseline to endpoint (Month 6): LS Mean difference (SE) HOE901-U300 versus Lantus [95% CI]	-0.01 (0.066) [-0.139 to 0.119]	
	Secondary endpoints		Comparison groups	HOE901-U300 (N=403)	Lantus (N=405)
	Severe and/or confirmed nocturnal hypoglycaemia between start of Week 9 and endpoint (Month 6)		n		
			n (%) with at least 1 nocturnal hypoglycaemia	87 (21.6)	113 (27.9)
			RR [95% CI] versus Lantus	0.77 [0.61 to 0.99]	
			p-value (CMH)	0.0380	
		Average pre-injection SMPG (mmol/L)	n	353	350
			Endpoint (Month 6): Mean (SD)	10.23 (3.03)	10.28 (3.05)
			Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-0.56 (0.278) [-1.101 to -0.010]	-0.51 (0.275) [-1.052 to 0.028]

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both in combination with oral antihyperglycaemic drug(s) in Patients with Type 2 Diabetes Mellitus with a 6-Month Safety Extension Period					
Study identifier	EFC11629 (EudraCT: 2010-023770-39)				
			Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI] p-value (ANCOVA)	-0.04 (0.201) [-0.438 to 0.350] 0.8279	
		Average pre-injection SMPG (mg/dL)	n	353	350
			Endpoint (Month 6): Mean (SD)	184.31 (54.51)	185.10 (54.90)
			Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-10.01 (5.004) [-19.833 to -0.184]	-9.22 (4.951) [-18.944 to 0.499]
			Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI] p-value (ANCOVA)	-0.79 (3.615) [-7.883 to 6.311] 0.8279	
	Variability of pre-injection SMPG (%)		n	353	350
			Endpoint (Month 6): Mean (SD)	19.84 (10.40)	20.37 (11.65)
			Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-2.34 (1.425) [-5.142 to 0.452]	-0.53 (1.408) [-3.297 to 2.231]

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both in combination with oral antihyperglycaemic drug(s) in Patients with Type 2 Diabetes Mellitus with a 6-Month Safety Extension Period				
Study identifier	EFC11629 (EudraCT: 2010-023770-39)			
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI]	-1.81 (1.029) [-3.833 to 0.210]	
	Other secondary endpoints	Comparison groups	HOE901-U300 (N=404)	Lantus (N=400)
	Number (%) of patients at endpoint (Month 6)	HbA_{1c} <7%	n=386	n=392
			118 (30.6)	119 (30.4)
		HbA_{1c} <7% and no emergent severe or confirmed hypoglycaemia	n=388	n=396
			93 (24.0)	94 (23.7)
		HbA_{1c} <7% and no nocturnal emergent severe or confirmed hypoglycaemia	n=387	n=394
			107 (27.6)	113 (28.7)
		HbA_{1c} ≤6.5%	n=386	n=392
			56 (14.5)	58 (14.8)
	Number (%) of patients at endpoint (Month 6)	FPG <5.6 mmol/L (100 mg/dL)	n=384	n=390
			113 (29.4)	131 (33.6)
		FPG <5.6 mmol/L (100 mg/dL) and no emergent severe or confirmed hypoglycaemia	n=386	n=395
			81 (21.0)	97 (24.6)
		FPG <5.6 mmol/L (100 mg/dL) and no nocturnal emergent severe or confirmed hypoglycaemia	n=385	n=393
			100 (26.0)	121 (30.8)
		FPG ≤6.7 mmol/L (120 mg/dL)	n=384	n=390
			187 (48.7)	211 (54.1)

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both in combination with oral antihyperglycaemic drug(s) in Patients with Type 2 Diabetes Mellitus with a 6-Month Safety Extension Period				
Study identifier	EFC11629 (EudraCT: 2010-023770-39)			
	24-hour plasma glucose based on 8-point SMPG (mmol/L)	Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-0.905 (0.2203) [-1.3373 to -0.4723]	-1.115 (0.2187) [-1.5447 to -0.6859]
	Variability of 24-hour plasma glucose based on 8-point SMPG (%)	Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-1.63 (1.302) [-4.191 to 0.921]	-0.90 (1.292) [-3.437 to 1.635]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI]	-0.73 (0.960) [-2.618 to 1.150]	
	Mean daily average basal insulin dose (U/kg)	Month 6 OC:		
			0.93	0.84
		Mean change from baseline	0.30	0.19
ANCOVA: analysis of covariance, CI: confidence interval, CMH: Cochran-Mantel-Haenszel, FPG: fasting plasma glucose, HbA_{1c}: glycated hemoglobin A_{1c}, LOCF: last observation carried forward, LS: least squares, mITT: modified intention-to-treat, N: number of randomized patients, n: number of patients with measurements, NPH: neutral protamine Hagedorn, OC: Observed Case, SC: subcutaneous, SD: standard deviation, SE: standard error, SMPG: self-monitored plasma glucose, T2DM: type 2 diabetes mellitus				

Table 10 - Summary of efficacy for trial EFC12347

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus in Insulin-Naïve Patients with Type 2 Diabetes Mellitus not Adequately Controlled with Non-Insulin Antihyperglycaemic Drugs with a 6-month Safety Extension Period		
Study identifier	EFC12347 (EudraCT: 2012-000146-35)	
Design	This was a Phase 3, 6-month, multicenter, randomized, open-label, parallel-group study followed by a 6-month safety extension period to compare the efficacy and safety of HOE901-U300 and Lantus in insulin-naïve patients with T2DM, and HbA_{1c} in the range 7% to 11%, not adequately controlled with non-insulin AHA. Patients were randomized in a 1:1 ratio to receive either HOE901-U300 or Lantus. The randomization was stratified by screening HbA_{1c} at screening (<8%, ≥8%) and geographical region (Non-Japan or Japan).	
	Screening period Main treatment phase Safety extension period Post-treatment follow-up	2 weeks 6 months 6 months 2 to 4 days
Statistical methods	A stepwise closed testing approach was used for the primary efficacy variable to assess noninferiority and superiority sequentially. To assess noninferiority, the upper bound of the two-sided 95% CI for the difference in the mean change in HbA_{1c} from baseline to endpoint between HOE901-U300 and Lantus was compared with the predefined noninferiority margin of 0.4% HbA_{1c}, a value <0.4% demonstrates noninferiority. If noninferiority was demonstrated, superiority of HOE901-U300 over Lantus was tested. The superiority of HOE901-U300 over Lantus was demonstrated if the upper bound of the two-sided 95% CI for the difference in the mean change in HbA_{1c} from baseline to endpoint between HOE901-U300 and Lantus on mITT population was <0 (zero).	
Treatment groups	HOE901-U300 (insulin glargine, 300 U/mL), modified Tactipen, SC injection every 24 hours in the evening patients were to continue using their non-insulin AHA 439 patients randomized	The initial daily dose of basal insulin was 0.2 U/kg, rounded to the closest number divisible by 3. Doses were titrated to achieve the target FPG in the range of 4.4 to 5.6 mmol/L (80 to 100 mg/dL). After reaching the target range, doses were adjusted for each patient to maintain glycaemic control over the remaining study duration.
	Lantus (insulin glargine 100 U/mL), Solostar, SC injection every 24 hours in the evening; patients were to continue using their non-insulin AHA 439 patients randomized	Same as HOE901-U300.
Endpoints and definitions	Primary efficacy endpoint	
	Change in HbA_{1c} (%)	Change from baseline to endpoint (Month 6) in patients with T2DM
	Secondary efficacy endpoints	

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus in Insulin-Naïve Patients with Type 2 Diabetes Mellitus not Adequately Controlled with Non-Insulin Antihyperglycaemic Drugs with a 6-month Safety Extension Period				
Study identifier	EFC12347 (EudraCT: 2012-000146-35)			
	Nocturnal hypoglycaemia	Incidence (%) of patients with at least 1 nocturnal hypoglycaemia, indicated as severe and/or confirmed by plasma glucose ≤3.9 mmol/L (70 mg/dL) that occurred between 00:00 and 05:59 hours, from start of Week 9 to Month 6		
	Pre-injection SMPG (mmol/L)	Change in pre-injection SMPG (mmol/L) (obtained within 30 minutes prior to injection of study drug; mean over last 7 days values) from baseline to endpoint (Month 6)		
	Variability of pre-injection SMPG (%)	Variability of pre-injection SMPG (obtained within 30 minutes prior to injection of study drug; coefficient of variation over last 7 days values) from baseline to endpoint (Month 6)		
	Other secondary efficacy endpoints			
	Number (%) of patients with target HbA_{1c} <7%	At Month 6 at Month 6 having experienced no hypoglycaemia event, indicated as severe and/or confirmed by plasma glucose <3.0 mmol/L (54 mg/dL) that occurred during the last 3 months of the main 6-month on-treatment period - any time of the day - between 00:00 and 05:59 hours		
	Number (%) of patients with target HbA_{1c} ≤6.5%	at Month 6		
	Number (%) of patients with FPG <5.6 mmol/L (100 mg/dL) / FPG ≤6.7 mmol/L (120 mg/dL)	at Month 6 at Month 6 having experienced no hypoglycaemia event, indicated as severe and/or confirmed by plasma glucose <3.0 mmol/L (54 mg/dL) that occurred during the last 3 months of the main 6-month on-treatment period at any time of the day		
	24-hour plasma glucose (mmol/L)	Change of mean 24-hour plasma glucose based on 8-point SMPG, from baseline to endpoint (Month 6)		
	Variability of 24-hour plasma glucose (%)	Change in variability of 24-hour plasma glucose based on 8-point SMPG		
	Daily average basal insulin dose (U/kg)	Change in daily average basal insulin dose from baseline to Month 6		
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Modified intention-to-treat (mITT) population – change from baseline to endpoint (Month 6, MMRM)			
		Comparison groups	HOE901-U300 (N=432)	Lantus (N=430)

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus in Insulin-Naïve Patients with Type 2 Diabetes Mellitus not Adequately Controlled with Non-Insulin Antihyperglycaemic Drugs with a 6-month Safety Extension Period				
Study identifier	EFC12347 (EudraCT: 2012-000146-35)			
	HbA_{1c} (%)	N	365	350
		Endpoint (Month 6): Mean (SD)	7.08 (0.96)	7.05 (0.95)
		Change from baseline to endpoint (Month 6): LS Mean (SE) [95% CI]	-1.42 (0.047) [-1.511 to -1.326]	-1.46 (0.048) [-1.555 to -1.367]
		Change from baseline to endpoint (Month 6): LS Mean difference (SE) HOE901-U300 versus Lantus [95% CI]	0.04 (0.067) [-0.090 to 0.174]	
	Secondary endpoints	Comparison groups	HOE901-U300 (N=432)	Lantus (N=430)
	Severe and/or confirmed nocturnal hypoglycaemia between start of Week 9 and Month 6	n (%) with at least 1 nocturnal hypoglycaemia	67 (15.5)	75 (17.4)
		RR [95% CI] versus Lantus	0.89 [0.66 to 1.20]	
		p-value (CMH)	0.4536	
	Average pre-injection SMPG (mmol/L)	N	173	179
		Endpoint (Month 6): Mean (SD)	8.90 (2.24)	8.68 (2.31)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-2.16 (0.162) [-2.478 to -1.842]	-2.33 (0.156) [-2.632 to -2.019]
		At endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI]	0.17 (0.224) [-0.275 to 0.605]	
	Average pre-injection SMPG (mg/dL)	N	173	179
		Endpoint (Month 6): Mean (SD)	160.37 (40.34)	156.33 (41.65)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-38.92 (2.912) [-44.646 to -33.192]	-41.89 (2.812) [-47.423 to -36.364]
		At endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI]	2.97 (4.028) [-4.946 to 10.895]	
	Variability of pre-injection SMPG (%)	N	358	327
		Endpoint (Month 6): Mean (SD)	18.80 (9.81)	18.38 (9.35)

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Study identifier	EFC12347 (EudraCT: 2012-000146-35)			
	(MMRM)	Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	18.70 (0.502) [17.719 to 19.690]	18.33 (0.521) [17.306 to 19.350]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) versus Lantus [95% CI]	0.38 (0.723) [-1.043 to 1.796]	
	Other secondary endpoints	Comparison groups	HOE901-U300 (N=432)	Lantus (N=430)
	Number (%) of patients at Month 6	N	432	430
		HbA_{1c} <7%	186 (43.1)	181 (42.1)
		HbA_{1c} <7% without severe/confirmed hypoglycaemia at any time of the day	175 (40.5)	163 (37.9)
		HbA_{1c} <7% without severe/confirmed nocturnal hypoglycaemia	184 (42.6)	175 (40.7)
		HbA_{1c} ≤6.5%	108 (25.0)	118 (27.4)
	Number (%) of patients at Month 6	N	432	430
		FPG <5.6 mmol/L (100 mg/dL)	113 (26.2)	127 (29.5)
		FPG <5.6 mmol/L (100 mg/dL) and no emergent severe or confirmed hypoglycaemia	104 (24.1)	110 (25.6)
		FPG <5.6 mmol/L (100 mg/dL) and no nocturnal emergent severe or confirmed hypoglycaemia	112 (25.9)	121 (28.1)
		FPG ≤6.7 mmol/L (120 mg/dL)	217 (50.2)	231 (53.7)
	24-hour plasma glucose based on 8-point SMPG (mmol/l [mg/dL])	Change from baseline to endpoint (Month 6): LS mean (SE)	-2.72 (-49.06)	-2.90 (-52.24)
		Change from baseline to endpoint (Month 6): LS mean difference HOE901-U300 versus Lantus (95% CI)	0.18 (-0.068 to 0.421)	
	Variability of 24-hour plasma glucose	Change from baseline to endpoint (Month 6): LS mean (95% CI)	1.53 (0.264 to 2.790)	1.41 (0.143 to 2.682)

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Study identifier	EFC12347 (EudraCT: 2012-000146-35)			
	based on 8-point SMPG (%)	Change from baseline to endpoint (Month 6): LS mean difference HOE901-U300 versus Lantus (95% CI)	0.11 (-1.676 to 1.905)	
	Mean daily basal insulin dose (U/kg)	Month 6 OC	0.62	0.53
		Mean change from baseline	0.43	0.34
CI: confidence interval, CMH: Cochran-Mantel-Haenszel, FPG: fasting plasma glucose, HbA_{1c}: glycated hemoglobin A_{1c}, LS: least squares, mITT: modified intention-to-treat, MMRM: mixed model for repeated measurements, N: number of randomized patients, n: number of patients with measurements, OC: Observed case, RR: relative risk, SC: subcutaneous, SD: standard deviation, SE: standard error, SMPG: self-monitored plasma glucose, T2DM: type 2 diabetes mellitus;				

Clinical studies in special populations

No studies were conducted specifically to address the efficacy of U300 in the elderly, in children, or in subjects with impaired renal or hepatic function. Due to the structural similarity between insulin glargine and human insulin, the same changes in pharmacokinetic (PK) and pharmacodynamic (PD) profiles, and therefore efficacy, are expected with both drugs in subjects with impaired renal or hepatic function. Careful dose titration is required in subjects with severe renal disease or hepatic failure because insulin metabolism is known to be impaired, and these subjects are often insulin resistant. Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances or stress.

Overall in all 4 studies EFC12456, EFC11628, EFC11629 and EFC12347 and the pooled analysis EFC11629 and EFC12347, the treatment effect (mean change in HbA_{1c} from baseline to endpoint [Month 6]) of U300 versus Lantus was consistent across tested subgroups defined by baseline/screening factors such as age, gender, race, ethnicities, baseline BMI, duration of diabetes, HbA_{1c} at screening (<8% or ≥8%) and geographical area, as indicated by p-values for treatment-by-subgroup interaction >0.10. In a few cases, interactions with treatment were observed (eg, geographical area in study EFC12456, duration of diabetes in study EFC11628); however, since similar findings were not observed in the other studies and as no adjustment for multiplicity was performed, no conclusion can be drawn on whether U300 or Lantus performs differently in some specific subgroups.

Analysis performed across trials (pooled analyses and meta-analysis)

Primary endpoint

Primary efficacy endpoint: change in HbA_{1c} from baseline to endpoint (Month 6)

The primary objective of these studies, to demonstrate non-inferiority of U300 to Lantus in the change in HbA_{1c} from baseline to endpoint (Month 6), was achieved in study EFC12456 in T1DM and in all 3 studies in T2DM covering the broad range of the population of patients with T2DM (Table 11). Based on the predefined non-inferiority margin of 0.4%, the non-inferiority of U300 compared with Lantus was shown as the upper bound of the 95% CI was below 0.4%, and meeting even more stringent

criteria with the observed upper bound in all studies below 0.3%.
In the study in T1DM and the 2 studies in insulin-pretreated patients with T2DM, the largest decrease of HbA_{1c} occurred during the first 3 months of treatment, with only minor further decreases between Month 3 and Month 6. In the study in insulin-naïve T2DM patients, HbA_{1c} continued to decrease in both treatment groups between Month 3 and Month 6.

Table 11 - Primary efficacy analysis - Summary of mean change in HbA_{1c} (%) from baseline to endpoint (Month 6) in the Phase 3 studies and in meta-analysis of EFC11629 and EFC12347 (MMRM analysis) - mITT population

	Treatment group			
Study	**U300**	**Lantus**	**LS Mean Difference (SE) vs. Lantus**	**95% CI**
T1DM				
EFC12456 n (mITT)	273	273		
Baseline (Mean)	8.13	8.12		
Month 6 endpoint (MMRM)	7.70	7.68		
LS Mean (SE) change from baseline to Month 6 endpoint (MMRM)	-0.40 (0.051)	-0.44 (0.051)	0.04 (0.072)	(-0.098 to 0.185)
T2DM				
EFC11628 n (mITT)	404	400		
Baseline (Mean)	8.13	8.14		
Month 6 endpoint (MMRM)	7.23	7.27		
LS Mean (SE) change from baseline to Month 6 endpoint (MMRM)	-0.90 (0.041)	-0.87 (0.041)	-0.03 (0.058)	(-0.144 to 0.083)
EFC11629 n (mITT)	403	405		
Baseline (Mean)	8.27	8.22		
Month 6 endpoint (MMRM)	7.47	7.49		
LS Mean (SE) change from baseline to Month 6 endpoint (MMRM)	-0.73 (0.048)	-0.70 (0.048)	-0.03 (0.068)	(-0.168 to 0.099)
EFC12347 n (mITT)	432	430		
Baseline (Mean)	8.49	8.58		
Month 6 endpoint (MMRM)	7.08	7.05		
LS Mean (SE) change from baseline to Month 6 endpoint (MMRM)	-1.42 (0.047)	-1.46 (0.048)	0.04 (0.067)	(-0.090 to 0.174)
Meta-analysis EFC11629 and EFC12347				
n (mITT)	835	835		
Baseline (Mean)	8.38	8.40		
Month 6 endpoint (MMRM)	7.27	7.27		
LS Mean (SE) change from baseline to Month 6 endpoint (MMRM)	-1.08 (0.034)	-1.09 (0.034)	0.01 (0.048)	(-0.083 to 0.106)

MMRM = Mixed model for repeated measurements; Month 6 endpoint (MMRM) value is either the observed value at month 6 or the value retrieved (time windows in the SAP)
MMRM with treatment (or randomized group for EFC12456), randomization strata of screening HbA1c, world region (or randomization strata of geographical region for EFC12347 and EFC12456), visit and visit-by-treatment interaction as fixed categorical effects, baseline value and

baseline-by-visit interaction as fixed continuous covariates
For meta-analysis, same MMRM as above with addition of fixed effect study, study-by-visit interaction and deletion of world region or randomization strata of geographical region

Secondary efficacy endpoints

First main secondary efficacy endpoint: Occurrence of nocturnal hypoglycaemia
The percentage of patients with nocturnal hypoglycaemia including the categories of severe and/or confirmed hypoglycaemia by SMPG ≤3.9 mmol/L (70 mg/dL) reported between 00:00 and 05:59 hours between Week 9 and Month 6 was similar in the U300 and Lantus groups in study EFC12456 in T1DM.
In the 3 studies in T2DM (EFC11628, EFC11629, EFC12347), the percentages were consistently lower in the U300 groups compared with the Lantus groups reaching statistical significance in the studies in insulin pretreated patients with risk reductions of 21% (EFC11628) and 23% (EFC11629). In study EFC12347 in insulin-naïve T2DM patients the risk reduction was 11%. In patients treated with basal insulin in combination with non-insulin AHA risk reduction was 18% (pooled analysis EFC11629 and EFC12347) (Table 12). The percentage of patients reporting severe and/or confirmed nocturnal hypoglycaemia in the EFC12347 study was overall the lowest among the 3 studies in T2DM, indicating the overall lower risk of hypoglycaemia in this patient population with relative shorter duration of T2DM and only recent start of insulin treatment.

Table 12 - Secondary efficacy analysis - Number (%) of patients with at least one severe and/or confirmed (SMPG ≤3.9 mmol/L [70 mg/dL]) nocturnal hypoglycaemia (00:00 to 05:59) occurring between start of Week 9 to Month 6, in pivotal Phase 3 studies and in meta-analysis of EFC11629 and EFC12347

	Severe and/or confirmed nocturnal hypoglycaemia (00:00 to 05:59)			
Phase 3 study Treatment group	n/N(%)	RR vs. Lantus (ab)	95% CI (ab)	p-value (abc)
T1DM - EFC12456				
U300	162/273 (59.3%)	1.06	(0.92 to 1.23)	NA
Lantus	153/273 (56.0%)			
T2DM - EFC11628				
U300	146/404 (36.1%)	0.79	(0.67 to 0.93)	0.0045
Lantus	184/400 (46.0%)			
T2DM - EFC11629				
U300	87/403 (21.6%)	0.77	(0.61 to 0.99)	0.0380
Lantus	113/405 (27.9%)			
T2DM - EFC12347				
U300	67/432 (15.5%)	0.89	(0.66 to 1.20)	0.4536
Lantus	75/430 (17.4%)			
Meta-analysis EFC11629 and EFC12347				
U300	154/835 (18.4%)	0.82	(0.68 to 0.99)	NA
Lantus	188/835 (22.5%)			

N = mITT population, n/N (%) = number and percentage of patients with at least one nocturnal hypoglycaemia event, indicated as severe and/or confirmed by plasma glucose ≤3.9 mmol/L (70 mg/dL)
a. Relative risks (RR) between U300 and Lantus using an analysis of Cochran-Mantel-Haenszel (CMH) with treatment as factor and stratified on randomization strata of screening HbA1c (<8.0, ≥8.0%). For EFC12347 model also stratified on randomization strata of geographical region (non-Japan,

Japan) . For EFC12456, model also stratified on randomization strata of geographical region (non-Japan, Japan) and daytime of injection (morning/evening)
b. For the meta-analysis of EFC11629 and EFC12347, a fixed effect meta-analysis using CMH method was used with treatment as factor and stratified on randomization strata of screening HbA1c (<8.0, ≥8.0%) and study
c. NA = not applicable for EFC12456 and for the meta-analysis of EFC11629 and EFC12347 because no hierarchical procedure was planned

Change in pre-injection SMPG from baseline to endpoint (Month 6)
In all 4 pivotal studies, the least square (LS) mean change from baseline to endpoint (Month 6) in average pre injection SMPG was similar in the U300 and Lantus groups. Similar results were also seen in the meta-analysis on the pooled data from the 2 studies (EFC11629 and EFC12347) with non-insulin AHA as background therapy. Superiority of U300 with respect to Lantus was not shown in EFC11628 and EFC11629.

Change in variability of pre-injection SMPG from baseline to endpoint (Month 6)
The variability of pre-injection SMPG, calculated as mean of coefficient of variation over at least 3 SMPG measurements during the 7 days preceding the visit, decreased from baseline to endpoint (Month 6) similarly in the U300 and Lantus treatment groups in EFC12456 and EFC11628. In study EFC11629 variability decreased more in the U300 group than Lantus group. As no statistically significant difference was shown for the 2nd main secondary efficacy endpoint in EFC11628 and EFC11629, no testing was done in these studies for the 3rd main secondary efficacy endpoint.

Other secondary efficacy endpoints
In all 4 studies, similar percentages of U300 and Lantus treated patients reached HbA_{1c} levels below 7.0% at Month 6 overall and without reporting severe and/or confirmed hypoglycaemia with the low threshold of <3.0 mmol/L (54 mg/dL) during the last 3 months of study treatment.
Fasting plasma glucose (measured in the central laboratory) showed overall substantial decreases in both treatment groups in the 4 studies with most of the decrease seen in the first 3 months of study treatment. Although the difference in the LS mean change of FPG in study EFC12347 was in favor of Lantus, it was not associated with a greater HbA_{1c} reduction in this study.
In all 4 studies, the results of 8-point SMPG profiles, mean change in 24-hour average plasma glucose and variability of 24-hour plasma glucose in insulin-pretreated patients showed consistently similar improvements in the U300 and Lantus groups at the end of the 6-month treatment.

Supportive studies
In extension studies of two of the pivotal trials, participants were asked to deviate from the usual time of injection at least 2 times per week by at 3 hours. This lead to small differences in HbA1c between flexible and fixed dosing intervals (HbA_{1c}, LS mean difference, substudy EFC11628: 0.05%, 95% CI: -0.189 to 0.298]; EFC11629: 0.13%, 95% CI: -0.152 to 0.415).
More than 50% of the patients with T1DM and approximately 40% of the patients with T2DM were AIA-positive at baseline. Anti-insulin antibody positive-patients in both the U300 and Lantus groups already had higher basal insulin doses at baseline compared with AIA-negative patients. Mean changes in U300 and Lantus doses from baseline to endpoint (Month 6) were similar regardless of the AIA status (positive or negative).

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The 4 Phase 3 studies were multinational, multicenter, open-label, centrally randomized, comparative, parallel group studies, each comprising a 6-month main study period followed by a 6-month comparative safety extension period. The studies EFC11628 and EFC11629 also included a 4-week post-treatment follow-up period after completion of the 52-week study duration. The active control was Lantus in all studies. The studies utilized a common core protocol that standardized most aspects of the study design, including the comparator Lantus (insulin glargine 100 U/mL), 1:1 randomization, stratification by screening HbA_{1c} (<8.0% versus ≥8.0%), inclusion/exclusion criteria, targets for fasting pre-breakfast self-monitored plasma glucose (SMPG), recommendations for dosing of U300 and Lantus, primary and secondary efficacy variables and safety variables, including the definitions used for the hypoglycaemia categories and analyses. All 4 Phase 3 studies were designed to show non-inferiority of U300 versus Lantus based on the change in HbA_{1c} from baseline to endpoint at Month 6 with a non-inferiority margin of 0.4% HbA_{1c}. All studies had finalised their extension periods by September 2014. These data were submitted for the T2DM studies during the procedure by the Applicant. Data for EFC12456 study (T1DM) were not yet available at the time of the initial MAA, but will be provided post-approval.

Separate studies were done in T1DM and T2DM due to the different underlying pathophysiologies. Three studies were done in T2DM to cover the broad spectrum of this patient population, including insulin-naïve patients not adequately controlled on non-insulin AHA and requiring insulin, patients already treated with basal insulin in combination with OAD, and patients requiring basal and mealtime insulin for glycaemic control. Adult patients at least 18 years of age with a screening HbA_{1c} in the range of ≥7.0 to ≤10.0% for insulin-pretreated patients (EFC11628, EFC11629, EFC12456) and ≤9.0% (PDY12777) or ≥7.0 to ≤11.0% in insulin-naïve patients (EFC12347) were eligible for the studies.

The design and conduct of the studies were appropriate to establish efficacy and safety of U300 in comparison to Lantus, keeping in mind the large similarities between the two products. As such, Lantus was the appropriate comparator.

The approach to assess efficacy of the U300 insulin by a non-inferiority trial is in line with regulatory guidance (CPMP/EWP/1080/00 Rev. 1) and accepted. However, the non-inferiority margin is not specified in this guideline and is not further justified in the dossier. In general, a non-inferiority margin of 0.3% is used in the assessment of glucose lowering drugs.

The Applicant has added substudies and a large number of exploratory secondary endpoints to the pivotal trials. These were all exploratory in nature, resulting in descriptive analyses.

Efficacy data and additional analyses

The participants in the trials (taken together) were well-representative of the target population for U300. As the trials employed a non-inferiority design, and participation in any trial is associated with HbA1c improvement, baseline HbA1c is of particular importance. The baseline values were between 8.12 and 8.58%, which is reasonable.

Across the main studies, the discontinuation rates were generally low (7-17%) and balanced between groups. In studies EFC12456 and EFC12347 about 15 % of patients in both study arms discontinued. The reasons for discontinuation were balanced between groups. Notably, the highest discontinuation rate was observed for “Other reasons”. The majority of discontinuations were not safety related. Single cases were due to perceived lack of efficacy or hypoglycaemia; however, these cases were balanced between groups.

Primary endpoint

In all studies, U300 was convincingly non-inferior to Lantus, with point estimates for the difference in HbA1c ranging from -0.03% to 0.04% and the highest upper limit of the 95% confidence interval at 0.185%; well below the pre-specified non-inferiority margin of 0.4%. Although a margin of 0.4% is

considered too wide for glucose lowering drugs and 0.3 is considered more appropriate, the highest upper limit is also well below that margin.

Secondary endpoints

Summary of secondary endpoint results

Nocturnal hypoglycaemia

Severe and/or confirmed hypoglycaemia (SMPG ≤3.9 mmol/L (70 mg/dL)) during the night was similar between groups in T1DM; in the 3 studies in T2DM the percentages were lower in the U300 groups compared with the Lantus groups reaching statistical significance in the studies in insulin pretreated patients with risk reductions of 21% (EFC11628: 36.1 vs 46.1%) and 23% (EFC11629: 21.6 vs 27.9%).

Change in pre-injection SMPG

In all 4 pivotal studies, the least square (LS) mean change from baseline to endpoint (Month 6) in average pre-injection SMPG was similar in the U300 and Lantus groups. The prolonged duration of action of U300 had been expected to result in better pre-injection SMPG; the Applicant explains the lack of a difference by the effects of mealtime insulin injections and/or meal intake (dinner). It is usual in clinical practice to cover relative shortage of long-acting insulin by mealtime short acting insulin.

Variability of pre-injection SMPG

The variability of pre-injection SMPG, calculated as mean of coefficient of variation over at least 3 SMPG measurements during the 7 days preceding the visit, decreased from baseline to endpoint (Month 6) similarly in the U300 and Lantus treatment groups in EFC12456 and EFC11628. In study EFC11629 variability decreased more in the U300 group than Lantus group, but no testing was done in accordance with the hierarchical statistical analysis.

FPG

In all 4 pivotal studies, FPG had decreased in the U300 and Lantus groups at endpoint (Month 6), with a difference in the LS mean change of FPG from baseline in favour of Lantus between 0.05 and 0.39 mmol/L. This was statistically significant in study EFC12347 and in the pooled analysis of EFC11629 and EFC12347. This is somewhat surprising as the fasting pre-breakfast SMPG was used to titrate the long-acting insulin dose.;

The prolonged action of U300 may have caused relative shift of long-acting insulin action from night to day. Notably, the prebreakfast SMPG (which was followed more closely than FPG) decreased more gradually with HOE901-U300 than with Lantus. The Applicant has clarified that the dose titration was indeed steeper in the HOE901-U300 group than in the Lantus group and that this was more pronounced in patients without nocturnal hypoglycaemia. The Applicant further proposed that the lack of difference between treatments could be due to the more pronounced effect of Lantus on FPG (when taken as an evening dose). This appears plausible.

The decrease in FPG was largest in the first 3 months of study treatment in all studies and both treatment groups

HbA_{1c} and FPG responder analyses

The percentages of patients reaching HbA_{1c} <7.0% and the percentages of patients reaching FPG <6.7 mmol/L (120 mg/dL) at Month 6 were comparable between the U300 and Lantus groups. Also, the percentages of patients reaching these levels of HbA_{1c} or FPG without reporting severe and/or confirmed hypoglycaemia by SMPG <3.0 mmol/L (54 mg/dL) any time of the day or between 00:00 and 05:59 hours during the last 3 months of the main 6-month on-treatment period were overall similar.

8-point SMPG profile

Eight-point profiles were comparable between treatment groups at baseline in all 4 studies and had decreased similarly at all timepoints at endpoint (Month 6) in both treatment groups.

24-hour average plasma glucose

In all 4 studies, 24-hour average plasma glucose based on the 8-point SMPG profile was comparable between the treatment groups and had decreased similarly in the U300 and Lantus group at Month 6.

In study PDY12777, the glucose variation over the day was investigated by means of CGM. Although the time spent within the target range (4.4 to 7.8 mmol/L [80 to 140 mg/dL]) was comparable for Lantus and HOE901-U300, the average glucose profile by hour of day appeared flatter with HOE901-U300. This is in line with the flatter PD profile and longer duration of action seen with HOE901-U300. The findings are not entirely in line with the findings in the CGM study in Japanese patients (PDY12335). The Applicant has clarified the differences. These were mainly due to differences in study design, conduct and evaluation. It is noted that when used in a basal-bolus regimen no clear differences in the CGM profiles are observed between HOE901-U300 and Lantus, which is somewhat unexpected considering the difference in hypoglycaemia pattern.

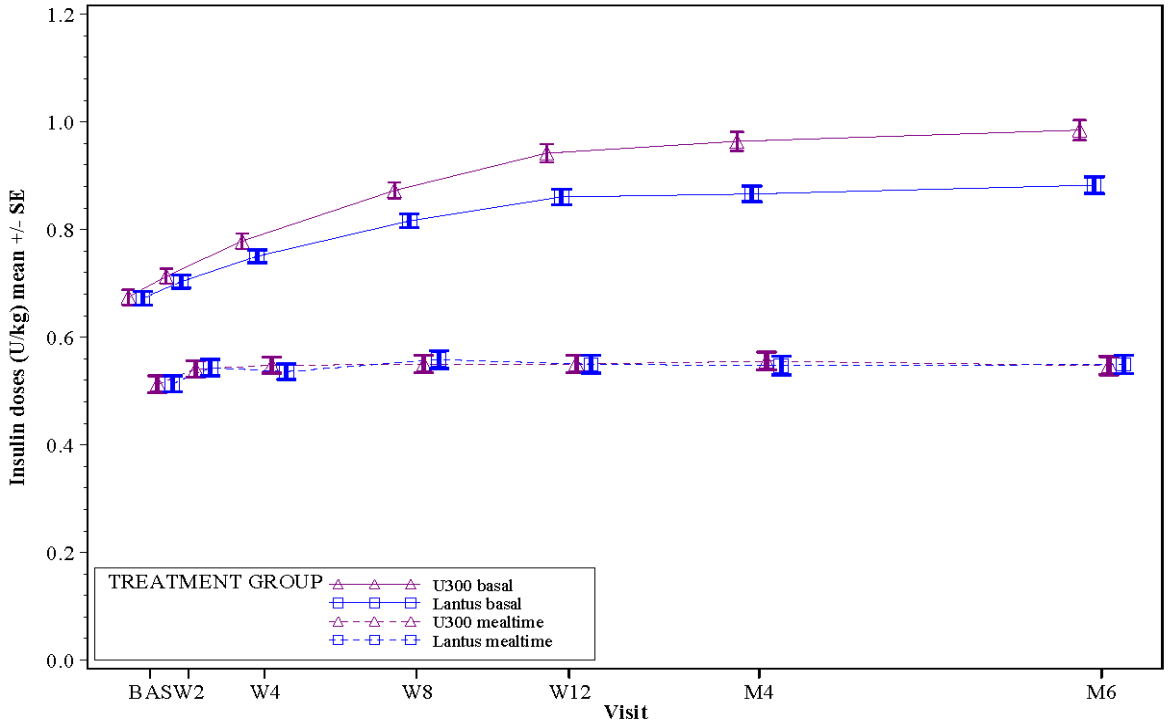
Fasting pre-breakfast SMPG

Basal insulin U300 or Lantus was titrated according to the fasting pre-breakfast SMPG. Switching from Lantus to U300 is associated with a temporary (2-4 week) increase in fasting SMPG. Decrease of fasting SMPG is faster with Lantus compared to more gradual with U300.

Doses of basal insulin and mealtime insulin preparations

Patients pretreated with insulin

After trial initiation, basal insulin use increased in both U300 and Lantus groups, but more in the U300 group, resulting in approximately 10% (EFC11628, EFC11629; T2DM) to 18% (EFC12456; T1DM) higher U300 doses than Lantus doses at Month 6. This is representatively illustrated by **Figure 8**.



# subjects						
U300 basal	403 400	396	392	382	378	371
Lantus basal	400 392	390	386	381	374	366
U300 mealtime	383 400	396	389	380	371	365
Lantus mealtime	381 389	389	381	378	366	362

Figure 8 - Mean (+/- SE) in average daily basal and mealtime insulin doses (U/kg) by visit during the main 6-month on-treatment period in EFC11628 mITT population

Insulin-naïve patients with T2DM

In study EFC12347 in insulin-naïve T2DM patients not adequately controlled on non-insulin AHA, the recommended starting dose was 0.2 U/kg for both U300 and Lantus. The U300 and Lantus doses were increased throughout the study. The increase in the insulin dose was similar in both treatment groups during the first 4 weeks of the study, thereafter, the U300 dose continued to increase at the same rate, while the Lantus dose continued to increase by smaller increments, resulting in a higher mean U300 dose (0.62 U/kg) than Lantus dose (0.54 U/kg) at Month 6.

Basal insulin in combination with a mealtime insulin analogue

Mealtime insulin doses remained almost unchanged in both treatment groups when basal insulin was combined with mealtime insulin. The post-lunch and post-dinner plasma glucose excursions in the 8-point SMPG profiles and the absence of a lower hypoglycaemia risk during daytime suggest that the optimization of the mealtime insulin doses versus the basal insulin doses could have been further improved.

Injection of the basal insulin in the morning or evening

In study EFC12456 patients with T1DM were assigned per randomization to morning or evening injection of U300 or Lantus. At Month 6 in the morning injection groups the daily U300 (baseline: 0.31 U/kg; Month 6: 0.49 U/kg) and Lantus doses (baseline: 0.32 U/kg; Month 6: 0.45 U/kg) were comparable. In the evening injection groups the U300 dose was up-titrated (baseline: 0.34 U/kg; Month 6: 0.45 U/kg), while the Lantus dose was kept almost unchanged during the study (baseline: 0.33 U/kg; Month 6: 0.36 U/kg), contributing to a relatively large difference between the U300 and Lantus doses in the evening injection groups. In both U300 and Lantus morning and evening injection groups, the mealtime insulin doses were comparable and were almost unchanged during the study.

At endpoint (Month 6), the total insulin dose (basal + mealtime insulin) was higher in both the U300 morning (0.83 U/kg) and evening (0.80 U/kg) injection groups than in the Lantus morning (0.76 U/kg) and evening (0.69 U/kg) injection groups.

The increase in the ratio of basal insulin over total insulin was similarly higher for U300 evening injections (evening 0.57) than for Lantus (evening 0.52), while increase for morning injections was similar (U300 morning 0.61; Lantus morning 0.60).

Injection devices in clinical studies

In studies EFC11628 and EFC11629 the modified Solostar pen was used for administration of U300, allowing dose settings in multiples of 3 U. In studies EFC12347 and EFC12456 the modified Tactipen was used allowing dose settings in multiples of 1.5 U. The Solostar pen was used for injection of Lantus in all studies. In all studies the dose recommendations were identical for U300 and Lantus, depending on the fasting pre-breakfast SMPG. The insulin titration data in the 4 pivotal studies suggest, that the Investigators/patients followed the titration recommendation in the study protocols in both treatment groups regardless of the pens used in the studies. This is shown by the substantial increase in the U300 and Lantus doses during the titration periods and the use of either the modified Solostar or the modified Tactipen did not result in a reluctance to titrate the U300 dose. It should however be kept in mind, that the protocol required upward titration steps of at least 10% of the insulin dose, precluding smaller steps which would have been possible with Lantus but not with U300.

The pen that is proposed to be marketed is a Solostar with 1U accuracy. The pen can deliver 80 U maximally and thus more patients will need to inject twice compared to the pens used in the clinical studies. However, the benefit of the new pen is that it allows for more precise adjustment (one unit) and mix-ups of the pens for U300 and Lantus do not lead to a different injected dose, as the absolute number of units injected is the same for both pens.

Rescue treatment

Rescue treatment was started in a low number of patients in both treatment groups without notable differences.

Efficacy in morning and evening injection

In study EFC12456 and in the exploratory CGM study PDY12777, both conducted in patients with T1DM, patients were randomized to receive U300 or Lantus once daily in the morning (any time prior to breakfast until lunch) or evening (anytime immediately prior to the evening meal until bedtime).

At the end of the 6-month treatment period in the study EFC12456, HbA_{1c} had decreased similarly in the morning injection groups of U300 and Lantus, whereas a smaller decrease was seen in the U300 evening injection group compared with the Lantus evening injection group. Comparing morning and evening injection groups within the U300 group, the morning injection resulted in a larger decrease of

HbA_{1c} than the evening injection, although the LS mean difference between U300 morning and evening injection group was not clinically relevant.

Extension phase

Data from the extension phases in the T2DM trials (12 months) showed that the effect on HbA1c is maintained over the 12 month period with only modest increase in insulin dose. The effect of U300 remains comparable to that of Lantus but with a lower rate of hypoglycaemia (and especially nocturnal hypoglycaemia) in insulin-experienced patients.

Discussion of secondary endpoints

The key secondary endpoint of nocturnal hypoglycaemia was achieved in two trials in T2DM. In T1DM, there was a slight increase in risk. When compared to the more comprehensive analysis of hypoglycaemias in the safety section, there are overall small advantages which may be clinically relevant for some patients.

Most other endpoints were exploratory and descriptive only. The results confirm the large similarities between Lantus and U300. As expected, hypoglycaemias and variability with U300 are somewhat reduced.

Basal Insulin use is increased with U300 by 10-18% compared to Lantus. The clinical relevance of this finding is unclear, but may be limited as this is not associated with increased hypoglycaemias or additional increase in weight (see Safety section). It may be due to the somewhat reduced bioavailability, as measured in PK/PD studies.

Most patients use Lantus in the evening. When U300 is compared to Lantus, the more prolonged release profile of U300 causes a shift in insulin availability from the night to the day. As the basal insulin dose is adjusted based on fasting glucose and thus on nightly insulin levels, more basal insulin will be required to achieve the same insulin exposure overnight. Apparently, the extra basal insulin that is available during the day has no clinical consequences. No reduction of prandial insulin is observed; apparently prandial insulin doses are mainly based on dietary habits.

2.5.3. Conclusions on the clinical efficacy

U300 has similar efficacy when compared to Lantus. The more gradual glucose lowering effect of U300 when compared to Lantus does not translate into important advantages. The higher use of basal insulin may be a disadvantage.

2.6. Clinical safety

Patient exposure

All subjects and patients from Phase 1 and Phase 2/3 studies who were randomized and received at least one dose of investigational medicinal product (IMP) were evaluated for safety. The studies supporting the clinical safety of U300 are EFC11628, EFC11629 and EFC12347 in patients with T2DM and studies EFC12456 and PDY12777 in T1DM (Table 13).

Table 13 - Duration of Exposure to U300 (all Phase 1 and Phase 2/3 studies)

	Number of subjects/patients treated							
Treatment Duration	≥1day		>12 weeks		>25 weeks		≥51 weeks	
	U300	Lantus	U300	Lantus	U300	Lantus	U300	Lantus
Completed clinical pharmacology studies			-	-	-	-		
Healthy subjects	23	24						
T1DM	140	91						
Phase 2/3 studies	1544	1543	1439	1440	1331	1317	100	105
T1DM	304	303	275	278	231	236	0	0
T2DM	1240	1240	1164	1162	1100	1081	100	105

Common adverse events

During the main 6-month period the number of patients with TEAEs and overall pattern of TEAEs were comparable between the treatment groups. TEAEs were reported in 62.8% and 58.9% of U300 and Lantus treated patients respectively in T1DM studies, and in 57.3% and 53.7% of patients, respectively in T2DM studies. In both treatment groups the most commonly reported TEAEs at the system organ class (SOC) level were Infections and Infestations, with nasopharyngitis and upper respiratory tract infection the most common preferred terms (PT) in both T1DM and T2DM (Table 14).

Table 14 - Summary of all TEAEs in ≥3% of all pooled U300 or all pooled Lantus patients (EFC11628, EFC11629, EFC12347, EFC12456, and PDY12777)

Number (%) patients	T1DM		T2DM		All studies	
	U300	Lantus	U300	Lantus	U300	Lantus
Preferred Term n (%)	(N=304)	(N=304)	(N=1242)	(N=1246)	(N=1546)	(N=1550)
Any class	191(62.8%)	179 (58.9%)	712 (57.3%)	669 (53.7%)	903(58.4%)	848(54.7%)
Nasopharyngitis	39 (12.8%)	33 (10.9%)	88 (7.1%)	72 (5.8%)	127 (8.2%)	105 (6.8%)
Upper respiratory tract infection	29 (9.5%)	23 (7.6%)	71 (5.7%)	67 (5.4%)	100 (6.5%)	90 (5.8%)
Headache	14 (4.6%)	14 (4.6%)	61 (4.9%)	47 (3.8%)	75 (4.9%)	61 (3.9%)
Diarrhoea	7 (2.3%)	6 (2.0%)	47 (3.8%)	38 (3.0%)	54 (3.5%)	44 (2.8%)
Nausea	8 (2.6%)	5 (1.6%)	40 (3.2%)	27 (2.2%)	48 (3.1%)	32 (2.1%)
Bronchitis	6 (2.0%)	6 (2.0%)	41 (3.3%)	42 (3.4%)	47 (3.0%)	48 (3.1%)

TEAEs sorted by frequency in all U300 patients.

Most of the events were mild to moderate in intensity, 5.1% of the U300 treated patients and 4.1% of the Lantus patients had an event of severe intensity; the most frequent in both groups being hypoglycaemia (U300 0.5% and Lantus 0.8%). The percentage of patients with TEAEs considered related to IMP treatment was low and similar in the U300 (5.6%) and Lantus (5.3%) groups; the most common TEAEs related to IMP were hypoglycaemia (U300 0.5% and Lantus 0.7%) and headache (U300 0.5% and Lantus 0.4%).

The results of the subgroup analyses for most common TEAEs were consistent with those for the overall population in the T1DM and the T2DM pools.

Hypoglycaemia

The definitions used for hypoglycaemia events are in common use and accepted. The Applicant approached hypoglycaemias from a large number of viewpoints (Table 15).

Table 15 - Aspects of hypoglycaemia

Category	severe hypoglycaemia, documented (≤3.9 mmol/L), documented hypoglycaemia <3.0 mmol/L, documented symptomatic / documented asymptomatic / probable symptomatic hypoglycaemia, relative hypoglycaemia, composite category of severe and/or confirmed hypoglycaemia
Period	0-6 months, 0-2 months, 2-6 months
Time of day	any, nocturnal, daytime, nocturnal + waking up, by hour of the day
Count	patients affected, number of events, event rate
Analysis	by trial, pooled T2DM.

Severe hypoglycaemia

In **T1DM** (study EFC12456), rates of severe hypoglycaemia events per patient-year exposure tended to be smaller in the U300 group compared with the Lantus group (Table 16). This difference is driven by daytime events. During the first 8 weeks of study treatment the rate of severe hypoglycaemia was similar between groups. Comparable rates were also found between treatment groups for the morning and evening injection groups, with lower rates after morning injection.

Table 16 - Number of severe hypoglycaemia events per patient-year in T1DM studies

Severe hypoglycaemia	**EFC12456**		**PDY12777**	
Number of events (rate/patient-years)	**U300**	**Lantus**	**U300**	**Lantus**
Total patient-years	124.10	126.83	9.27	8.56
Any time of the day	30 (0.24)	43 (0.34)	1 (0.11)	3 (0.35)
Nocturnal (00:00 – 05:59)	10 (0.08)	7 (0.06)	0	2 (0.23)
Daytime (06:00 – 23:59)	20 (0.16)	36 (0.28)	1 (0.11)	1 (0.12)

In all 3 studies in **T2DM** severe hypoglycaemia was reported with similar frequency in the U300 and Lantus treatment groups (Table 17); with U300, 28/1242 (2.3%) patients experienced severe hypoglycaemia, with Lantus 33/1246 (2.6%) patients. The highest number of severe hypoglycaemia

was reported in study EFC11628 in patients with basal insulin in combination with mealtime insulin. The event rates per patient-year for severe hypoglycaemia were low and comparable between the treatment groups in all 3 studies. During the initial 8 weeks of study treatment, a comparable percentage of patients reported severe hypoglycaemia, and similarly the rate of severe hypoglycaemia per patient-year in each of the 3 studies in T2DM was comparable.

Table 17 - Number of severe hypoglycaemia events and rate per patient-year in EFC11628, EFC11629 and EFC12347

Severe hypoglycaemia Number of events (rate / patient-years)	**EFC11628**		**EFC11629**		**EFC12347**	
	U300	Lantus	U300	Lantus	U300	Lantus
Total patient-years	194.86	193.40	191.33	193.80	200.98	197.73
Any time of the day	53 (0.27)	47 (0.24)	5 (0.03)	12 (0.06)	4 (0.02)	4 (0.02)
Nocturnal 00:00 – 05:59	12 (0.06)	15 (0.08)	0	2 (0.01)	0	0
by sleep status0	-	-	-	-	0	0
Daytime 06:00 – 23:59	41 (0.21)	32 (0.17)	5 (0.03)	10 (0.05)	4 (0.02)	4 (0.02)

a Sleep status: Hypoglycaemia waking the patient from sleep (not applicable to EFC11628 and EFC11629 where wake status was not collected) Extracted from

All hypoglycaemia

Some important classes of hypoglycaemia events are summarised in **Table 18**.

In both studies in **T1DM**, comparable percentages of patients reported at least one hypoglycaemia event for each individual category of hypoglycaemia including the category of severe and/or confirmed hypoglycaemia. Also, comparable percentages of patients in both treatment groups reported nocturnal or daytime hypoglycaemia. The graph of the cumulative mean number of severe and/or confirmed (≤3.9 mmol/L [70 mg/dL]) hypoglycaemia events suggests comparable number of events during the first 3 months of study treatment in the U300 and Lantus group, thereafter, the number of events increases modestly in the U300 group over the Lantus group (Figure 9).

During the first 8 weeks of study treatment hypoglycaemia events of any category were reported by a comparable percentage of patients in both treatment groups. Risk reductions in the U300 group were found for the number (%) patients reporting nocturnal hypoglycaemia during the first 8 weeks of study treatment for nocturnal hypoglycaemia.

During Month 3 to Month 6 (endpoint) of study treatment, all hypoglycaemia reported any time of the day and nocturnal hypoglycaemia were reported by overall comparable percentages of patients in the U300 and Lantus treatment groups. Analyses of the hypoglycaemia event rate per patient-year exposure show numerically higher event rates in the U300 treatment group for symptomatic hypoglycaemia documented by SMPG ≤3.9 mmol/L (70 mg/dL) and, mostly driven by this category, for severe and/or confirmed hypoglycaemia.

Table 18 - Overview of hypoglycaemia

	T1DM	T2DM		
	EFC1245	EFC1162	EFC1162	EFC1234

	6		8		9		7	
	U300	Lantus	U300	Lantus	U300	Lantus	U300	Lantus
N	274	275	404	402	403	406	435	438
Any time of the day								
Any severity	257 (93.8%)	258 (93.8%)	337 (83.4%)	356 (88.6%)	288 (71.5%)	322 (79.3%)	217 (49.9%)	242 (55.3%)
Severe								
Any time of the day	18 (6.6%)	26 (9.5%)	20 (5.0%)	23 (5.7%)	4 (1.0%)	6 (1.5%)	4 (0.9%)	4 (0.9%)
Nocturnal (00:00 – 05:59)	6 (2.2%)	7 (2.5%)	8 (2.0%)	10 (2.5%)	0	2 (0.5%)	0	0
Nocturnal by sleep status	6 (2.2%)	5 (1.8%)	-	-	-	-	0	0
Daytime (06:00 – 23:59)	14 (5.1%)	19 (6.9%)	17 (4.2%)	16 (4.0%)	4 (1.0%)	5 (1.2%)	4 (0.9%)	4 (0.9%)
Documented symptomatic								
≤ 3.9 mmol/L (70 mg/dL)	233 (85.0%)	230 (83.6%)	283 (70.0%)	313 (77.9%)	200 (49.6%)	233 (57.4%)	133 (30.6%)	157 (35.8%)
< 3.0 mmol/L (54 mg/dL)	189 (69.0%)	192 (69.8%)	151 (37.4%)	167 (41.5%)	83 (20.6%)	109 (26.8%)	33 (7.6%)	61 (13.9%)
Asymptomatic								
≤ 3.9 mmol/L (70 mg/dL)	192 (70.1%)	209 (76.0%)	255 (63.1%)	274 (68.2%)	200 (49.6%)	238 (58.6%)	137 (31.5%)	169 (38.6%)
< 3.0 mmol/L (54 mg/dL)	93 (33.9%)	107 (38.9%)	69 (17.1%)	66 (16.4%)	43 (10.7%)	59 (14.5%)	7 (1.6%)	8 (1.8%)
Severe and/or								

confirmed								
≤ 3.9 mmol/L (70 mg/dL)	255 (93.1%)	257 (93.5%)	331 (81.9%)	353 (87.8%)	282 (70.0%)	314 (77.3%)	201 (46.2%)	230 (52.5%)
< 3.0 mmol/L (54 mg/dL)	214 (78.1%)	221 (80.4%)	181 (44.8%)	201 (50.0%)	110 (27.3%)	143 (35.2%)	43 (9.9%)	71 (16.2%)
Nocturnal								
Any severity	191 (69.7%)	196 (71.3%)	183 (45.3%)	240 (59.7%)	123 (30.5%)	169 (41.6%)	88 (20.2%)	105 (24.0%)
Severe	6 (2.2%)	7 (2.5%)	8 (2.0%)	10 (2.5%)	0	2 (0.5%)	0	0
Documented symptomatic								
≤ 3.9 mmol/L (70 mg/dL)	162 (59.1%)	159 (57.8%)	145 (35.9%)	194 (48.3%)	91 (22.6%)	126 (31.0%)	54 (12.4%)	68 (15.5%)
< 3.0 mmol/L (54 mg/dL)	112 (40.9%)	107 (38.9%)	49 (12.1%)	68 (16.9%)	33 (8.2%)	47 (11.6%)	14 (3.2%)	28 (6.4%)
Asymptomatic								
≤ 3.9 mmol/L (70 mg/dL)	77 (28.1%)	96 (34.9%)	84 (20.8%)	102 (25.4%)	43 (10.7%)	77 (19.0%)	44 (10.1%)	56 (12.8%)
< 3.0 mmol/L (54 mg/dL)	27 (9.9%)	27 (9.8%)	9 (2.2%)	13 (3.2%)	10 (2.5%)	9 (2.2%)	3 (0.7%)	1 (0.2%)
Severe and/or confirmed								
≤ 3.9 mmol/L (70 mg/dL)	188 (68.6%)	193 (70.2%)	180 (44.6%)	231 (57.5%)	114 (28.3%)	162 (39.9%)	78 (17.9%)	103 (23.5%)
< 3.0	127	126	63	82	40	54	17	29

mmol/L (54 mg/dL)	(46.4%)	(45.8%)	(15.6%)	(20.4%)	(9.9%)	(13.3%)	(3.9%)	(6.6%)

favours U300; favours Lantus

Any time of the day (upper graph) **Nocturnal hypoglycaemia (lower graph)**

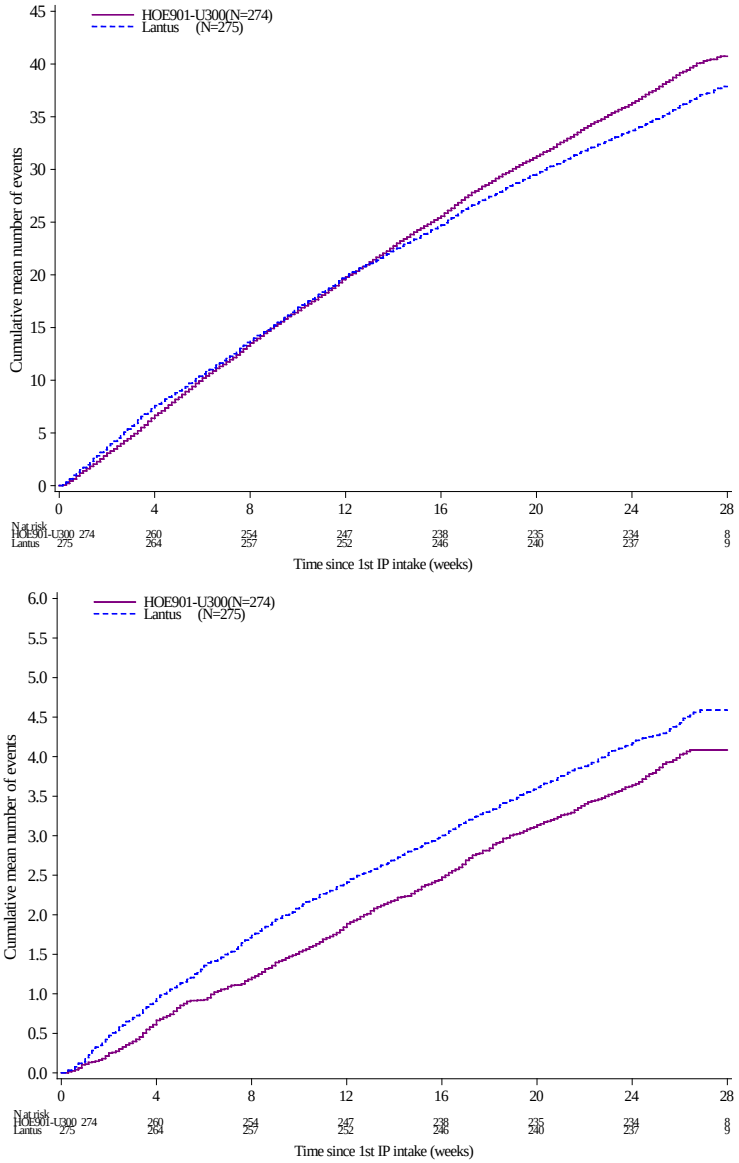


Figure 9 - EFC12456 - Cumulative mean number of severe and/or confirmed hypoglycaemia by plasma glucose ≤3.9 mmol/L (70 mg/dL) per patient during the 6-month on-treatment period (Nelson-Aalen estimates)

In all studies in **T2DM,** concomitant use of sulfonylureas was prohibited in order to not jeopardize the hypoglycaemia analyses by hypoglycaemia caused by sulfonylureas. In all 3 studies the percentage of patients reporting hypoglycaemia of any category was numerically lower in the U300 groups compared with the Lantus groups; severe hypoglycaemia and asymptomatic hypoglycaemia with SMPG < 3.0 mmol/L (54 mg/dL) were reported by a similar percentage of patients.

In study EFC11628 in patients using basal insulin in combination with mealtime insulin, event rates per patient-year exposure were comparable between the U300 and Lantus group for all categories of

hypoglycaemia. Relative risk vs Lantus for any hypoglycaemia was 0.94 (95% CI 0.80-1.11). In the other T2DM studies, in patients using basal insulin in combination with non-insulin AHA, event rates per patient-year exposure were lower in the U300 group than in the Lantus group. Relative risk vs Lantus for any hypoglycaemia was 0.77 (95% CI 0.66-0.90).

In all 3 studies in T2DM all types of nocturnal hypoglycaemia were reported by a lower percentage of patients in the U300 group compared with the Lantus group. Relative risk vs Lantus for any nocturnal hypoglycaemia was 0.76 (95% CI 0.66-0.87); comparable percentages of patients were found for asymptomatic hypoglycaemia with SMPG <3.0 mmol/L (54 mg/dL)(RR vs Lantus 0.69 [95% CI 0.30-1.59]). In the studies in T2DM, daytime hypoglycaemia was reported by a similar (in combination with mealtime insulin) or lower (in combination with non-insulin AHA) percentage of patients in the U300 compared with Lantus group depending on the type of hypoglycaemia.

In all 3 studies the cumulative number of events was lower in the U300 group than in the Lantus group for both hypoglycaemia any time of the day and nocturnal hypoglycaemia events. Differences in favour of U300 are most prominent for nocturnal hypoglycaemia in the studies in insulin-pretreated patients (EFC11628 and EFC11629) and for hypoglycaemia any time of the day in the 2 studies where the basal insulin was given in combination with non-insulin AHA (EFC11629 and EFC12347). Notably, any separation between the 2 treatment groups starts already during the first weeks of study treatment, ie, still in the transition period when changing over from another insulin regimen or in the first weeks of insulin treatment in insulin-naïve patients.

In all 3 studies in T2DM, during the first 8 weeks of study treatment, hypoglycaemia events of all categories were reported by lower percentages of U300 than Lantus treated patients. During the first 8 weeks of study treatment, nocturnal hypoglycaemia was reported by lower percentages of patients in the U300 group compared with the Lantus groups in all 3 studies in T2DM. During Month 3 to Month 6 (endpoint) of study treatment, in all 3 studies in T2DM, hypoglycaemia any time of the day continued to be reported by a lower percentage of patients and at a lower event rate per patient-year exposure in the U300 group than in the Lantus group. The risk of nocturnal hypoglycaemia, regardless if shown by percentage of patients reporting at least one event or by event rate per patient-year exposure continued to be lower in the U300 group compared with the Lantus group during this study period.

During the 3-month administration **substudies** of studies EFC11628 and EFC11629 in patients with T2DM, hypoglycaemia events occurring any time of the day and nocturnal hypoglycaemia occurring between 00.00 and 05.59 hours, overall and for each category of hypoglycaemia, were reported by comparable percentages of patients in the U300 adaptable dosing interval group and U300 fixed dosing interval group.

In study EFC12456 in patients with T1DM, hypoglycaemia events occurring any time of the day and nocturnal hypoglycaemia occurring between 00.00 and 05.59 hours, overall and for each category of hypoglycaemia, were reported by comparable percentages of patients and at comparable rates per patient-year in the U300 morning and evening injection groups. In comparison with Lantus, event rates for hypoglycaemia occurring between 06.00 and 24.00 hours tended to be higher with U300 than Lantus for both the morning and evening injection groups (events per patient-year exposure for severe and/or confirmed hypoglycaemia [SMPG ≤3.9 mmol/L; 70 mg/dL], morning injection group: U300 71.48, Lantus 62.90; evening injection U300 69.38, Lantus 64.23).

In T1DM and T2DM, for hypoglycaemia analyses, similar results were observed across **subgroups** as defined by demographic or baseline characteristics. In the T2DM studies, the hypoglycaemia incidence was consistently lower in the U300 group than the Lantus group or at least similar in all subgroups defined by age, race, gender, ethnicity, BMI, HbA_{1c} level and duration of diabetes.

Adverse events of special interest

Injection Site Reactions

No safety signal was detected for injection site reaction TEAEs in the T1DM and T2DM pools for patients receiving U300 or Lantus.

The number of patients reporting any injection site reactions was comparable between the treatment groups, 2.5% of the U300 treated patients and 2.8% of the Lantus treated patients reported injection site reactions (T1DM: U300: 8 patients [2.6%]; Lantus: 5 patients [1.6%] and in T2DM: U300: 30 patients [2.4%]; Lantus: 39 patients [3.1%]) during the main 6-month study periods.

Hypersensitivity Reactions

No safety signal was detected for hypersensitivity reactions, which were reported by comparable percentages of patients in the Phase 2/3 studies overall (U300 5.3% and Lantus 4.5%) and in the T1DM studies (U300 6.6% and Lantus 4.6%) and T2DM studies (U300 5.0% and Lantus 4.4%). The most common hypersensitivity reactions were rash in both the U300 (13 patients, 0.8%) and Lantus (7 patients [0.5%]) groups.

Most events were reported as mild or moderate in intensity. The majority of patients recovered or improved while treatment was ongoing.

Study treatment was discontinued in one Lantus treated patient with T2DM because of injection site rash.

Malignancy

No safety signal was detected for malignancy TEAEs in the T1DM and T2DM pools for patients receiving U300 or Lantus . The number of cases was comparable between the treatment groups; U300: 6 patients (0.4%) and Lantus: 10 patients (0.6%).

Cardiovascular safety

No CV safety signal was detected in the T1DM and T2DM pools for patients receiving U300 or Lantus.

Events of the SOC Cardiac disorders were reported by comparable percentages of U300 and Lantus treated patients overall (U300 2.2% and Lantus 2.9%), in the T1DM studies (U300 1.0% and Lantus 1.3%) and in the T2DM studies (U300 2.5% and Lantus 3.3%).

The U300 clinical development program has not been designed to specifically assess the CV risk of U300, as the CV safety profile of the active ingredient insulin glargine has been established for Lantus. Major CV events (MACE) including CV death, non-fatal myocardial infarction and non-fatal stroke were identified by searching the AE and SAE data base using Standardized MedDRA Queries and PTs.

The percentage of patients with any MACE identified by the data base search was low and comparable in the U300 (0.6%) and Lantus (1.0%) groups, and similarly in the T1DM (U300 0.3% and Lantus 0.7%) and T2DM studies (U300 0.7% and Lantus 1.1%).

Table 19 - Major cardiovascular events

Number (%) patients	T1DM		T2DM		All studies	
	U300	Lantus	U300	Lantus	U300	Lantus
Preferred Term n (%)	(N=304)	(N=304)	(N=1242)	(N=1246)	(N=1546)	(N=1550)
Any CV death, non-fatal MI, non-fatal stroke	1 (0.3%)	2 (0.7%)	9 (0.7%)	14 (1.1%)	10 (0.6%)	16 (1.0%)

Any cardiovascular death	1 (0.3%)	0	3 (0.2%)	1 (<0.1%)	4 (0.3%)	1 (<0.1%)
Any non-fatal MI	0	0	4 (0.3%)	4 (0.3%)	4 (0.3%)	4 (0.3%)
Any non-fatal stroke	0	2 (0.7%)	2 (0.2%)	10 (0.8%)	2 (0.1%)	12 (0.8%)

CV=cardiovascular; MI=myocardial infarction

As AEs identified in this search may include events that are not MACE, a thorough medical review of all the potential MACE listed in the above table was done. MACE was confirmed in:

- T1DM in one U300 treated patient (sudden death with severe coronary artery disease with chest pain),
- T2DM in 6 U300 treated patients (3 CV deaths, 3 non-fatal MIs) and 9 Lantus treated patients (1 CV death, 3 non-fatal MIs and 5 non-fatal strokes).

All patients experiencing serious cardiac TEAEs, including MACE, had pre-existing, event related pathology. None of the events were considered as related to the IMP or NIMP by the Investigator.

Hepatic safety

No safety signal was detected for hepatic TEAEs on T1DM and T2DM pools for patients receiving U300 or Lantus.

Serious adverse event and deaths

Overall, serious TEAEs were reported by 5.4% of the patients in both the U300 and Lantus groups, and by comparable percentages of U300 and Lantus patients in the T1DM studies (U300 5.9% and Lantus 7.2%) and T2DM studies (U300 5.2% and Lantus 5.0%), with no single event driving the results.

The most common serious TEAE in the T1DM studies was hypoglycaemia (U300 3.0% and Lantus 3.9%; T2DM: U300 <0.1%, Lantus 0.2%) and the most common in the T2DM studies was coronary artery disease (U300 0.2%, Lantus <0.1%); T1DM: U300 one event, no events on Lantus). The most common SOC with serious TEAEs were Cardiac disorders (U300 1.2% and Lantus 1.0%), mostly due to reports in the T2DM studies (U300 1.3%; Lantus 1.2%). All patients experiencing serious cardiac TEAEs had pre-existing, significant event related pathology, none of the events were considered as related to the IMP or NIMP by the Investigator.

At the cut-off date of 29 October 2013, SAEs were reported during the ongoing extension periods of studies EFC11628 (n= 68 patients), EFC11629 (n=30 patients), EFC12347 (n=11 patients) and EFC12456 (n=12 patients). In the Japanese studies, SAEs were reported for 14 patients in EFC12449 (Japan, T1DM), and 14 patients in EFC12512 (Japan, T2DM).

No serious TEAEs were reported during the Phase 1 program.

During the main 6-month study periods in the Phase 3 studies, serious TEAEs with fatal outcome were reported by a comparable percentage of patients in the U300 (5/1546, 0.3%) and Lantus (3/1550, 0.2%) groups. In the studies in T1DM, the only TEAE with fatal outcome was reported in 1/304 (0.3%) patient in the U300 group (sudden death, coronary artery disease, chest pain). In the studies in T2DM, TEAEs with fatal outcome were reported in 4/1242 (0.3%) patients in the U300 group and 3/1246 (0.2%) patients in the Lantus group. Causes of death in the U300 group included bronchogenic carcinoma, possible myocardial infarction, sudden death in the course of coronary artery disease, and worsening of atherosclerotic heart disease. In the Lantus group the reported fatal TEAEs were recurrent depression and drug overdose (benzodiazepines), judged to be a suicide, concomitant

worsening of chronic heart failure (NYHA IV), chronic kidney failure and decompensated diabetes, and exacerbation of chronic pyelonephritis.

Adverse events with fatal outcome were reported after treatment discontinuation in the 6-month study period in 2 patients in the U300 group, both in study EFC11628 (fatal septic thrombosis; fatal pulmonary embolism after total knee replacement).

None of the serious TEAEs with fatal outcome were considered related to the IMP or non-IMP.

At the time of the cut-off for the 6-month study reports, 2 deaths were reported in the extension periods, one in the Lantus group (acute cardiopulmonary arrest) and one in the U300 group (acute myocardial infarction). The event with fatal outcome in the U300 group was considered related to the IMP and non-IMP (metformin).

No TEAEs with fatal outcome were reported in the Phase 1 studies, in the Phase 2 study and during the 3-month administration substudy periods of the EFC11628 and EFC11629 studies.

As of the dossier cut-off date of 29 October 2013, 4 patients had died in the ongoing safety extension periods of the Phase 3 studies. Causes of death were bronchopneumonia, myocardial infarction, oesophageal adenocarcinoma stage IV and liver cancer. None of these 4 deaths were considered related to IMP by the Investigator.

Laboratory findings

Laboratory tests and vital signs did not reveal new or unexpected safety issues. Body weight increased more with Lantus than with U300, despite higher insulin use in the U300 group.

Table 20 - Change in body weight during 6 months on-treatment period (Assessor's table)

kg	U300	Lantus
T1DM	+0.46	+1.02
T2DM	+0.52	+0.79

Safety in special populations

The results of the subgroup analyses (age group, gender, race, ethnicity, baseline BMI categories, baseline eGFR categories, and hepatic disease ongoing at baseline) for common TEAEs were generally consistent with those for the overall population in the T1DM and T2DM pools.

For the age group ≥65 to <75 years, the incidence of common TEAEs was similar in both treatment groups. For the age group ≥75 years, interpretation was limited because of the low number of patients in this subgroup; however, no safety signal was detected.

Immunological events

At baseline, a similar percentage of U300 and Lantus patients were positive for AIAs in T1DM (61.7% U300 and 53.6% Lantus) as well as T2DM (41.6% U300 and 37.7% Lantus). Throughout the main 6-month treatment period, the percentage of AIA-positive patients slightly increased in T1DM patients, in both the U300 and Lantus groups, and remained similar in all T2DM patients. Among the AIA-positive patients, the percentage of those with antibodies cross-reacting with human insulin was similar between treatment groups for T1DM and T2DM. No major differences over time or between treatment groups were observed for antibody titer.

Percentages of patients with any TEAE tended to be higher for AIA-positive than negative patients in both, T1DM and T2DM, although the low denominator in the T1DM AIA-negative groups has to be taken into consideration. In T1DM, 50.9% of U300 and 48.3% of Lantus treated AIA-negative patients had any TEAE, compared with 65% of U300 and 61.3% of Lantus AIA-positive patients. Similarly in T2DM, in both, U300 and Lantus groups, the percentages of patients reporting any TEAEs was higher in the AIA-positive groups (U300 43.1%; Lantus 40.3%) compared with the AIA-negative groups (U300 36.6%; Lantus 35.5%), with no single event contributing to the larger number of patients with events. There was no difference in the percentages of patients reporting any TEAE in the high titer and low titer groups.

Hypoglycaemia events, injection site reactions and hypersensitivity reactions were reported by similar percentages of AIA-positive and AIA-negative patients in T1DM and T2DM.

These data suggest that there is no difference in the insulin antibody response and in the clinical effects associated with the insulin antibody formation in the U300 and Lantus groups.

Discontinuation due to adverse events

The percentage of patients with TEAEs leading to treatment discontinuation was low and comparable between treatment groups overall (U300 1.4% and Lantus 1.2%), and in the studies in T1DM (U300 1.3% and Lantus 1.0%) and T2DM (U300 1.4% and Lantus 1.3%). The pattern of TEAEs leading to discontinuation was similar in the U300 and Lantus groups, with no single event driving the results in either treatment group.

Post marketing experience

U300 has not been marketed in any country.

The efficacy and safety of insulin glargine as 100 U/mL has been shown in more than 200 000 patients with T1DM or T2DM included in clinical trials and observational studies. The benefit/risk profile of insulin glargine as 100 U/mL is well-established.

2.6.1. Discussion on clinical safety

Acknowledging the vast experience with Lantus, and the similarities between Lantus and U300, the Applicant's approach to focus the safety evaluation on the differences between U100 and U300 was considered appropriate by CHMP. These would include the effects of the different PK/PD, which could

lead to hypoglycaemia. On the other hand, local effects, including different immunogenicity, could be important. Accordingly, no new investigations on interactions were performed, which is acceptable.
The documented exposure is sufficient, both in comparison to the guideline (ICH-E1) and taking into account the experience with Lantus. In the initial submission, the safety database included 1544 patients exposed to U300, of whom 100 for at least 1 year. The extension phases were finalised by September 2014 and the safety data from the extensions of the T2DM trials were submitted during the procedure and included additionally 1011 patients exposed to U300 for at least 1 year. No safety concerns did arise from these data. Data for EFC12456 study (T1DM) were not yet available, and will be provided post-approval.
Hypoglycaemia rates with U300 were not higher than with Lantus. Most subjects who use Lantus have an evening injection. When this is compared to an injection with a similar amount of U300, this results for U300 in lower basal insulin levels during the night and higher basal insulin levels during the day. Accordingly, for U300 nocturnal hypoglycaemia events were somewhat lower and daytime hypoglycaemia events were higher in some categories, especially in combination with mealtime insulin. Most differences were small. The Applicant showed that mealtime insulin in combination with basal insulin contributes significantly to the increase in the number of daytime hypoglycaemia events. This was especially obvious in T1DM, with more hypoglycaemias in the U300 group. In T2DM the differences in hypoglycaemia were in favour of U300. CHMP agreed with the Applicant that mealtime insulin doses could have been further optimised, in particular in T1DM patients. The review of "all hypoglycaemias" showed that, in the T1DM population, hypoglycaemia was reported by almost all patients. This is in line with data from other studies in this population. Somewhat more severe hypoglycaemia events were reported with Lantus than with HOE901-U300. However, numbers are very small and thus no firm conclusions can be drawn. TEAEs were reported in 62.8% and 58.9% of U300 and Lantus treated patients respectively in T1DM studies, and in 57.3% and 53.7% of patients, respectively in T2DM studies. 5.1% of the U300 treated patients and 4.1% of the Lantus patients had an event of severe intensity; the most frequent in both groups being hypoglycaemia. A causal relation between events like nasopharyngitis (the most frequent AE) and PK/PD of insulin seems implausible. Rather, the difference between Lantus and U300 groups may be related to the open label design of the trials.
No safety signal was detected from the analysis of AEs of special interest, including injection site reactions, hypersensitivity reactions and cardiovascular safety. Also analyses of serious adverse events, deaths and discontinuations were unremarkable. The PK/PD data, however, evoked some concern regarding long-term safety with regards to injection site reactions. The Applicant has provided adequate data explaining the apparent difference in systemic exposure. These data in combination with the clinical safety data support keeping the current recommendation in the SmPC for rotation of the injection site.
Laboratory tests and vital signs did not reveal new or unexpected safety issues. Body weight increased more with Lantus than with U300, despite higher insulin use in the U300 group.
There is no difference in the insulin antibody response and in the clinical effects associated with the insulin antibody formation in the U300 and Lantus groups.
Based on the similarity between U300 and Lantus, no new analyses of interactions are deemed relevant.

2.6.2. Conclusions on the clinical safety

The safety profile of U300 is largely similar to that of Lantus and acceptable. Compared to Lantus the more stable basal insulin levels may lead to a reduction in hypoglycaemias in some situations.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The Applicant has submitted a signed Summary of the MAH's Pharmacovigilance System (version 2.0, dated 12 June 2014). Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the CHMP considers the Summary acceptable.

2.8. Risk Management Plan

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

The PRAC considered that the risk management plan version 4.5 is acceptable. The PRAC advice is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.5 with the following content:

Safety concerns

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Hypoglycaemia Medication errors (insulin mix-ups) Injection site reactions Hypersensitivity reactions
Important potential risks	Malignancies Antigenicity Medication error (inappropriate dose injected, following needle blocked in absence of compliance with instructions for use) Medication error (unnecessary re-calculation of the units needed) Medication error (inappropriate use, ie, extraction of insulin from the pen using a syringe) Medication error (switching between 100U/mL and 300U/mL without dose adjustment)
Missing information	Use in pregnancy (U300 only) Use in paediatric population (U300 only)

Pharmacovigilance plan

Table 2.2: Ongoing and planned studies in the PhV development plan

plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
PASS: UK SoloStar Differentiation Study (Category 3)	To evaluate the ease of differentiating between SoloStar pens containing different types of insulin with the current and new labels.	Medication errors (insulin mix-up)	Planned start 02-Feb-2015	Final study report planned 08-Jun-2015

PASS: Post authorization safety study; UK: United Kingdom

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

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.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimization activities	Additional risk minimization activities
Important identified risks		
Hypoglycaemia	SmPC, package leaflet, prescription only medicine.	None
Medication errors (insulin mix-up)	SmPC, package leaflet/instructions for use, packaging, prescription only medicine. One single trade name per concentration available on the market at the same time: Lantus is the trade name for U100; Toujeo is the trade name for U300. High level of differentiation in colors and packaging.	None
Injection site reactions	SmPC, package leaflet, prescription only medicine.	None
Hypersensitivity reactions	SmPC, package leaflet, prescription only medicine.	None
Important potential risks		
Malignancies	Prescription only medicine.	None
Antigenicity	SmPC, package leaflet, prescription only medicine.	None

Safety concern	Routine risk minimization activities	Additional risk minimization activities
Medication error (inappropriate dose injected, following needle blocked in absence of compliance with instructions for use).	SmPC, package leaflet/instructions for use, packaging, prescription only medicine.	None
Medication error (unnecessary re-calculation of the units needed)	SmPC, package leaflet/instructions for use, prescription only medicine.	None
Medication error (inappropriate use, ie, extraction of insulin from the pen using a syringe)	SmPC, package leaflet/instructions for use, prescription only medicine.	None
Medication error (switching between 100U/mL and 300U/mL without dose adjustment)	SmPC, package leaflet, prescription only medicine. One single trade name per concentration available on the market at the same time: Lantus is the trade name for U100; Toujeo is the trade name for U300. High level of differentiation in colors and packaging.	Before Toujeo launch: HCP educational material: HCP brochure Patient educational material: Patient brochure to patients treated with Toujeo.
Missing information		
Use in pregnancy (U300 only)	SmPC, package leaflet, prescription only medicine.	None
Use in paediatric population (U300 only)	SmPC, package leaflet, prescription only medicine.	None

SmPC: Summary of Product Characteristics

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(s).

2.9. Product information

2.9.1. 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

U300 in Toujeo is a new strength/potency of insulin glargine. It was proposed in a line extension to insulin glargine 100 U/mL (Optisulin). It has the same composition as the commercial formulation of insulin glargine 100 U/mL (Lantus, Optisulin) except for adjustment of 3 times the amount of active pharmaceutical ingredient and corresponding zinc content. The efficacy and safety of insulin glargine are well established.

Insulin glargine has the same metabolism after SC injection regardless of its source. However, the U300 and U100 formulations are not bio-equivalent. The difference between U300 and Lantus (U100) comes only from the PK/PD profiles of the 2 formulations as shown in the Phase 1 PK/PD clamp studies, which showed a flatter and more prolonged (up to 36 hours) profile of the insulin concentration and glucose lowering activity of U300 compared with Lantus at the same doses. With this time-action profile, U300 was expected to provide a more constant 24-hour basal insulin supply when compared to Lantus).

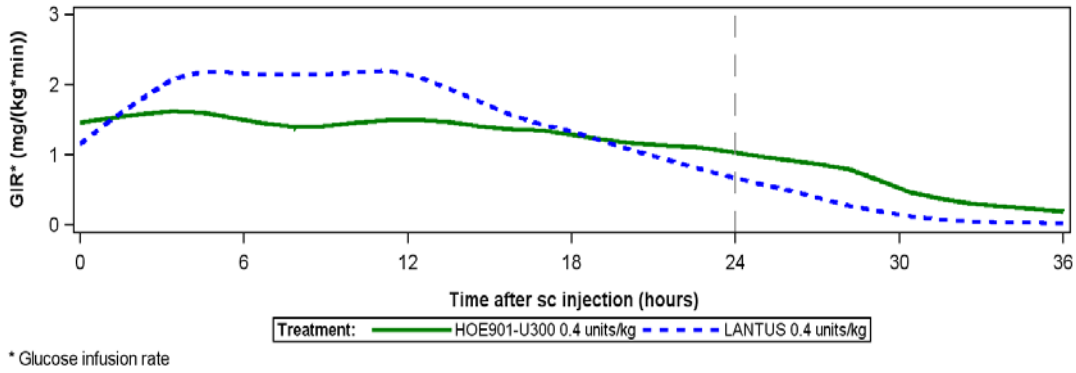


Figure 10 - TDR11626 - 36-hour mean smoothed glucose infusion rate profiles at steady state for 0.4 U/kg Lantus (dotted line) and 0.4 U/kg U300 (solid line)

Efficacy of U300 was investigated in studies including a broad range of adult patients with T1DM and T2DM using different established anti-hyperglycaemic treatment approaches, including basal insulin in combination with mealtime insulin or basal insulin in combination with non-insulin AHA in patients with T2DM.

Non-inferiority of U300 over Lantus on HbA_{1c} change from baseline was shown in all Phase 3 studies with the upper bounds of the 95% CI below 0.185% which was well below the pre-specified margin of 0.4%.

The secondary endpoint of nocturnal severe and/or confirmed hypoglycaemia (SMPG ≤3.9 mmol/L (70 mg/dL)) during the night was in general similar between groups in T1DM and the 3 studies in T2DM, however, the percentages were lower in the U300 groups compared with the Lantus groups reaching statistical significance in the studies in insulin pre-treated patients with risk reductions of 21% (study EFC11628: 36.1 vs 46.1%) and 23% (study EFC11629: 21.6 vs 27.9%).

Data from the extension phases in the T2DM trials (12 months) showed that the effect on HbA1c is maintained over the 12 month period with only modest increase in insulin dose. The effect of U300 remains comparable to that of Lantus but with a lower rate of hypoglycaemia (and especially nocturnal hypoglycaemia) in insulin-experienced patients.

Uncertainty in the knowledge about the beneficial effects

Exploratory data in 3 months extensions show that occasional deviations from precise 24hour dosing is expected to be safe. The trial was relatively short and no power calculation was provided, making the findings uncertain. On theoretical grounds, occasional flexibility is expected to be safe.

Due to the higher concentration, the volume to be injected is smaller, which may be less painful.

Risks

Unfavourable effects

The safety evaluation was based on 1544 patients exposed to U300, of whom 100 were exposed for at least 1 year. The analysis focused on hypoglycaemias and injection site issues, which is appropriate given the large similarities to Lantus.

In comparison to Lantus, hypoglycaemias occurred somewhat less frequently in most categories investigated.

U300 was well tolerated and had a general safety profile, including injection site reactions, similar to the well-established safety profile of Lantus. The evaluation of systemic hypersensitivity reactions and AIAs suggest an immunogenic potential similar to Lantus.

Data on immunogenicity at 12 months was provided with the submission of the data from the extension phases for the pivotal T2DM studies that were finalised by September 2014. Antibodies against insulin were detected in similar proportions of patients in U300 and Lantus groups at 12 months.

In all pharmacokinetic studies U300 was administered subcutaneously by injection in the periumbilical area of the abdomen. The SmPC recommends injection in the abdomen wall, the deltoid or the thigh. Data from the clinical phase 3 studies was provided which support keeping the current recommendation in the SmPC for rotation of the injection site.

Uncertainty in the knowledge about the unfavourable effects

In order to obtain a similar effect on HbA1c, 10-18% higher doses of U300 than Lantus were given. The difference in dose between U300 and Lantus is consistent with the 17% lower 24-hour exposure of -U300 compared with Lantus at fixed, equal daily doses (0.4 U/kg) in steady-state conditions in the PK/PD study TDR11626.

The different pharmacokinetic and pharmacodynamic profiles of insulin glargine from Lantus and U300 are due to different absorption rates from the subcutaneous precipitate, the mechanism behind this difference remains unclear. Considering the lower systemic exposure also at steady state, it may be assumed that a higher proportion of U300 is either retained or degraded within the subcutaneous tissue which may be exposed to higher insulin levels than with Lantus. The Applicant has, however, provided adequate data explaining the apparent difference in systemic exposure.

In their discussion, the Applicant suggested that mealtime insulin doses as used by the participants in the trial were not optimal, based on patterns of hypoglycaemia, variability of glucose measurements and possibly increase in total use of insulin. Data indeed suggest that mealtime insulin contributes to the incidence of hypoglycaemia. The difference between U300 and Lantus is especially obvious in T1DM, with more hypoglycaemias in the U300 group, whereas in T2DM the differences in hypoglycaemia were in favour of U300.

Benefit-risk balance

Importance of favourable and unfavourable effects

In many aspects U300 is similar to Lantus. There is extensive experience with Lantus and the benefit/risk of Lantus is well-established. The similarity with Lantus strongly supported the benefit/risk assessment.

The PK/PD differences, resulting in a flatter basal insulin curve, could be considered a theoretical advantage. However, the clinical trials did not show major clinical advantages of this flatter profile. In some patients, however, a reduction in hypoglycaemias may be important, and thus a valuable additional therapeutic option.

The reduction in injection volume could be of importance especially for patients who require large amounts of insulin. However, the limitation to 80 units per injection requires these patients to use still more than one injection, to some extent negating the most obvious advantage.

The average increased dose of insulin up to 18% is a theoretical disadvantage when a switch is made from 100 U/ml (Lantus) to U300. It is consistent with the lower systemic exposure. It has consequences for patients who switch from U300 to 100 U/ml insulin glargine as a dose reduction of 20% with subsequent titration may be needed. The extended residence time of U300 insulin glargine did not result in clinically relevant differences in anti-insulin antibody titers.

Although the pre-specified non-inferiority margin of 0.4% is considered as too wide the actual upper limit was 0.185%, which is well below the more desired margin of 0.3%.

U300 is not simply interchangeable with other long-acting insulins, including 100 U/ml insulin glargine. Importantly, when switching between insulin glargine 100 U/ml and U300, different doses may be needed to achieve target ranges for plasma glucose levels giving rise to a potential risk of medication error. This risk is addressed both in advice given in the SmPC and as an additional risk minimisation measure in the form of educational material (brochure) for health care professional and patient.

Benefit-risk balance

The benefit-risk balance of insulin glargine 300 U/ml is positive.

Discussion on the benefit-risk balance

Insulin glargine U300 has flatter PK/PD characteristics than Lantus and is not bioequivalent with insulin glargine 100 U/ml necessitating adaptation of the dose when a switch is made. After dose titration U300 has demonstrated comparable efficacy, safety and tolerability to Lantus in a broad population of patients with T1DM and T2DM with different pre-treatment regimens and dose requirements of insulin.

For T2DM there was a reduced risk for hypoglycaemia. In T1DM the only advantage is the reduction in injection volume. For patients who require more than 80 units of basal insulin, the volume but not the number of injections can be reduced.

Conclusion

The overall B/R of Toujeo, insulin glargine 300 units/ml solution for injection in a pre-filled pen is positive.

4. Recommendations

Final Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk/benefit balance of Toujeo 300 units/ml in the treatment of diabetes mellitus in adults is favourable and therefore recommends the granting of the extension of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

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**

Prior to launch of Toujeo 300 units/ml in each Member State the Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects, with the National Competent Authority.

The MAH shall ensure that in each Member State where Toujeo 300 units/ml is marketed, all healthcare professionals (HCPs) who are expected to prescribe or dispense Toujeo 300 units/ml, as well as all patients or their carers who are expected to use Toujeo 300 units/ml, are provided with educational material to address the risk(s) of Medication error (switching between 100 units/ml and 300 units/ml without dose adjustment).

The educational materials for healthcare professionals shall contain the following key elements:

- That insulin glargine 100 units/ml and insulin glargine 300 units/ml (Toujeo 300 units/ml) are not bioequivalent and are therefore not interchangeable without dose adjustment.

- That dose adjustment is needed when patients are switched from one to the other strength:
- After titration, on average a 10-18% higher basal insulin dose are needed to achieve target ranges for plasma glucose levels when using the 300 units/ml formulation compared to the 100 units/ml formulation.
- Switching from the 300 units/ml to the 100 units/ml concentration results in an increased risk of hypoglycaemic events, mainly in the first week after the switch. To reduce the risk of hypoglycaemia, patients who are changing their basal insulin regimen from an insulin regimen with once daily Toujeo 300 units/ml (insulin glargine 300 units/ml) to a once daily regimen with insulin glargine 100 units/ml should reduce their dose by 20%;
- When switching from a treatment regimen with an intermediate or long-acting insulin product to a regimen with Toujeo 300 units/ml, a change of the dose of the basal insulin may be required and the concomitant anti-hyperglycaemic treatment may need to be adjusted. Close metabolic monitoring is recommended during the switch and in the initial weeks thereafter;
- Patients need to be instructed that insulin glargine 100 units/ml products and Toujeo 300 units/ml are not interchangeable and dose adjustments need to be made;
- Blood glucose monitoring by patients is needed during the switch and the initial weeks thereafter;
- Reporting of medication errors or any side effects.

The educational material for patients and/or carers to address the risk(s) of Medication error (switching between 100 units/ml and 300 units/ml without dose adjustment) shall contain the following key elements:

- That insulin glargine 100 units/ml and insulin glargine 300 units/ml (Toujeo 300 units/ml) are not bioequivalent and are therefore not interchangeable without dose adjustment.
- That the switch from one insulin therapy to another should only be done when prescribed by their healthcare provider;
- That the dose newly recommended by their healthcare provider should always be followed;
- That blood glucose need to be closely monitored during the switch and the initial weeks thereafter;
- That they should consult their healthcare provider for further information;
- Reporting of medication errors or any side effects.

The target audience and the modalities for distribution of all of these materials are to be agreed at Member State Level. The MAH shall agree the final text and the context of the educational material for HCPs and patients together with a communication plan, with the National Competent Authority in each Member State prior to launch of the medicinal product.

In addition, CHMP recommends the variation(s) to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		**Type**	**Annex(es) affected**
A.2.a	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	IAin	I, IIIA, IIIB and A

To vary the invented name from Optisulin to Toujeo.